
PharmPK Archives



David Bourne, Ph.D.

PharmPK Archives

1995 - 96

These archives presents the discussions submitted to the PharmPK (pharmpk@boomer.org - <http://www.pharmpk.com/>) forum since November 1994. The discussion submission have been only lightly moderated and have NOT been checked for accuracy. Some topics are not complete, answers may be incomplete or even incorrect. Please don't base any clinical or medical decisions on these discussion. Check citations and consult clinical and medical references. Comments and corrections welcome, David Bourne (david@boomer.org)



THE BEGINNING

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1994

- ❖ *Started in November 1994 after discussion at **AAPS** with Brian Corrigan, a graduate student at the time. I had started a website in February of that year and a listserv related to pharmacokinetics seemed like a good idea.*
- ❖ *OU Health Science had and has excellent internet connectivity and I had software that ran easily on my little Macintosh. Apache webserver, macjoromo listserv software and a home grown Fortran program to create the archive pages.*
- ❖ *AAPS, PPDM Section Service Award 2006*
- ❖ *Now (Jan 2013) over 3,750 (email addresses) members*
- ❖ *Plain text messages to PharmPK@boomer.org are 'lightly' moderated*
- ❖ *The archives are a collection of these messages with time sensitive (job advertisement/conference notes) removed. They are available online at <http://www.pharmpk.com/>*

Lag in Urine Clearance - Urine/Plasma Correlation

On 27 Dec 94

I have a problem that is just the sort of thing that should be bounced off of a hundred plus pharmacokineticists. I am conducting a study on renal clearance of a drug. Analysis is done on the timed urinary output of the subjects over a 48 hour period. In virtually every subject, the first peak is detected 5 hours post-administration. A second peak, 80-120% of the first peak, is detected at 10 hours post-administration. The drug is excreted 97% in urine and my analysis procedure converts all conjugates into free drug. The time lag between the two peaks is too long for enterohepatic recycling and too high for CSF dumping. For most of the subjects, the timing of the peaks correspond to 1:00 and 6:00 pm, but the same relative timing post-dose is observed in subjects taking their dose at 4:00 am and at noon.

Has anyone else observed a 5 hour lag between peaks in urine or serum analysis? If so, were you ever able to explain its origin? I will entertain any and all explanations barring alien interaction and sunspots.

Kris Holt

On 27 Dec 94

I assume you are measuring steadily decreasing amounts of drug excreted into urine from the start but are seeing abnormal increases ('peaks') at 1 and 6 pm (in most of the subjects). If a meal is given at say 12 noon - 2 pm and 5 - 7 pm recycling may explain your results. Bile dumping could result from a meal or anticipation of a meal. My guess - anyone else?

What sort of assay are you using?

On 27 Dec 1994

There is a possibility that a window of absorption exist for this drug in the more distal and perhaps in the large intestine?

Majid Vakily

On 27 Dec 1994

First and foremost you seem to think that the second peak in urine output of the drug is due to the bodies handling of the compound and is unrelated to the formulation of the drug (enterohepatic cycling), if this were the case then you should see a double peak with dose of oral solution or an immediate release prep. Do you see a double peak in this case? Are double peaks reported for IV bolus? I know that this sounds really stupid, but have you checked to make sure that you are doing your calculations correctly and are not somehow making a erroneous calculation that leads to a higher than expected calculation in rates of urine excretion? Had to ask that one since it would be such an easy explanation. Until you dose some people with a oral solution or IV bolus I don't think you will be able to say much of anything about what is going on. Next question is did you see double peaks in every bodies profile? How many people were dosed? Was everyone fasted or did people have food also? How was the drug dosed, with water? Of course cimetidine is the great example of a double peak. In the case of cimetidine the magnitude or presence of the double peak is variable. I think that it would be surprising if you saw TOO much consistency in your data. Finally more stupid questions, are you sure that some of what your seeing could be due to urine collection and or handling methods? Were the same type of containers used through the entire period? Assay methods validated with these containers? I am thinking that you may want to think about surface-binding with containers, etc. (Pretty far-fetched, right?). Finally on the handling trail, what about the hydration of people in the study? Were study subjects allowed water? Is the drug reabsorbed in the kidney?

I think that you need to do the oral solution thing before you do anything else. More than likely what you are seeing in phenomenon that is due to the absorption of drug from the dosage form. Have you tried a similar drug in the same formulation?

On 3 Feb 1995

Can anyone suggest a few good papers on the correlation of plasma concentration/time data to urinary excretion? I'm interested in data for drugs in which nearly all excretion (i.e. 95-100%) is through the kidneys, either as parent compound or as a simple metabolite such as a glucuronide. Urinary excretion could be represented by dU/dt, cumulative recovery, or percent left to be excreted. Any help on this subject would be greatly appreciated.

Kris Holt

On 3 Feb 1995

You may want to look at some recent papers dealing with the pharmacokinetics of sotalol. Rob Carr, a fellow graduate student working with me in Dr R.T. Fosters lab, has done extensive research into the pharmacokinetics of this compound which is eliminated almost exclusively by the kidneys.

John Grundy

On 6 Feb 1995

There is an excellent textbook by Evans, Schentag & Jusco: Applied Pharmacokinetics - Principles of Therapeutic Drug Monitoring, Applied Therapeutics Inc., Vancouver, WA, 3rd Ed., 1992 that contains lots of information about renal function and drug clearance. You may find it useful.

A not so recent paper - that I co-authored - is: J.Wolff, D.Bigler, C.B.Christensen, S.N.Rasmussen, H.B.Andersen & K.H.Tnnesen 1988 Influence of renal function on the elimination of morphine and morphine glucuronides, *Eur. J. Clin. Pharmacol.*, **34**, 353-357.

Soren Norgaard Rasmussen

Pharmacodynamic/Pharmacokinetic Software

On 30 Nov 94

In an attempt to get some sort of dialogue going I'm going to ask about PK/PD computer packages that you all use.

What, if any, software do you use? What doesn't it do that you would like it to? What platform does it run on? What platform would you like it to run on?

I don't want this to turn into a MyFit is better than YourFit argument but I'm sure many of us would be interested to hear YOUR views.

Frank J Hollis

On 30 Nov 1994

Its nice that somebody finally break the ice. The programs we normally use are PCNONLIN and Lagran. A combination of the two are usually enough to take care of our conventional data analysis. With PCNONLIN, we often find that stiff data are not well fit. With LAGRAN, there is a problem of handling a huge data set. We are also experimenting with MATLAB, a program frequently used by chemical engineers. Initial experience tells us that this program can be used to handle complicated models.

This is a start, I hope we can hear more from the other people.

Yun Tam

On 30 Nov 1994

In addition to using PCNONLIN and Lagran we have used MKMODEL and JANA in our laboratory to model data. Does anyone else have experience with using other modeling programs that are user friendly and efficient? In addition, members of our laboratory have been using neural network programs to predict drug concentrations does any-

one have any experience with these programs? Brainmaker seems to be a good neural net program that is relatively easy to run what other programs are commercially available?

Neal Davies

On 1 Dec 1994

I use MKMODEL to explore complex models and for quick turn around on simple problems.

I use NONMEM for all population analyses. For me there are no other choices :-)

Nick Holford

On 30 Nov 1994

In our lab. we routinely use pnonlin for data fitting and analyzing our data. Lagran is another software that we use occasionally. Pnonlin, however, is the main software. we have done some linked PK/PD modeling using this software. As Dr. Tam mentioned sometimes is really is time consuming to work we this software. recently we are trying to start learning nonmem. Furthermore, NN seems a good package. I personally would like to learn about matlab more. This package seems is good for handling complicated modeling. I would appreciate if somebody sends me some information about this software (supplier, advantages, disadvantages.)

Majid Vakilynejad

On 1 Dec 1994

We use the same program for both pharmacokinetic/pharmacodynamic analysis and neural network predictions, FUNFIT. Unfortunately, it is not commercially available and is not user friendly, but it is powerful enough to meet our needs at the University of Iowa.

Ron Herman

On 2 Dec 1994

I just ran into a commercial package entitled "Scientist" from Micromath. The package is billed as an "...integrated software for experimental data fitting" (runs under Windows). The examples look at PK problems, model dependent and model independent examples are included.

I have just purchased the product. After "playing" with it for several weeks I will report back on its usefulness

On 2 Dec 1994

With regard the survey of pkin software I would like to tell you that I am trying to maintain a WWW page listing many such software programs. If you would like to send me (at david@boomer.org) more information on any such pk/pd software package I'd be happy to add it to the WWW page(s). Try: <http://www.pharmpk.com/soft.html>

David Bourne

On 2 Dec 1994

We have tried to stay current with the advances of the pkin software, but have not yet had any experience with neural networks. I would be interested in either a public or private discussion of the use/necessity of this system.

I do my initial data entry and manipulation with PSI-Plot from Poly Software International (Utah, ver. 3.0). Others in the department use Excel. Most of us use RSTRIP for fitting. I am also using Gillespie's PCDCON for deconvolution of urinary excretion data.

Kris Holt

On 2 Dec 1994

In our lab we have been using the programs BOOMER/MULTIFORTE for modeling PK/PD data. They are user friendly and can be used for simple models to complex models. They can be used for physiological modeling too. The programs perform simulation and fitting and includes Bayesian optimization. Models and integrated or differential equations can be expressed as a sequence of parameters in BOOMER or using Fortran state-

ments in MULTIFORTE. Supplied as compiled programs for Macintosh, MSDOS and VAXVMS systems. Would like to know if any of you have used these programs and your experiences with them.

Brinda Koneru

On 3 Dec 1994

You have mentioned about a software called funfit. Is it possible that you kindly provide me with more information about this program?

Majid Vakilynejad

On 4 Dec 1994

Since we are on the topic of pk/pd software I would like to know what type of software people are using for chromatographic analysis with their HPLC's. We are using E-Z-Chrom which has not proven to be user friendly at all. Other labs in our Faculty have been using Milenium. What other software is commercially available and is being used out there?

Neal Davies

On 6 Dec 1994

Re the recent posting about software for HPLC, I thought I might inform you that the Hungarian company CompuDrug Chemistry, Ltd. produces a programme called EluEx, designed to assist in HPLC method development for C-18 RP-HPLC. EluEx suggests the optimal mobile phase composition for separation, and includes a pKa calculating module as well as graphical simulation of the chromatogramme.

For details, contact Dr. Zoltan Bencz at

CompuDrug Chemistry, Ltd., Furst Sandor utca 5, H-1136 Budapest, Hungary

Internet: bz@cdk-cgx.hu

Dr. S. Shapiro

On 9 Dec 1994

Where can I find information on clinical pharmacokinetic softwares or programs for use in clinical settings?

Pierre-Paul Leblanc

On 27 Dec 1994

What simulation software/languages are being used out there? Has anyone heard of a language specifically for simulation called SIAM or SLAM? I've also heard that there is an internet users group for simulation similar to this for PK. Any ideas about this? How about vendors for simulation software?

Mark Sale

On 3 Jan 1995

We are using:

1. Simusolv, a superset of ACSL which also does fitting, excellent but very expensive (running on SPARCstation).
2. Stella II on pc or Mac (has interesting features but limited by the numerical algorithms it uses, verify your results with another package if possible).
3. NONMEM (for population simulations).
4. ADAPT II

William Bachman

On 10 Jan 1995

There is a specific simulation program called SAAM which originated from the NIH and was available in the 70s on mainframe. I understand it is now available for the pc but I do not know the source of it. Maybe NIH would know. To my knowledge this program was custom designed for simulations same as NONLIN is custom designed for data fitting.

Iqbal Ramzan

On 10 Jan 1995

If you have an interest in SAAM, you should contact Loren A. Zech at the NIH. He has been largely responsible for the continued development and distribution of this software. The latest version I know of is SAAM_{3I}.

His address is: Loren A. Zech. Lab of Mathematical Biology, NCI, NIH, Bethesda, MD 20892

Ron Sawchuk

On 10 Jan 1995

I have used STELLA quite a bit for simulation of pharmacokinetic systems for teaching and research. I have taught an elective course in pharmacokinetic simulation to pharmacy students for 4 years at the University of Minnesota, and find that the animation component makes it a great instructional tool. It allows for sensitivity analysis, as well.

STELLA was developed for the Mac, but is now available for the Windows environment.

STELLA II vers 3.0.5 is marketed by High Performance Systems, Hanover NH.

Ron Sawchuk

On 10 Jan 1995

In reply to Iqbal Ramzan's and Ronald Sawchuk's responses to Mark Sale's query regarding simulation software:

SAAM/CONSAM is available for the PC from either Loren Zech at NIH (or David Foster at the University of Washington). More information about the NIH program (and the program itself) may be obtained at <http://www.ncifcrf.gov:2001/-grief/info.html>

If this doesn't work, try <http://www-lmmb.ncifcrf.gov/-grief/info.html>

[NOTE: At 14 Apr 95 the URL <http://www-saam.nci.nih.gov/> seems like a good starting point. db]

The NIH and Washington versions of CONSAM are NOT THE SAME. Primarily, they differ in the way they do screen graphics. Both use the original SAAM numerical algo-

rithms (circa 1960's). Foster's group has just released SAAM II for Sun workstations with PC and Mac versions to follow. For information, I'd suggest contacting Dr Foster at the above address.

William F. Beltz, Ph.D.

On 20 Jan 1995

I'm Director of Pharmacy at Brookside Hospital in San Pablo (Bay Area). Several years ago I wrote a basic program to help dose patients on aminoglycosides. I have recently made it available as Freeware on the Net. Also included is Gentex.Doc, the documentation.

I don't know how useful this will be to the members of this list as it seems that most of you are Unix based researchers, but it's there if you want it.

Neil Sandow, Pharm.D.

SECTION 3

Neural Net Software

On 1 Dec 1994

I would love to get some information about the Brainmaker. Do you have any references that you might be able to quote?

Chetan D. Lathia

On 1 Dec 1994

We use the same program for both pharmacokinetic/pharmacodynamic analysis and neural network predictions, FUNFIT. Unfortunately, it is not commercially available and is not user friendly, but it is powerful enough to meet our needs at the University of Iowa.

Ron Herman

On 2 Dec 1994

Frank Hoke (Glaxo Research Institute: 919-990-5157) will be hosting a seminar at next years AAPS meetings on neural nets. Ward Systems Group has some software for PK/PD that you may be interested in looking at.

On 2 Dec 1994

Could somebody thro' some light on the 'Application of Neural Nets in PK/PD' ..any relevant papers/publications/programs...

Jagadeesh Aluri

On 2 Dec 1994

This is by no means complete, but it is a place to start:

1. Erb RJ 1993 Introduction to backpropagation neural network computation. *Pharm Res* **10**, 165-170
2. Hussain AS, Johnson RD, Vachharajani NN and Ritschel WA 1993 Feasibility of developing a neural network for prediction of human pharmacokinetic parameters from animal data. *Pharm Res*, **10**, 466-469
3. Veng-Pedersen P and Modi NB 1993 Application of neural networks to pharmacodynamics. *J Pharm Sci*, **82**, 918-926
4. Veng-Pedersen P and Modi NB 1992 Neural networks in pharmacodynamic modeling. Is current modeling practice of complex kinetic systems at a dead end? *J Pharmacokin Biopharm*, **20**, 397-412.

Ron Herman

On 2 Dec 1994

A few comments regarding neural networks for PK/PD applications:

1. The delta-backpropagation network should be considered to be a "multiple nonlinear regression analysis" tool which does not require a user to define the function.
2. Sufficiently large data base is generally needed for network training and validation.
3. The trained network should be used as a simulation tool to identify relationships between input and output variables. These relationships can be used for more "formal" model building or hypothesis testing.
4. Research is needed for developing indicators or metrics for network performance. Without these use of neural networks will be limited to "informal" data analysis.

Ajaz Hussain

On 2 Dec 1994

Our lab has had some success using a neural network package from California Scientific (Palo Alto, California). Someone previously mentioned that Ward Systems has Specific softwre for Pk/Pd analysis. Could anyone elaborate on this further?

Brian Corrigan



2

1995

Alcohol pks

On 18 Oct 1995 at 22:27:51

Peter,

I would appreciate receiving any available information (especially references) concerning the absorption of alcohol (ethanol) in humans. What is an accepted K_a value for alcohol? Most papers in the forensic literature focus on the time of the peak BAC and then, in effect, treat alcohol absorption as a zero-order process (with parameters dependent upon the type of alcoholic beverage consumed).

You might take a look at a review on ethanol PK in *Clinical Pharmacokinetics* 1987; 13:273-292 for an overview of absorption models. A simple first-order absorption model (as implied by your request for an 'accepted k_a ') is probably as inappropriate as asking for an 'accepted half-life' for ethanol i.e. models which describe ethanol input and elimination usually need to be more sophisticated than the elementary first-order one compartment stuff. But it depends on your application of the model how fancy you need to be. Ethanol has rate dependent extraction when taken orally (probably in the liver - I don't accept the gastric ADH hypothesis). So if you really want to model oral absorption you can't assume the extent of absorption will be independent of absorption rate.

--

Nick Holford

Dept Pharmacology & Clinical Pharmacology University of Auckland, Private Bag 92019, Auckland, New Zealand <http://www.phm.auckland.ac.nz>

On 22 Oct 1995 at 11:21:47

Maybe I'm all wet, but if you're looking for a K_a for EtOH, it would seem that you would have to separate the absorption component from the elimination portion. Saturation of the elimination mechanism would be needed. At that point, you could do a comparison between oral absorption and IV infusion. (as long as you had a big enough sample population)

Bob Brennan

On 28 Oct 1995 at 21:21:43

Take for example, treatment of a methanol overdose. Ethanol treatment can be very close to the enzyme saturation point. If at that point, you converted from IV EtOH to PO EtOH, wouldn't that give you some decent ka info?

Bob Brennan

Aminoglycoside stability

On 18 Dec 1995 at 09:44:42

Does anyone have any information on the stability of aminoglycoside solutions stored at -20C

The UK NEQAS for Antibiotic Assays is provided by:

Department of Microbiology, Southmead Health Services NHS Trust, Bristol BS10 5NB, UK.

<http://www.ibmpcug.co.uk/~lwhite/index.html>

Dr Les White

On 19 Dec 1995 at 13:34:41

Check the reference of Brown et al. 1991 on gentamicin in J Assoc Off Anal Chem. It provides stability of gent at various temperatures and pHs.

Rob Hunter

Analytical Methods for Moisture

On 25 Oct 1995 at 10:34:39

Anyone familiar with Karl Fischer method for determining moisture content.

Where can I become familiar with his studies?

On 26 Oct 1995 at 19:05:13

There is a full description in the section of 'Water determination' of **USP** 23, p.1840 (mine is Asian edition), 1995.

YJ Lee

On 26 Oct 1995 at 19:05:17

The following book has a very good summary on KF method:

Douglas A. Skoog, Donald M. West: **Fundamentals of Analytical Chemistry**, 3rd Ed., Holt, Rinehart and Winston, 1976, p. 607-610

For review on the subject of KF reagent also see J. Mitchell, *Anal.Chem.*, 23, 1069 (1951) and J. Mitchell and D.M. Smith, **Aquametry**. New York; Interscience Publishers, Inc., 1948

Also, I'd suggest you to examine the United States and British Pharmacopaeias.

Good luck,

Andrej Skerjanec

HPB, Ottawa

Blinding Clinical Studies

On 21 Nov 1995 at 16:07:00

We are conducting a clinical study using a combination of drug A and drug B or placebo in tablet formulations. We wish to blind this study by placing these tablets in a container for oral administration.

The historical device 'cachet' has been suggested. A cachet ranges in size from 3/4 to 1/8 inch in diameter and consists of two concave pieces of wafer made of flour and water. They are sealed by moistening the margins and pressing pressing firmly together. Are these available? We need approximately 11,000 of them.

Please share any experience regarding blinding techniques.

Thank-you for your assistance.

Derek A. Ganes, Ph.D.

Director, Biopharmaceutics, Biovail Corporation International, Contract Research Division,
460 Comstock Road, Toronto, Ontario, Canada M1L 4S4

On 22 Nov 1995 at 10:48:14

Tablets in a capsule are the normal blinded supplies for this kind of study.

M Chasin

On 27 Nov 1995 at 10:49:48

Thank-you for your comments regarding the use of tablets in capsules for the blinding of clinical supplies.

Unfortunately, the tablets can not be put in a reasonably sized capsule because of the large diameter of one of the tablets. This is why the 'cachet' was suggested.

Derek A. Ganes, Ph.D.

Biovail Corporation International

On 28 Nov 1995 at 14:04:15

In France, 'cachet' is still available. I know a company which can provide you what you want :

Jacques Trevidic

Cooperative Pharmaceutique Francaise, 32 Bd Victor Hugo, BP 294, 44010 NANTES,
FRANCE

On 29 Jan 1996 at 13:37:37

I meant to tell you that Capsugel have a range of shells suitable for your need.

Izzy Kanfer

Convolution and Deconvolution techniques to assess Bioavailability

On 18 Dec 1995 at 09:44:40

Can someone explain what these techniques are? Where these should be used and what are the advantages/disadvantages of using these techniques.

Please also post any references and/or books about these techniques.

Thanks

Masood Bhatti

Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, Canada

On 18 Dec 1995 at 14:23:44

Convolution and deconvolution techniques are not necessarily used to answer the question of bioavailability. The Wagner Nelson method and Loo-Reigelman methods are forms of deconvolution. Deconvolution techniques are used to assess rates of absorption and require I.V. data. Some names to get you started are W. J. Jusko and P. V. Peterson.

However, this is a fairly complicated subject.

Steve Bramer

On 19 Dec 1995 at 13:34:42

Convolution and deconvolution techniques are not necessarily used to answer the question of bioavailability. The Wagner Nelson method and Loo-Reigelman methods are forms of deconvolution. Deconvolution

Same area but slightly different direction. I had thought of **WN** and **LR** as specialized examples of deconvolution and had included them as such under Deconvolution in my book which was published earlier this year. One reviewer expressed the opinion that this was incorrect. Do any others on the PharmPK list have an opinion about this? Thanks.

David Bourne

Dear colleague,

All arguments presented below are based on the assumption that the disposition kinetics of the drug is linear.

The drug bioavailability in the circulatory system after extravascular administration is defined in two ways, i.e. as the extent of bioavailability and the rate of bioavailability (1). The system describing the drug input into the circulatory system after extravascular administration can be defined in the Laplace s-domain by Eq.1

$$H_{\{c\}}(s) = X_{\{c\}}(s)/Y_{\{ex\}}(s) \quad (1)$$

where $H_{\{c\}}(s)$, $X_{\{c\}}(s)$ and $Y_{\{ex\}}(s)$ are the system transfer function, output and input, respectively (2). $X_{\{c\}}(s)$ represents the drug input into the circulatory system. Since this input is not available for measurement, to estimate the system transfer function the following systems can be used:

The system describing the drug input into the circulatory system after intravascular administration can be defined in the Laplace s-domain by Eq.2

$$H_{\{iv\}}(s) = X_{\{p,iv\}}(s)/Y_{\{iv\}}(s) \quad (2)$$

where $H_{\{iv\}}(s)$, $X_{\{p,iv\}}(s)$ and $Y_{\{iv\}}(s)$ are the system transfer function, output and input, respectively. $X_{\{p,iv\}}(s)$ represents the peripheral system output. The system describing the drug input into the circulatory system after extravascular administration can be defined in the Laplace s-domain by

Eq.3

$$H_{\{ex\}}(s) = X_{\{p,ex\}}(s)/Y_{\{ex\}}(s) \quad (3)$$

where $H_{\{ex\}}(s)$, $X_{\{p,ex\}}(s)$ and $Y_{\{ex\}}(s)$ are the system transfer function, output and input, respectively. $X_{\{p,ex\}}(s)$ represents the peripheral system output.

Since

$$H_{\{ex\}}(s) = H_{\{iv\}}(s) \cdot H_{\{c\}}(s) \quad (4)$$

the transfer function $H_{\{c\}}(s)$ can be expressed in the form of Eq.5, using the definitions given by Eqs.2 and 3

$$H_{\{c\}}(s) = (X_{\{p,ex\}}(s) \cdot Y_{\{iv\}}(s)) / (X_{\{p,iv\}}(s) \cdot Y_{\{ex\}}(s)) \quad (5)$$

For the equal inputs,

$$Y_{\{iv\}}(s) = Y_{\{ex\}}(s) \quad (6)$$

Eq.5 can be rewritten in the simple form of Eq.7

$$H_{\{c\}}(s) = (X_{\{p,ex\}}(s)) / (X_{\{p,iv\}}(s)) \quad (7)$$

Eqs.5 and 6 enable to estimate the drug bioavailability on the basis of the measured functions $X_{\{p,ex\}}$, $Y_{\{iv\}}$, $X_{\{p,iv\}}$ and $Y_{\{ex\}}$. The gain parameter (2) of the model of the transfer function $H_{\{c\}}$ approaches the extent of the drug bioavailability. The model

of the weighting function, corresponding to the model of this transfer function approaches the rate of the drug availability after extravascular administration.

In the specific case of equal intravascular and extravascular inputs (Eq.6), the weighting function can be estimated using deconvolution methods in the time domain. The literature on numerical and analytical deconvolution methods is extensive. Analytical deconvolution methods are mostly devoted to relatively simple models (3) which do not contain shunt and time delays and which models of transfer functions do not contain complex poles (2,4). The CXT program, described in our study (5) and available at

<http://www.pharmpk.com/soft.html>

option: software,

enables to estimate the system weighting function for equal and/or non equal intravascular and extravascular inputs.

Sincerely,

Dedik, Ladislav

Durisoova, Maria

REFERENCES

1. Wagner, J.: **Fundamentals of Clinical Pharmacokinetics**, The Hamilton Press, Inc. Hamilton, Illinois, 1975.
2. Dedik, L., and Durisoova, M.: Frequency response method in pharmacokinetics. *J. Pharmacokin. Biopharm.*, **22**, 1994, 293-307.
3. Gillespie, W.R., and Veng-Pedersen, P: A polyexponential deconvolution method. Evaluation of the "gastrointestinal bioavailability" and mean in vivo dissolution time of some ibuprofen dosage forms on appropriate constraints on the initial input response when applying deconvolution. *J. Pharmacokin. Biopharm.*, **13**, 1985, 289-307.
4. Dedik, L., Durisoova, M., and Balan, M.: Building a structured model of a complex pharmacokinetic system with time delay. **Bull. Math. Biol.**, *57*, 1995, 787-808.
5. Dedik, L., Durisoova, M.: CXT - a programme for analysis of linear dynamic systems in the frequency domain. **Int. J. Bio-Med. Comput.**, *39*, 1995, 231-241.

On 20 Dec 1995 at 13:52:51

Wagner-Nelson is considered a specialized (read limited ?) form of deconvolution. Limited to a single compartment analysis with first order absorption. Application of convolution of deconvolution does not require a compartmental assumption. Other assumptions do apply.

Deconvolution can be used to characterize the absorption profile (and hence assess bioavailability) among other things. And deconvolution does not require that an intravenous administration to be applied. It depends on the question!

Nishit Modi.

On 10 Jan 1996 at 13:09:08

I consider LR and WN as parametric forms of deconvolution. However, I also consider conventional nonlinear regression to be a method of parametric deconvolution when it is used to identify a disposition function.

Steve Shafer

On 19 Jan 1996 at 11:14:32

For the linear dynamic system defined by the weighting function $WF(t)$, input function $I(t)$ and output function $O(t)$, the system output can be expressed by Eq.1

$$O(t) = f_1(I(t), WF(t)) \quad (1)$$

where t represents time.

The function f_1 is the convolutive integral. The system weighting function and the system input can be expressed in the form of Eq.2 and Eq.3, respectively

$$WF(t) = f_2(I(t), O(t)) \quad (2)$$

$$I(t) = f_3(WF(t), O(t)) \quad (3)$$

The methods for determination of the system weighting function and the system input on the basis of Eq.2 and Eq.3, respectively, are called deconvolution methods.

The Wagner-Nelson method enables to determine the system input $I(t)$ if the mathematical model of drug elimination is known and if the system output $O(t)$ can be measured after extravascular administration. This method enables to reach the same result as

does Eq.3 but it does not employ the properties of the convolutive integral. It follows then that, in principle, the Wagner-Nelson method is not a deconvolution method. However, it is obvious that if the known mathematical model of the drug elimination has the weighting function $WF(t)$, then the same result is obtained whether the deconvolution method based on Eq.3 or the Wagner-Nelson method is used.

Dedik Ladislav, Durisova Maria

Double Sites Kinetic - Software

On 21 Feb 1995

Hello to the recipients of the pharmacokinetic List,

For my data, I'm looking for software (Mac is preferred) which could fit them according a double sites (with no cooperatively) Kinetic. Do somebody have informations where I could find it on the net (ftp site ?)

Hugues Abriel

On 2 Mar 95

I have some software, Boomer, which runs on the Mac and does PK analyses. What sort of equations do you mean by 'double sites'. Two enzyme sites? I have the manual on my WWW server:

<http://www.boomer.org/>

I have free versions available for download. If you don't see you model in the descriptions let me know what your equation look like.

David Bourne

On 2 Mar 95

For nonlinear least-squares curve-fitting (of any (!!!) model, 1- and 2-sites, pharmacokinetics, pharmacodynamics) I am perfectly happy with Systat 5.03, in particular the Simplex optimization. Systat is one of the big commercially available packages (SPSS is the other) and is also available in a Mac-version. Systat is produced and sold by Systat Inc., 1800 Sherman Avn., Evanston, IL 60201-3793, USA, tel. +1 (708) 864 5670, fax. +1 (708) 492 3567. There will probably be a representative in CH.

Andries Koster

Frequency response method

On 17 Mar 95

I would like to invite your attention to applications of the frequency response method to pharmacokinetics (1-4). The frequency response method, common in system engineering, is based on an approximation of the frequency response of a linear dynamic system, calculated from input-output measurements, by a frequency model of the system transfer function in the frequency domain. In general, the influence of the system structure on the form of the system frequency response is much more distinct than on the form of the system output. This is of great advantage in modeling the system frequency response instead of the system output, commonly used in pharmacokinetics.

1. Dedik, L. and M. Durisova 1994 Frequency Response Method in Pharmacokinetics. *J. Pharmacokin. Biopharm.* **22**, 293-307.
2. Durisova, M. and L. Dedik 1994 Comparative Study of Human Pentacaine Pharmacokinetics in Time and Frequency Domain. *Meth. Find. Exp. Clin. Pharmacol.* **16**, 219-232.
3. Durisova, M, Dedik, L, and Balan, M. 1995 Building a structured model of a complex pharmacokinetic system with time delays. *Bull.Math.Biol.*, accepted, in press.
4. Dedik,L. and M.Durisova 1995 CXT-A Programme for Analysis of Linear Dynamic Systems in the Frequency Domain. *Int. J. Bio-Med. Comput.*, accepted, in press.

Maria Durisova

HPLC Standard Curve

On 6 Dec 1995 at 14:12:38

Dear Pharmacokineticists,

I am a Masters by Research student who is studying pharmacokinetic data of cancer drugs in humans. My background is Statistics, and some of the things you may take for granted, we don't. I have a question:

I would like to know whether, in general, an intercept is fitted to a **HPLC** standard 'curve'. I see that sometimes it is forced through the origin and then sometimes it is not. It appears that the intercept is also often not significant in the regression, however this is usually insufficient grounds for removing it. It's better to have a physical reasoning. As far as I've been told, no-one knows what happens between the lowest measurable concentration and zero. It's definitely not a straight line. But at zero concentration, the peak should be zero (obviously), however that again is insufficient grounds for removing the intercept. It also appears that fitting an intercept allows a better fit to the three or four values that make up a 'standard'.

Lukas Zdanius

On 8 Dec 1995 at 10:39:05

In our company, there are strict guidelines about not forcing the intercept through zero. The range of quantification is bounded by nonzero calibration standards. Weighted linear regression is used to fit the range if an unweighted fit is unsatisfactory. The limit of quantification is the lowest calibration standard that, upon back-calculation, gives satisfactory precision and accuracy results.

A useful general guide may be found in *J. Pharm. Sci.*, **81**(3):309-312, 1992, or *J. AOAC Int.* **75**(1):19A-26A, 1992.

Varun Garg

On 11 Dec 1995 at 10:46:11

I would like to know whether, in general, an intercept is fitted to a HPLC standard 'curve'.

Dear Luke,

A standard curve is valid only between the lowest and highest concentrations. The regression should not be forced through the origin (how do you know the curve is linear below the lowest standard concentration) nor should the standard curve be extrapolated below the lowest concentration - or above the highest. Thus, the intercept of a standard curve is unimportant. To estimate concentrations lower than your lowest standard, you must choose a new lower standard concentration and include it in your standard curve.

Jo Cato

On 11 Dec 1995 at 12:24:44

Hi Dear Luke,

With regard to including or excluding the intercept from the Std. curve, you should consider the magnitude of the intercept compared to the ratio of drug/**IS** for the lowest concentration that you have in your std. calib. curve. In general, if the intercept is 10 times smaller than the mentioned ratio, one can simply omit that from the estimation of concentration of the unknown samples. However, if the intercept is relatively high and/or inclusion of intercept decreases the error of estimation of unknown samples within a run, one should consider the intercept.

M. Vakily

Faculty of Pharmacy and Pharmaceutical Sc., University of Alberta, Edmonton, Alberta, Canada

On 11 Dec 1995 at 12:24:45

I'm not certain if this is helpful or not. I am currently in a pharmacometrics fellowship and still learning, but here goes..

I have had the pleasure of attending Dr. Roger Jelliffe's Population PK/PD course. One of the books he gives out is about characterizing the error patterns of assays. Its whole title is 'Pharmacoinformatics: Equations for Serum Drug Assay Error Patterns; Implications for Therapeutic Drug Monitoring and Dosage.' It talks about polynomial descriptions of assay error.

Robert M Shore

On 13 Dec 1995 at 14:09:28

There are 'right answers' here but probably the most important thing to do is what has already been done here i.e. to think about your particular problem and ask if an intercept is reasonable. I agree that the theoretical predication is that the peak should be zero when conc is zero but it is possible to have a systematic error at zero e.g. by not calibrating the machine properly. But I think the main issue here is the nature of the error model not the structural model. An error model that predicts the variance of the peak at each conc can be constructed that say makes the variance proportional to the predicted peak squared plus an additive component which allows for the error (mean zero) at a conc of zero. Software that allows this and other more flexible variants of this error model has been around for a while but I dont know if many conc analysts (as opposed to data analysts) are aware of that.

--

Nick Holford, Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand, <http://www.phm.auckland.ac.nz>

On 13 Dec 1995 at 14:09:31

Thanks for all the responses regarding whether an intercept should be fitted to a HPLC curve. I received about 14, and will reply to each one in time. It appears that there is stronger grounds for keeping the intercept.

Lukas Zdanius

School of Statistics

Nicotine Patch and Cotinine Measurements

On 24 Aug 1995 14:49:50

We use urinary and salivary cotinine levels to assess the degree of study subjects' compliance with smoking cessation protocols. A new protocol may involve use of nicotine patches. I presume this would invalidate the use of cotinine monitoring to assess compliance, but are there data already about the relationships of cotinine levels to transdermal nicotine? Does anyone have experience with other techniques to determine how much a subject is / is not smoking?

Marcel J. Casavant, MD

Children's Hospital, Columbus OH

On 24 Aug 1995 17:23:17

We used CO analyzers for our nicotine patch/I.V. studies here at Maine

Jim Cotter

Clinical Research Mgmt., Medical Center Research Institute.

On 29 Aug 1995 22:41:35

We have used cotinine levels in our clinical pharmacology studies to determine if a subject smokes, or has been exposed to smoke. It turns out that although our lab reference range lists >50 ng/ml to be upper limit of normal, many of our subjects have levels of 100-200 ng/mL. Although the subjects deny smoking, passive exposure to smoke is something you will have to deal with. You should ask yourself if it is compliance that you want to document or the actual quantitation of nicotine systemic exposure.

J Paul

Pharmacokinetics of Lamotrigin

On 3 Feb 1995

Hello All.

I would like to know if somebody has information on population pharmacokinetic data on a new anti-epileptic drug: LAMOTRIGIN?

Soren N. Rasmussen

On 3 Feb 1995

1. M.K. Yau, T.H. Grasela, J.B. Fiedler-Kelly, E. Cox, A.A. Lai, G.P. Womble, J.P. Hubbell. Population Pharmacokinetics of Lamotrigine from Three Add-on Controlled Clinical Trials in Adult Patients with Epilepsy. Abstract presented at American Epilepsy Society Annual Meeting, Sheraton Bal Harbour Hotel, Miami, Florida, December 3-9, 1993.
2. J.B. Fiedler-Kelly, T.H. Grasela, M.K. Yau, L. Philips, S. Spencer, D.A. Smith, A.A. Lai. Lamotrigine Population Pharmacokinetics from Three Add-on Open Clinical Trials in Pediatric Patients with Epilepsy. Abstract presented at American Epilepsy Society Annual Meeting, Sheraton Bal Harbour Hotel, Miami, Florida, December 3-9, 1993.
3. M.K. Yau, A.A. Lai, G.P. Womble, W.A. Wargin, T.H. Grasela, J.B. Fiedler-Kelly. Lamotrigine Pharmacodynamics in Adult Patients - Safety and Efficacy. Abstract presented at American Society for Clinical Pharmacology and Therapeutics Annual Meeting, New Orleans Marriott, New Orleans Louisiana, March 30-April 1, 1994.
4. M.K. Yau, A.A. Lai, J.B. Fiedler-Kelly, T.H. Grasela. Logistic Regression Analyses of Lamotrigine Pharmacodynamics in Adult Patients with Epilepsy Enrolled in Three Well-Controlled Add-on Clinical Trials. Abstract presented at American Epilepsy Society Annual Meeting, Sheraton New Orleans Hotel, New Orleans, Louisiana, December 2-8, 1994.

Brian Sadler

Pharmacokinetics and MathCad

On 1 Dec 1995 at 11:49:47

Does anyone have a library of pharmacokinetic functions for MathCad they would be willing to share?

Thanks

Merlin V. Nelson

On 4 Dec 1995 at 17:21:37

Hi Merlin,

I have MathCad programs for simulating two simple models: multiple-dose, 2-compartment model, first-order absorption with a lag-time; multiple-dose, 2-compartment model, zero-order infusion.

Perhaps a directory should be created for MathCad files in the Stanford PK/PD repository.

Derek A. Ganes, Ph.D.

Director, Biopharmaceutics, Biovail Corporation International, Contract Research Division, 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4

On 5 Dec 1995 at 11:05:37

PharmPK mailing list recipients:

In response to the e-mail from Dr. Ganes, I have set up a directory for PK/PD files for MathCad in the repository I maintain at Stanford. To send files, connect using anonymous FTP to [pkpd.icon.palo-alto.med.va.gov](ftp://pkpd.icon.palo-alto.med.va.gov), and log into the directory "newfiles.dir". You will have read/write permission in that directory. Download your files to that directory, and

send me an e-mail about what you have downloaded. I will transfer them to the MathCad directory.

Thanks in advance for making your **PK/PD** software publicly available.

Steve Shafer

Phenytoin Dosed by Total or Lean Body Weight

On 8 Feb 1995

One of the pharmacists asked this tonight...

Should IV Dilantin be dosed on a total body weight or a lean body weight?

He said he had attended a seminar and had this data somewhere, but couldn't find it in any of our sources at work.

Leo Horishny

On 8 Feb 1995

The questions of dosing phenytoin based on IBW or TBW is still somewhat in questions. I refer you to a reference (de Oca GM, Gums JG, Robinson JD. Phenytoin dosing in obese patients: Two case reports. *Drug Intelligence and Clinical Pharmacy* 1988; 22: 708-10.) that may help. In essence the author state that dose needs to be adjusted in obese patients because they have large volumes of distribution. They quote Abernathy and Greenblatt (Abernathy DR, Greenblatt DJ. Phenytoin disposition in obesity. 1985 *Archives of Neurology*, 42 468-71.) that a dosing weight is equivalent to $IBW + [1.33(TBW-IBW)]$. In my experience, IBW under doses obese patients and does not result in therapeutic serum phenytoin concentrations. I would suggest that using serum phenytoin concentrations to adjust dosing would definitely be necessary in these patients combined with a non-linear bayesian dosing program to achieve early therapeutic serum concentrations.

Michael Burton

On 8 Feb 1995

I agree in my experience the use of a nutritional weight that is some where between the IBW and the ABW results in a better estimate of the actual Vd of an obese patient. I use $ABW + (1.2(ABW-IBW))$. You can also use this approach to help adjust the dosage in preg-

nant patients as their volume of distribution changes throughout the gestation period. If the mother was at steady state prior to the pregnancy, you can adjust the dose using pre-pregnant weight and current weight instead of ABW and IBW.

Carol Boyes

On 11 Feb 1995

Several people responded to the query, "Should IV Dilantin be dosed on Lean Body Weight versus Total Body Weight?"

Two formulae were presented:

Dose=IBW+[1.33(TBW-IBW)] *Arch. of Neur.*, 1985, **42**, 468-71

Dose=ABW+[1.2(ABW-IBW)] C. Boyes R.Ph.

Both these formulae calculated give answers GREATER than the TOTAL body weight

For Example:

IBW = 70kg Dose = 70kg+[1.33 (120kg-70kg)]

D = 70kg+[1.22 (120kg-70kg)]

TBW= 120kg Dose = 70kg+[1.33 (50kg)]

D = 70kg+[1.22 (50kg)]

Dose = 70kg+[66.5kg]

D = 70kg+[61kg]

Dose = 136.5kg

D = 131kg

Ought not the calculation be:

D = 70kg+[0.33 (120kg-70kg)]

D = 70kg+[0.33 (50kg)]

$$D = 70\text{kg} + [16.5\text{kg}]$$

$$D = 86.5\text{kg}$$

0.33 is what is used at Bethesda North. This was offered by Michelle Svinte, PharmD and Andrew Lantz, RPh

Leo Horishny

On 13 Feb 1995

I suspect that if you use $IBW + [0.33(TBW-IBW)]$ or $IBW + [0.2(TBW-IBW)]$ that this will give the correct dosing weight. We use this scheme for aminoglycosides and it works.

Michael Burton

On 17 Feb 1995

Thanks for the compliment. I'm not sure I'm an "authority" but I have reviewed the literature extensively and work with lots of epilepsy patients. The formula by Abernethy is the only proposed formula out there, that I know of, for dosing phenytoin in obese individuals. If I understand some of the message, you are concerned that it calculates a BW higher than the patient's original weight--that's correct. In fact, Abernethy states that the Vd in obese individuals may be higher. Personally, I do not have direct clinical experience with using this formula in obese patients. When used, the doses calculated are oftentimes "enormous". My suggestion has usually been to 1) use the formula to calculate a dose then 2) give a dose that all are comfortable with (based on experience and the condition of the patient). Sometimes this is about 1/2 of the calculated dose. Once the dose is administered, then re-assess the patient and perhaps obtain a serum concentration. If the patient is still seizing, you can then administer the other 1/2 of the calculated loading dose. In other words--the formula is probably correct, but clinicians haven't readily accepted the doses needed, therefore clinical judgement must be used.

Hope this "non-answer" helps.

This comment is from Nina Graves at U. of Minnesota. She has more experience with phenytoin dosing than me so I asked if she would agree with the formula for dose weight

of phenytoin in obesity: dose weight = $IBW [1.33(ABW-IBW)]$ as proposed in *Arch Neur* 1985, **42**. 468-71

Keep in mind that all drugs do not distribute like aminoglycosides. Phenytoin is apparently highly lipophilic, unlike aminoglycosides.

David Axt1

pKa for ketoconazole

On 1 Nov 1995 at 22:34:22

There are a young graduate student doing a research on extraction of ketoconazole (Nizoral) from soap, to estimate aging and caducity date for a pharmacological development of ketoconazole.

Chemical Abstracts is not available locally. None of our sources of information have this data. Lange's **Handbook of Chemistry** was the only book with info related... but not for ketoconazole.

She needs, specifically, the value of pKa for ketoconazole in acid and basic medium, the 2-fase binomial distribution for extraction or any technique related to determine both values...

Carlos Alberto Sanchez Velasco

Centro de Informacion y Documentacion para la Docencia y la Investigacion, Universidad Veracruzana, Xalapa, Veracruz, MEXICO

On 3 Nov 1995 at 10:00:36

There are a young graduate student doing a research on extraction of ketoconazole (Nizoral) from soap, to estimate aging and caducity date for a pharmacological development of ketoconazole.

Carlos: Dr. Mann and I studied the dissolution of keto in this article: 9. Carlson JA, Mann HJ, Canafax DM. Effect of pH on ketoconazole disintegration and dissolution. *Am J Hosp Pharm* 1983; **40**:1334-1336. We use a very basic spectrophotometric assay for this study. Hope it helps you.

Daniel M Canafax

PKPD Wheal Flare

On 24 Feb 1995

I am interested in a PKPD link between adult antihistamine pk/wheal & flare to pediatrics. I understand that the wheal and flare is not validated for antihistamines. Does anyone have any experience here?

Brad Gillespie

On 25 Feb 1995

My experience of people who make unsupported assertions such as 'x is not validated for y' is that I have difficulty understanding the problem. There have been published accounts of PKPD models for antihistamines which describe wheal and flare responses in relation to plasma concs via effect cpt models (of the top of my head I cannot cite you a reference but can do so when I get back to work on Monday). But the issue is what is your real problem? What are you wanting to do with any models of PKPD links for antihistamine wheal and flare? What is the pediatric angle? What on earth does 'validation' mean to YOU?

Nick Holford

On 27 Feb 1995

Have you looked at any indirect PK/PD models for this? Perhaps some work in this area may be of use to you. And I quite agree with what Dr. Holford said! In this work, you just have to go ahead and try it, and see if the results are useful or not. That's about as close to 'validation' as it gets, I think. ;-)

Diane Mould

On 27 Feb 1995

If I may I would suggest that you contact Dr. Keith Simons, Professor, Faculty of Pharmacy, U of Manitoba, Winnipeg, CAD. He and his wife, Estelle, are experts in the area of antihistamine kinetics and their study in peds..... They may be able to help you.

Jim Axelson

Propofol Pharmacokinetics

On 26 Apr 95

Could someone give me a number for the SERUM level of Propofol that would be achieved during a prolonged (>6 hours @ 30micrograms/kilogram b.w.) infusion of Propofol in an ICU setting?

Narayan Baliga

On 27 Apr 95

I have an un-referenced statement that the clearance of propofol is 104 L/h (in a 70 kg person?). The terminal $t_{1/2}$ (3 cpt model) is said to be 4 h but distribution half-lives of about 0.5 h are probably the main determinant of the conc at 6 h.

The question does not specify the infusion rate clearly. I assume that the rate is 30 mcg/kg/h and not a total dose of 30 mcg/kg over 6 h.

So assuming steady state at 6 h the predicted conc is

$$C_{ss} = \text{Rate In}/\text{Clearance} = 30 \text{ ug/kg/h} * 70 \text{ kg} / 104 \text{ l/h} = 20 \text{ ug/L}$$

Nick Holford

On 27 Apr 95

Thank you Nick. The rate we use is 30 micrograms/kg/minute not per hour. Also I was after the plasma level of propofol. I understand a large portion of propofol enters the red cells but I could not get a reference on the actual proportion of redcell-bound : protein-bound : free in plasma during a steady state.

Narayan Baliga

On 28 Apr 95

OK. I suspect the clearance I quoted of 104 L/h is for plasma (blood CL would be very unlikely at that value). So you can use it to predict plasma propofol. Given the rate of 30 ug/kg/min that would predict a conc of about 1200 ug/L or 1.2 mg/L. Does that sound correct?

Nick Holford

On 5 May 95

The pharmacokinetics of propofol are best described by a multicompartmental model. Thus, calculations based on clearance and V_{dss} are not likely to be helpful, except as steady state is approached. I would agree with Nick's assumption that by 6 hours steady state will be approximated, although the half-life in ICU studies is in the area of 2-4 days. The pharmacokinetics of propofol are also likely to be moderately nonlinear, as propofol's clearance exceeds liver blood flow, and propofol decreases cardiac output and liver blood flow in a concentration dependent manner. Nonlinearity of propofol pharmacokinetics have been demonstrated in dogs, but not in human studies to date.

I would suggest downloading a simulation program, which you can use to predict the propofol concentrations from any arbitrary drug infusion regimen. You can find three such programs, STANPUMP, STELPUMP, and IVA-SIM on my software repository, available via WWW page at URL:

<http://pkpd.icon.palo-alto.med.va.gov>

There are a variety of propofol pharmacokinetic published. STANPUMP contains specific ICU pharmacokinetics, based on high-resolution PK studies performed here at Stanford. I would guess there is more to your question than just wanting an estimate of plasma propofol concentration, and please feel free to contact me at the e-mail address below for additional questions.

I haven't been able to identify any reference of the RBC:plasma partition coefficient for propofol, but Zeneca has studied this. They tell me that unpublished studies performed internally show a partition ratio of 1:1.

Steve Shafer

Rat/Mouse Blood Flow

On 21 Feb 1995

I am interested in books or references about blood flux through the kidneys of male and female mouse. (Not rat Wistar). If you know it or where I can find it.

Ignacio Segarra

On 21 Feb 1995

Here are a couple of references which list the blood flow through the major organs of mouse. (Not given separately for male and female mouse)

1. Leonard E. Gerlowski and Rakesh K. Jain 1983 *J. Pharm. Sci.*, **72**, 1103.
2. Brian Davies and Tim Morris 1993 *Pharmaceutical Research*, **10**, 1093.

Brinda Koneru

On 21 Feb 1995

A good reference that deals with blood flow, organ weights and volumes as well as other important physiological parameters in a number of species, is that by B. Davies and T. Morris 1993 *Pharm. Res.*, **10**, No. 7, 1093-1095. Renal blood flow in the mouse (0.02kg) is cited as 1.3 mL/min. Two references for parameters in the mouse are cited.

Ron Sawchuk

On 2 Mar 95

I am constructing a large-scale PBPK model of inhalation of gaseous toxicants by rats and mice. I have found references that give values of organ weights (for most organs) as fractions of body weight (done by careful dissection) and blood flow rates through these or-

gans (by radioactive microspheres) for rats. Does anyone know of similar compilations for the mouse? Thanks for your assistance.

Michael C. Kohn

On 3 Mar 95

The organ weights and tissue perfusion rates for Sprague-Dawley rats can be found in M.D. Delp et al. 1991 *Am. J. Physiol.*, **261**, H1487--1493. Another source is W.L. Roth et al. 1993 *Risk Analysis*, **13**, 531--543

Ron Sawchuk

Reversible Metabolic Systems

On 11 Jan 1995

In a paper by Cheng and Jusko (*Pharm. Res.* (1990), 10, 1003-1010) the method for calculation of distribution clearance in a reversible metabolic system is presented. Equation 38 page 1005 needs $C'(0)$, the first derivative of $C(t)$ at time 0. How is this first derivative obtained. Can anyone provide an equation, method or reference for the calculation of $C'(0)$.

How are the equations for the calculation of the parameters of this model affected if there is chemical interconversion, not enzymic, in both the central compartment and peripheral spaces.

On 12 Jan 1995

a) $C'(0)$ is usually assumed to be 0 before the drug is administered :-)

b) Enzymes are chemicals. Makes no difference to the model. You just need to put in a suitable model element to account for the conversion e.g. to a separate compartment.

Nick Holford

Search for Compendium of Cytochrome P₄₅₀ drug interactions

On 3 Nov 1995 at 10:00:34

Is there a compendium available of cytochrome P₄₅₀ isoenzyme interactions with various drugs? Is there one that is in progress? There are many articles in this growing field, but I am looking for a complete, but simple table that lists drugs and P₄₅₀ isoenzyme interactions (ie inhibit, enhance, induce, etc).

J Paul

On 3 Nov 1995 at 15:58:52

There is a list by S. Saklad, Pharm.D. at http://saklad.uthscsa.edu/CYP_and_Drugs.html, which he apparently took from: Antidepressants and Cytochrome P₄₅₀ Enzyme Involvement (DeVane CL. *J Clin Psychiatry* 1994;**55**[12 Suppl]:38-45.

I have heard that there is a table in a recent '95 Clinical Pharmacokinetics article by Preskorn and Magnus: I haven't been able to get the complete citation yet, but if anyone else knows I'm interested too.

Bill Budris

Single-dose Aminoglycoside Therapy

On 22 Jun 1995 17:18:55

Do any of the pharmacy practitioners on this list work at institutions which dose IV aminoglycosides on a q24h basis? If so, please describe your experience with this regimen.

Paul Trusten, R.Ph.

VA Medical Center, Northampton MA

On 22 Jun 1995 16:15:44

We've been dosing aminoglycosides on a 'q24h' basis for a year or so with excellent results. Of course, some patients are on an even longer frequency (i.e. q48h) when their renal function dictates.

Many patients are dosed with a single 10 hour 'random' level after the initial load. I have encouraged practitioners to obtain a peak and a level at approx 2-3 x the anticipated $t_{1/2}$ when there is significant doubt that the patient will fall into the category of 'normal'. By doing so, you have all the information you need to calculate the volume of distribution and clearance. Then, if necessary, you have what you need to design a rational dosing regimen if the levels don't come out the way you wanted them to.

We have had no cases of aminoglycoside related nephrotoxicity using this approach, so far.

Neil Sandow

On 22 Jun 1995 20:19:24

Yes we use single dose gentamicin when ever we can (mainly for convenience and cost control) if peak and trough predictions warrant. In the main it seems to work just as well as q12 or q8h dosing.

Ben Holland

On 23 Jun 1995 19:24:45

Do any of the pharmacy practitioners on this list work at institutions which dose IV aminoglycosides on a q24h basis? If so, please describe your experience with this regimen.

Take a look at the June edition of Brit J Clin Pharmacol for some NZ experience from Evan Begg.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag

On Fri, 23 Jun 1995 08:35:55

An excellent review article is "Once-daily administration of aminoglycosides" in *Annals of Pharmacotherapy* 1994 June **28**(6):757-66.

Catherine Heyneman, Pharm.D.

Idaho State University College of Pharmacy, Drug Information Service

On 23 Jun 1995 14:20:22

We estimate the initial daily dose based on severity of infection (mild: maximum dose 3 mg/kg/d; moderate: 4.5 mg/kg/d; severe: 6 mg/kg/d). The daily dose is then modified based on estimated CrCl. Patients with estimated CrCl <50 are generally dosed once-daily. Those with CrCl >50 are dosed q 12h OR q 24h depending on the clinical situation and/or comfort level of pharmacist, physician, etc.

When using q24h dosing as above, we are primarily interested in achieving a desired AUC, and secondarily a high peak level. We use a single 5 hr post-dose value to estimate AUC- later time points seem to vary too much depending in Ke. Target value: 3 mg/L for "mild"; 4.5 mg/L for "moderate"; 6 mg/L for "severe" (ironically, the same numbers as maximum doses listed above).

As I alluded above, we don't use q 24h in all patients: most commonly, it is used in ICU patients, home care patients, and patients with UTI +/- bacteremia. One must be cautious in reporting nephrotoxicity rates, as nephrotoxicity will be low regardless of dosing method if the duration of therapy averages < 4 days.

Steve Ebert

On Sat, 24 Jun 1995 09:21:52

We've been dosing aminoglycosides on a 'q24h' basis for a year or so with excellent results. Of course, some patients are on an even longer frequency (i.e. q48h) when their renal function dictates.

Many patients are dosed with a single 10 hour 'random' level after the initial load. I have encouraged practitioners to obtain a peak and a level at approx 2-3 x the anticipated $t_{1/2}$ when there is significant doubt that the patient will fall into the category of 'normal'. By doing so, you have all the information you need to calculate the volume of distribution and clearance.

Then, if necessary, you have what you need to design a rational dosing regimen if the levels don't come out the way you wanted them to.

We have had no cases of aminoglycoside related nephrotoxicity using this approach, so far.

We, too have been using once-daily dosing for about a year, although the only MD's that seem to use it are Infectious disease people. It is not yet in common usage. A couple of follow-up questions.

What information does a random 10 hour level give you, and what adjustments do you make based on that?

What peak and trough levels do you aim for? Are you concerned about ototoxicity with higher peaks. Do you routinely do audiometry in these patients?

How do you initially dose the patient, empirically? I.e., 5mg/kg/day or something else?

What "loading dose" vs. "maintenance dose do you use? Our MD's just use the 5mg/kg/day dose, without a load. How do you adjust for patient's with elevated creatinine?

Lastly, do you use this approach in immunocompromised patients? Does the post-antibiotic effect which accounts for the efficacy and logic of this approach also hold true for the immunocompromised patient?

We too, have not seen an increase in cases of nephrotoxicity that can be attributed to therapy, but that may change as more cases are reviewed in the literature.

Nathan Pruitt

On 27 Jun 1995 22:17:37

We, too have been using once-daily dosing for about a year, although the only MD's that seem to use it are Infectious disease people. It is not yet in common usage. A couple of follow-up questions.

What information does a random 10 hour level give you, and what adjustments do you make based on that?

If you use the (shudder) nomogram supplied by Harford(?) and the 10 hour level falls below the toxic line, then it is assumed that the risks of nephrotoxicity with q24h dosing are minimal.

What peak and trough levels do you aim for? Are you concerned about ototoxicity with higher peaks. Do you routinely do audiometry in these patients?

With this approach we aim for peaks ~15-20 and 8-12 hours below 2 mcg/ml.

How do you initially dose the patient, empirically? Ie., 5mg/kg/day or something else? What "loading dose" vs. "maintainence dose do you use? Our MD's just use the 5mg/kg/day dose, without a load. How do you adjust for patient's with elevated creatinine?

Yes, 5mg/kg/day will do it for patients close to their ideal body weights. No need for a larger loading dose since levels fall so low before each dose, accumulation is minimal.

When the creatinine is elevated or the patient otherwise is problematic we will often draw serial levels to enable us to dose with better precision.

Lastly, do you use this approach in immunocompromised patients? Does the post-antibiotic effect which accounts for the efficacy and logic of this approach also hold true for the immunocompromised patient?

No, probably not. In these patients we generally don't trust the post-antibiotic effect. We tend to dose these patients with greater frequency.

Neil Sandow, Pharm.D.

Brookside Hospital, San Pablo, CA

On 28 Jun 1995 08:19:58

As a newcomer to the "group" I apologise for joining the conversation at a late stage. I assume the dialogue is concerning gentamicin.

We also discussed the possibility of introducing once daily dosing for neutropenic patients, but felt there was little evidence to support this and have continued to use 8-12 hour dosing schedules.

In Glasgow, a nomogram has been developed using data from a NONMEM analysis and the population data have also been incorporated into a Bayesian algorithm for dosage modification.

Duncan Jodrell

Edinburgh University.

On 28 Jun 95 09:37:26

There are several studies of once daily dosing in neutopenic patients: J Drug Dev 1988;1(Suppl 3):119-124. Ann Intern Med 1993;119:584-593. (The EROTC study of 677 patients). J Antimicrob Chemother 1978;4S:85-101 We use extended interval dosing in neutropenic patients, but switch to traditional dosing methods when the infection is not responding and the 8-12hr drug level is undetectable (particularly if gentamicin is the only gram-negative coverage). We designed nomogram similar to Nicolau's at Hartford, but use a 5mg/kg dose.

A complete list of citations is available on my homepage: <http://osler.wustl.edu/~reichley/>

Richard Reichley

Clinical Pharmacist, Pharmacokinetics, Barnes and Jewish Hospitals at Washington University Medical Center, St. Louis, MO 63110

On 30 Jun 1995 23:22:38

We are now routinely using q24h dosing. Doses are 5mg/kg for patients predicted to have a "normal" Vd and 7.5 mg/kg for large Vd. We measure only a 12 hour level and try to keep it <3 mcg/ml, however, I sometimes will increase the dose if it is < 1 mcg/ml. In about 80 patients we have not identified any dose related treatment failures, or nephrotoxicity. Costs are also less due to less frequent dosing, and fewer serum levels measured.

Carl Heisel, RPh.

Emanuel Hospital, Portland

Urinary excretion rate to plasma concentrations

On 12 Dec 1995 at 16:23:06

Dear Colleagues

I would like some opinions from members of the group on the practice of determining plasma concentrations of a drug from urinary excretion data. I have recently come across this method in a paper and wondered how accurate or valid data (eg $t_{1/2, z}$) based on this method actually are. In addition, I also know the drug undergoes active renal excretion.

The method is used when plasma concentrations fall below the limit of quantitation and the urinary excretion rate for the drug is used to determine plasma concentrations situated in the middle of the collection interval by dividing the excretion rate in the interval (dA_e/dt) by the renal clearance calculated from when plasma levels could be determined (CLR 0-x hr).

I thank you in advance for your assistance.

Dave Boulton

School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand

On 13 Dec 1995 at 14:09:29

Urine PK analyses are better than nothing and can provide useful estimates of K and, therefore, half-life. The absolute bioavailability (F) can be obtained if the drug is excreted totally unchanged, or provided all metabolites are identified, are known to be excreted in urine, and all can be measured (often easier said than done). Renal clearance can be calculated by dividing the total amount excreted unchanged during a urine collection interval by the plasma during that interval, although it is better to have urine collections and AUC to infinity.

Clearance (systemic) and volume of distribution cannot be obtained from urine data alone.

In switching from plasma to urine one has to ensure of course that, assay performance is adequate and comparable in both biological fluids.

The major problem occurs with drugs of very short (say <1 hr) and very long half-life (> 24 hr) -- The former makes it difficult to get enough data, while the latter is susceptible to problems from missed samplings since all urine should be taken over several days. Furthermore, unless the pre-terminal (distribution) phases are inordinately long then it is unlikely that subjects can pass a sufficient number of urine samples to capture this part of the PK profile. This also occurs for non-intravenous administration in that the absorption phase is often so rapid that no more than 1 or 2 samples of urine can be collected even when subjects are "pre-hydrated" before dosing (which in itself can be problematical, e.g. with oral administration of solid dosage forms).

Nonetheless, urine measurements can provide useful data for PK. For example, we recently used urinary excretion data to study the mechanism of absorption of amoxicillin (see : *Eur J Pharm Biopharm* **40**,374-378,1994; *Br J Clin Pharmac* **38**,274-277,1994). Hope this is of some help.

Bruce Charles

Pharmacy Department, Univ. Queensland, Brisbane, Australia.

On 13 Dec 1995 at 14:09:33

The validity of this depends on the constancy of renal clearance and the quality of the urine excretion data. This is one method that can be used to check for long terminal half-lives which are not evident from the plasma data, provided the two criteria mentioned above are fulfilled.

Leon Aarons

Pharmacy Department, University of Manchester, Manchester, M13 9PL, U.K.

On 14 Dec 1995 at 10:14:13

Dear Dave,

A good deal of our research involves following the excretion rates of drugs because we do not have the facilities for taking blood samples from human volunteers. The assumption that must be met for urinary analysis is that drug is excreted from the central compartment by a definable process, usually first order. The other consideration is that you will only get information on the fate of that portion of the parent compound that is analyzed in urine; ie - analysis of a metabolite will only give information on that fraction of the dose that is excreted as the metabolite.

Set up your spreadsheet with columns for time, midpoint, volume, and concentration. Time is the time since the dose was taken. midpoint is the center of the sampling interval (sample at 1 and 2 hours; the midpoint for the 2 hour sample is 1.5 hours). Volume is the TOTAL urinary output since the last sample; your subjects must give you virtually every drop they produce from time 0 to the end of the sampling period (12 hours, 24, 36 ... just have to measure it to know for sure). Concentration is determined in the normal manner by HPLC or whatever instrument you use.

CALCULATIONS:

1. mg recovered = concentration * volume
2. urinary clearance = $dU/dt = (\text{mg recovered}) / (\text{sampling interval})$

Some spreadsheets can't handle subtracting a cell from the next one in the column. In that case, $dU/dt = \text{mg_recov} / (2 * (\text{time} - \text{midpoint}))$

Under ideal conditions, a plot of urinary clearance vs. midpoint will exactly parallel plasma concentration (with an arbitrary scaling factor). We have used this fact in the formulation of several bioequivalent products under the assumption that if two formulations are bioequivalent, then they should be excreted in a bioequivalent manner. Urinary clearance gives you a non-invasive tool oth early formulation work for bioequivalence; you switch to blood when you're close.

Urinary clearance is especially powerful when combined with a deconvolution program such as PCDCON by Bill Gillespie. Using dU/dt as the input function and K_e (either from literature or from clearance by subjects taking an immediate release dose of the drug un-

der investigation) as the impulse response, you can get both the cumulative input of drug into the previous compartment and the rate of input.

NOTE: I said previous compartment. If you are measuring a drug that is excreted intact, then the input calculated by deconvolution is input into the central compartment. If you are measuring a metabolite, then you are measuring the input of drug from the central compartment into the metabolizing organ/enzymatic system. So with intact drug, you are measuring k_a . If the drug is in an **SR** or **CR** formulation and you assume that absorbance is much faster than dissolution, then the input rate from deconvolution is the in vivo dissolution rate.

I hope that this will help you decide whether to use urinary clearance or not. If you have any further questions, e-mail directly.

Kris Holt

Graduate Research Assistant, Oregon State University

On 15 Dec 1995 at 16:17:42

Dear Leon

Thanks for your comprehensive reply to my query regarding conversion of urinary excretion rate to plasma concentrations. I must admit I initially thought this practice would be a little suspect for quality quantitative work but the responses I have received have changed my mind and I see that the technique is useful in quite a number of situations.

Thanks again.

Dave Boulton

School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand



3

1996

Accumulation ratio calculation

On 30 Oct 1996 at 23:05:44

I would appreciate if any members of PharmPK can advise me on what should be a very simple question on how to calculate accumulation ratio (**AR**).

Drugs were administered either once (**QD**) daily or twice daily (**BID**) for 8 consecutive days. AUC_{0-dosing interval} and AUC_{0-infinity} are available for both days 1 and 8 on QD and BID.

Is AR:

1. $\text{AUC}_{0\text{-dosing interval day8}} / \text{AUC}_{0\text{-dosing interval day1}}$
2. $\text{AUC}_{0\text{-infinity day8}} / \text{AUC}_{0\text{-infinity day1}}$
3. $\text{AUC}_{0\text{-dosing interval day8}} / \text{AUC}_{0\text{-infinity day1}}$

All three ways have been suggested but there must be one correct way of calculating AR

many thanks in advance

Faruq H Noormohamed

Department of Therapeutics, Chelsea and Westminster Hospital, 369 Fulham Road, LONDON SW10 9NH

On 31 Oct 1996 at 12:28:07

Is AR:

1. $\text{AUC}_{0\text{-dosing interval day8}} / \text{AUC}_{0\text{-dosing interval day1}}$

This fits closest to my own definition of AR which is the ratio of the conc at **SS** (or after N doses) to the conc after the first dose at the same time after the dose e.g. the ratio of the trough conc at SS to the conc immediately before the second dose. Using the **AUC**

gives some kind of time averaged conc on day 8 divided by the conc averaged over the same period after the first dose.

$$2. \text{AUC}_{0-\infty} \text{ day8} / \text{AUC}_{0-\infty} \text{ day1}$$

No. Doesn't fit my definition of AR.

$$3. \text{AUC}_{0-\text{dosing interval}} \text{ day8} / \text{AUC}_{0-\infty} \text{ day1}$$

No. This ratio should be ≤ 1 (approaches 1 as steady state is reached). The AR should always be > 1 .

--

Nick Holford,

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019,,
Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 31 Oct 1996 at 12:28:28,

Faruq:

There is no unique definition of the accumulation ratio (AR), so there is no *correct* way of its calculating. In Gibaldi & Perrier (2nd edition) you will find 3 versions of AR:

$$1. \text{AR} = C_{\text{ss_min}} / C_{\text{I_min}},$$

where the subscript min corresponds to the plasma concentration immediately before the dose intake. If the dose is administered in the post-absorptive, post-distributive phase this definition of AR will result in a well-known equation:

$$\text{AR} = 1 / (1 - \exp(-\lambda_z \cdot \tau)) \quad (1)$$

$$2. \text{AR} = C_{\text{ss_max}} / C_{\text{I_max}},$$

where the subscript max indicates that the peak concentration is used in calculating AR. If the drug kinetics can be described by the one-compartment model you will get again Equation (1).

$$3. \text{AR} = C_{\text{ss_av}} / C_{\text{I_av}},$$

where average concentrations at steady state and during the first dose are used. The latter definition is the most common since it results in a simple non-compartmental formula, and is, therefore, the most appropriate:

$$AR = AUC_{ss_tau}/AUC_{I_tau}$$

Thus, in you three formulas:

1. $AUC_{Co-dosing\ interval\ day\ 8}/AUC_{Co-dosing\ interval\ day\ 1}$
2. $AUC_{Co-infinity\ day\ 8}/AUC_{Co-infinity\ day\ 1}$
3. $AUC_{Co-dosing\ interval\ day\ 8}/AUC_{Co-infinity\ day\ 1}$

the first one is consistent with the latter definition. However, to get an unbiased estimate, steady state should be achieved at day 8, otherwise you will under-estimate AR.

By the way, if you have steady state at day 8, your third formula will give unity if the kinetics of your drug is linear and time-invariant. If there is auto-induction the ratio will be lower than one. In the case of auto-inhibition it will be higher than one. So, this ratio is of importance, too.

Vladimir Piotrovskij, Ph.D. , Janssen Research Foundation, Clinical Pharmacokinetics, B-2340 Beerse, Belgium

On 31 Oct 1996 at 12:29:32

Faruq:

By a definition, the AR (or often referred to as "fraction of the steady state, achieved in the K-th period of the dosing schedule" is calculated as the ratio between the AUC in the K-th period and the AUC in a period at steady state. As AUC in a period at steady state is equal to the AUC to infinity after the first dosing, obviously the correct way is number 3.

Ivan Nestorov, PhD

Albumin in TPN

On 19 Nov 1996 at 17:08:16

We currently have two small (2.33kg and 3.88kg) children in our PICU.

Both were premature but with no pulmonary complications. They came in with cases of RSV which subsequently led to ARDS. They were very sick puppies from the start.

We started giving them parenteral nutrition early on. Initially the feeding was conservative and now, because of lower TP and Albumin levels, the docs have decided to get aggressive. Both are currently on High Frequency Oscillation Vents, and sedated. One is also on Vecuronium. Not good candidates for enteral feeds.

The attendings want to add Albumin to the TPN to increase serum levels. There is no sign of hepatic dysfunction or acute renal failure so I can only surmise that the lowered TP and Albumin levels are due to malnutrition. My argument was to increase glucose and protein and the TP and Albumin would follow shortly after.

A second reason for wanting Albumin was to increase oncotic pressure?? I believe that there are other ways to do this that are less expensive and more effective.

Does anyone have any data to support or dismiss the addition of Albumin to TPNs for the purpose of increasing serum levels. Are there any studies of the kinetics involved in the absorption and distribution of Albumin in neonates. Is the addition of lipids to the mix going to promote the distribution of Albumin as one attending contends?

This is a recurring argument. I need the literature to either convince me or the docs once and for all. I am also doing a med-line search to augment any information that you may have.

Please, anecdotal accounts are also welcomed.

Robert G. Aucoin RPh

Peds Clinical Pharmacist, OLOL RMC, Baton Rouge, LA

On 20 Nov 1996 at 12:02:28

Robert

From my basic science perspective, both you and the physicians have good points. Malnutrition seems the likely explanation for the hypoproteinemia, and unless there is an undetected hepatic problem, increased parenteral glucose and amino acids should solve it. But this process may be too slow or there may be a defect in hepatic albumin secretion as a consequence of the infants' prematurity. Especially if the patients are showing signs of edema, the priming dose of albumin sounds like a good idea assuming there are no immune-system consequences in response to i.v. albumin.

Combining your proposal with the physicians' proposal will result in a sort of primed infusion of albumin with the priming dose consisting of albumin itself and the infusion consisting of its biosynthetic precursors.

If the plan is to infuse albumin i.v., absorption should not be an issue, and distribution should be as it normally is for hepatocellular-secreted albumin. If the parenteral route is not i.v., then addition of albumin could be detrimental since it will increase extravascular oncotic pressure and actually promote edema.

You are of course correct that there are other ways to increase oncotic pressure, but albumin is certainly the way evolution solved the problem.

I'm unsure I understand the point you make about adding lipids to the mix and the consequences for albumin distribution. Distribution should not be an issue if the parenteral route is i.v.

Robert D Phair PhD

BioInformatics Services: <http://www.webcom.com/rphair>

On 20 Nov 1996 at 16:04:17

Bob,

There is rarely a second reason for giving iv albumin. The main reason and often the only one is to increase plasma oncotic pressure. Thus, the short answer to your question is that in the absence of fluid / hemodynamic problems, there is no rational for exogenous albumin. The best way to elevate plasma albumin is support hepatic protein production through good nutrition.

N. Anaizi, PhD RPh

Univ of Rochester Med. Center

On 22 Nov 1996 at 11:50:01

This isn't my area so I won't even pretend I have any of the answers. I'm the clinical specialist for a spinal cord injury unit. On the few occasions when we do use albumin it will only maintain oncotic pressure for a short period of time, right? Isn't this because extrinsic albumin has a very short half-life? Anyway, I have passed this message to a colleague in Orlando Florida who is a peds. specialist like yourself. Hopefully, he will be able to respond.

Tom Mobley

On 25 Nov 1996 at 10:07:53

The attendings want to add Albumin to the TPN to increase serum levels. There is no sign of hepatic dysfunction or acute renal failure so I can only surmise that the lowered TP and Albumin levels are due to malnutrition.

Not necessarily. Premies and term neonates are hypoalbuminemic, relative to older kids. And if these two have active ARDS, lung capillaries are leakier to albumin.

My argument was to increase glucose and protein and the TP and Albumin would follow shortly after.

Agree, to the point that you have to provide enough amino acid substrate to prevent albumin from being scavenged as an energy/protein source.

A second reason for wanting Albumin was to increase oncotic pressure?? I believe that there are other ways to do this that are less expensive and more effective.

Can't think of anything else except mannitol or hypertonic saline, neither one of which seems like a good idea to me. Do the neonatologists want to increase oncotic pressure to supernormal or simply give the kids pressure they would otherwise have? If the former, is that a treatment modality for ARDS? If the latter, better to do it before they become edematous.

Does anyone have any data to support or dismiss the addition of Albumin to TPNs for the purpose of increasing serum levels.

Can't say for neonates. Our adult patients on TPN are, however, always hypoalbuminemic, and they don't catch up very quickly on TPN alone.

Is the addition of lipids to the mix going to promote the distribution of Albumin as one attending contends?

Have never heard of this. I'd be interested in learning the mechanism, if it's true.

Wouldn't be why I'd use lipids, anyway.

Randy Trinkle, BScPharm, BA

Dept. of Pharmacy, Dawson Creek & District Hospital, Dawson Creek, BC

Aminoglycoside - daily dosing

On 6 May 1996 at 8:17:00

I am a hospital pharmacist, and recently we have been receiving orders for high doses of aminoglycosides to be used once daily. Both gentamicin and tobramycin. Doses range from 250mg to 300 mg given once daily.

Doyle Wilkinson, R. Ph.

Doctor's Regional Hospital

On 7 May 1996 at 11:18:01

Doyle

I was at the National Pediatric Infectious Disease Conference last month in New Orleans, LA, and mention was made of once a day dosing of aminoglycosides. Docs there expect to see this in their hospital in the near future. There is also literature around verifying the use on once daily dosing. It seems the logic behind all of this is that a high peak is not the problem with aminoglycosides, its the sustained trough. I don't have the literature references at home but I will get what I can and post it to the group. There have been several questions on medical list concerning this lately with no good reply that I have seen. I don't presume to offer the perfect or even best response. I only hope to stimulate a little conversation and learn something in the process.

Robert Aucoin RPh

Peds Clinical Pharmacist, Baton Rouge, LA

On 8 May 1996 at 10:40:51

We do this routinely at my institution and it is a popular topic when I do CE programs. For a recent article, look for a meta-analysis by Michael Barza in a recent issue of Lancet

(I'm pretty sure it was within the last month or so). Their conclusion was that "...[once-daily] aminoglycosides in patients without pre-existing renal impairment is as effective as multiple daily dosing, has a lower risk of nephrotoxicity, and no greater risk of ototoxicity. Given the additional convenience and reduced cost, once daily dosing should be the preferred mode of administration."

Gary D. Theilman, Pharm.D.

Assistant Professor, Dept of Clinical Pharmacy Practice, School of Pharmacy, University of Mississippi

<http://fiona.umsmed.edu/~theilman>

Aminoglycosides Consensus Document

On 7 Oct 1996 at 11:11:51

Dear Colleague,

You may recall that a few months ago, the PharmPK list initiated a parallel avenue for a more organized, purposeful discussion whose ultimate aim is to integrate our "collective wisdom" on specific topics in "consensus documents". The process begins with a coordinator preparing an initial document, which is then posted for the group to read and critique. Feedback should be directed to the coordinator, who will then revise the initial document as necessary. The final product will then be published as a document reflecting our consensus on the topic.

We have chosen three topics of current clinical interest:

1. Vancomycin kinetics and monitoring.
2. Administration of Beta-Lactams (intermittent vs cont. inf.).
3. Once-daily aminoglycoside dosing.

I was selected as the coordinator for the 3rd topic. I have completed the initial document. Dr. David Bourne has now posted it on the web site. You may find it in the following page:
<http://www.pharmpk.com/consensus/odacd.html>

Please take the time to read it, and give me your feedback

Thanks

N. Anaizi

On 18 Oct 1996 at 11:53:46

I'm delighted to be able to read the initial text of the ODD Aminoglycoside consensus document. This is exactly the type of thing we need. I would also like very much to review the documents on Vancomycin and Beta-Lactams.

Could anyone tell me where they are?

Bob Brennan

[The ODD Aminoglycoside consensus document is the only one I've seen. Is there anyone else preparing documents on these other topics? I'd be happy to place the works-in-progress on the server for review and comment - db]

ASA and SA Modeling

On 26 Apr 1996 at 15:04:11

We are interested in modeling and simulation of pharmacokinetics: absorption, tissue distribution and release of acetylsalicylic acid and salicylic acid (ASPEGIC).

We would be interested in any information and references to papers discussing the clinical studies as well as laboratory.

Abdelkader Ainaoui

Universite Jean Monnet, Laboratoire de Chimie des Materiaux, et Chimie Industrielle, 23, rue Dr. P. Michelon, 42023 ST-ETIENNE CEDEX 2 FRANCE

On 30 Apr 1996 at 11:13:52

This is for the dog: Chen, C. N., Coleman, D. L., Andrade, J. D., Temple, A. R. 1978
Pharmacokinetic model for salicylate in cerebrospinal fluid, blood, organs, and tissues,
Journal of Pharmaceutical Sciences **67**:38-45

Susan E. Shoaf, PhD

On 2 May 1996 at 10:33:02

Reference:

Aarons, Hopkins, Rowland, Brossel and Thiercelin, *Pharmaceutical Research* 1989 vol **6**
(no.8) p660 Routes of administration and sex differences in the pharmacokinetics of
aspirin, administered as its lysine salt.

This is a paper describing a study performed at Medeval Ltd, in Manchester, England, in conjunction with Synthelabo, Paris, which may be of use.

John Davis

Pharmacokineticist, Medeval Ltd

<http://www.man.ac.uk/vuman/med.htm>

On 2 May 1996 at 10:33:04

Dear Dr. Ainaout,

You can find relevant information in our recent article:

D. Dubovska, V.K.Piotrovskij et al. Pharmacokinetics of acetylsalicylic acid and its metabolites at low doses: A compartmental modeling. *Meth Find Exp Clin Pharmacol*, 1995, **17**(1): 67-77.

There is there a lot of references to earlier publications about ASA, SA and other metabolites kinetics in man.

Vladimir Piotrovskij, Ph.D.

Janssen Research Foundation, Clinical Pharmacokinetics, Turnhoutseweg 30, B-2340

Aspirin bioavailability

On 2 Dec 1996 at 10:24:50

Hello,

I am a first year pharm. D student who is researching a project comparing 81 mg aspirin doses brand name vs. generic brands (enteric coated). I have heard that there might be some bioavailability problems with the generic enteric coated aspirin products, but I haven't been able to find any real data on this. Does anyone have any suggestions?

Brad Hein, RPh

On 3 Dec 1996 at 14:17:41

Dear Bradley,

You might try to search the issue of aspirin kinetics under the name of Gerhard Levy, PharmD, He "wrote the book" on the issue of aspirin kinetics, dosage form effects, absorption, etc.

Jim Axelson

On 3 Dec 1996 at 17:15:01

You may have already thought of this, but have you referred to the OTC handbook (by APhA)? Since this is a referenced text, it may contain the citation for your question. Good luck.

Arasb Ateshkadi, Pharm.D.

Assistant Professor, Department of Pharmacy Practice, College of Pharmacy, University of Utah, 258 Skaggs Hall, Salt Lake City, UT 84112

On 4 Dec 1996 at 10:45:00

It's my impression that companies making generics must file data with the FDA to prove bioequivalence. You might consider calling the companies and having them send you a copy of the report they filed with FDA.

Steven C. Ebert, Pharm.D., FCCP

Clinical Specialist, Infectious Diseases, Clinical Associate Professor of Pharmacy, Department of Pharmacy, Meriter Hospital, 202 S. Park Street

AUC calculations

On 22 Mar 1996 at 11:32:47

In calculating the AUC for any particular profile. it is normally correct to use a linear method for the ascending portion of the curve (up to C_{max}) and a log method for the descending portion. This is very straight-forward when dealing with nice, smooth "up and down" profiles. The question is this - what method(s) should be utilised when a profile rises to C_{max} , then starts to fall, but during the descending phase perhaps concentrations rise again, but not as high as C_{max} , then fall again. Should a linear method be used between two data points when the second point is higher than the first, irrespective of whether it is post- C_{max} , or should a log method be used for all points post- C_{max} ?

Chris Davie

Department of Pharmacokinetics, SmithKline Beecham Pharmaceuticals R&D

On 25 Mar 1996 at 09:44:47

The theoretical basis for using the log AUC method is founded on the assumption that it is describing an exponential decline. While wobbling in the region of the peak conc there is no advantage of the log method (but it is probably not much worse). Trapezoidal AUC is after all only an approximation suitable for generating initial estimates for non-linear regression models so its not really a big deal either way :-)

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 25 Mar 1996 at 09:44:50

This is a very interesting question. We have done PK data analysis for Pharmaceutical companies where multiple peaks in plasma conc-time profile were observed. We used linear method for the ascending (generally convex in nature) as well as descending (generally concave and log-linear)

portion of the curve (the results of the PK data analysis were also submitted to FDA). The reasoning being that the linear method usually underestimates the AUC in the ascending phase, which is somewhat balanced by the overestimation of the AUC in the descending phase. However, the presence of multiple peaks further complicates the calculation of AUC. So my suggestion is to use linear method for whole profile unless you have very strong reasons to use log method for descending portion of the profile.

If it is imperative to use log method for descending profile, I think, real answers can not be easily found without doing simulation studies with some type of sensitivity analysis.

G. Krishna

Medical College of Virginia, Virginia Commonwealth University

On 26 Mar 1996 at 10:56:53

The linear trapezoidal rule has been proven to give biased estimates of AUC both at the ascending and descending parts of concentration-time curves. However, since the sampling is usually more frequent before the peak as compared to the tail of the curve, the bias can be neglected at the ascending part, and also near the peak(s). The log-trapezoidal rule also results in bias at the ascending part of the curve, however, it gives the exact estimate of areas under descending log-linear profiles (noiseless). If the noise is low (less than 10 %), the log-trapezoidal rule is preferable, especially in cases of long half-lives. It becomes even more important when calculating the first moment (AUMC).

Vladimir Piotrovskij, Ph.D.

Janssen Research Foundation, Clinical Pharmacokinetics, B-2340 Beerse, Belgium

On 27 Mar 1996 at 13:41:06

One approach is based on the sign of the second derivative as described by Proost (*J Pharm Sci* **74**: 793-794, 1985) which we have implemented into a "deconvolution" program (*Pharm Res* **5**: 247-248, 1988).

Gary A. Thompson, Ph.D.

Clinical Pharmacology, Procter and Gamble, 11450 Grooms Rd., Cincinnati, OH 45242

On 28 Mar 1996 at 15:59:29

Concerning the discussion about estimating AUC for noisy or multiple concentration peak data, people should remember that interpolation and then integration by Lagrange polynomials is an entirely general method of integration and is independent of the local concavity or convexity of the data. The Lagrange method was implemented several years ago by ML Rocci, Jr and WJ Jusko, "LAGRAN program for area and moments in pharmacokinetic analysis" *Computer Programs in Biomedicine* **16**: 203-216 (1983). One problem with Lagrange method is that it occasionally suffers from oscillations yielding poor estimates of area. The Lagrange method and the issue of oscillations is discussed in KC Yeh and KC Kwan, "A Comparison of Numerical Integrating Algorithms by Trapezoidal, Lagrange, and Spline Approximation" *Journal of Pharmacokinetics and Biopharmaceutics (JPB)* **6**: 79-98 (1978).

R. Purves has done a rigorous comparison of many methods of estimating AUC and AUMC. I recommend his paper: "Optimum Numerical Integration Methods for Estimation of Area-Under-the-Curve (AUC) and Area-Under-the-Moment-Curve (AUMC)" in *JPB* **20**: 211-226 (1992). In the paper, Purves describes what he found to be the optimal algorithm for estimating AUC and AUMC. This method involves a parabola through the origin for regions of the concentration curve having negative curvature and the standard log trapezoidal method elsewhere.

Finally, in the forthcoming April issue of *J Pharm Sci* is an article by JM Gallo and myself describing our program NCOMP which implements both the Lagrange method and the Purves method for noncompartmental analysis of pharmacokinetic data.

Paul B. Laub

Dept. of Medical Oncology, 364 West Bldg., Fox Chase Cancer Center, 7701 Burholme
Ave. Phila. PA 19111 USA

Bayesian pharmacokinetics

On 21 Jun 1996 at 14:44:24

Can anyone suggest some references which I can read which describe the basic foundational principles underlying bayesian pharmacokinetics? I would especially like a few sources which just go over the basic principles without getting too technical. I've heard that Bayes theorem represents some kind of statistical technique using population parameters or something. I've seen it compared in studies and advertised in pharmacokinetic programs to "traditional" pharmacokinetic techniques but have never had a really good conception of what it represents or how to utilize it. Any help would be greatly appreciated.

Thanks

Randy Kuiper, RPh.

Great Falls, MT

On 21 Jun 1996 at 22:51:48

There are several articles written on Bayesian theory relating to pharmacokinetics.

Sheiner LB, Rosenberg B, Melmon KL. Modelling of individual pharmacokinetics for computer-aided drug dosage. *Computers and biomedical research* 1972; **5**: 441-459. (One of the original articles)

Sheiner LB, Beal SL, Rosenberg B, et al. Forecasting individual pharmacokinetics. *Clinical Pharmacology and Therapeutics* 1979; **26**: 294-305.

Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetics parameters from routine clinical data. *Journal of Pharmacokinetics and Biopharmaceutics* 1977; **5**: 445-79.

Sheiner LB, Beal SL. Bayesian individualization of pharmacokinetics: Simple implementation and comparison with non-bayesian methods. *Journal of Pharmaceutical Sciences* 1982; **71**: 1344-8.

Schumacher GE, Barr JT. Bayesian approaches to pharmacokinetic decision making. *Clinical Pharmacy* 1984; **3**: 525-30. A straightforward simple review.

Vozech S, Steimer JL. Feedback control methods for drug dosage optimisation. Concepts, classification and clinical application. *Clinical Pharmacokinetics* 1985; **10**: 457-476.

I hope these references help.

Michael Burton

On 24 Jun 1996 at 10:39:29

As the matter of fact, there is no Bayesian pharmacokinetics. There is a method of obtaining individual estimates of PK parameters from few measurements (not sufficient to get them in a standard way by fitting a model to these measurements) which is called Bayesian individualization. To apply it, you should know (i) the PK model, (ii) population averages of model parameters, (iii) inter-individual variability in these parameters, and (iv) residual (intra-individual) variability in your measurements not explained by inter-individual differences in PK parameters. Then, you need a nonlinear regression program which minimizes an objective function of special form called Bayesian objective function.

In addition to the references given by Michael Burton I would recommend several more recent publications:

Proost, J.H. Adaptive control of drug dosage regimens using maximum a posteriori probability Bayesian fitting. *Int J Clin Pharm Therapeutics*, 1995, **33**: 531-536.

Wakefield, J. and Racine-Poon, A. An application of Bayesian population pharmacokinetic/pharmacodynamic models to dose recommendation. *Stat Med*. 1995; **14**(9-10):971-986.

Tanigawara, Y.; Yano, I.; Kawakatsu, K.; Nishimura, K.; Yasuhara, M., and Hori, R. Predictive performance of the Bayesian analysis - effects of blood sampling time, population parameters, and pharmacostatistical model. *Journal of Pharmacokinetics and Biopharmaceutics*. 1994; **22**(1):59-71.

El-Desoky, E.; Meinshausen, J.; Buhl, K.; Engel, G.; Haringskaim, A.; Drewelow, B., and Klotz, U. Generation of pharmacokinetic data during routine therapeutic drug monitoring: Bayesian approach vs pharmacokinetic studies. *Ther. Drug. Monit.* 1993; 15(4):281-288.

You can find a lot of references to more specific publications in these papers.

Vladimir Piotrovskij, Ph.D.

Janssen Research Foundation, Clinical Pharmacokinetics, B-2340 Beerse, Belgium

On 25 Jun 1996 at 12:10:48

Perhaps a statement on Bayesian methodology of pharmacokinetic analysis and its cost-utility in a clinical setting would be a useful topic, vis a vis our previous discussions on consensus statements.

Steven Ebert

Body surface area calculation

On 18 Oct 1996 at 13:57:23

I need to convert a human drug dose in mg/(meter squared) to a comparable dose in rats. How does one calculate the surface area of a rat. Is there a formula? In addition, how can the human dose be converted into a rat dose on a mg/kg basis?

Tom Wallace

On 21 Oct 1996 at 09:50:31

I do not know how to calculate the surface area of a rat! but I think you don't need to. I have always used the conversion $1 \text{ mg/kg} = 6 \text{ mg/sq.m}$ for rats. (In mice $1 \text{ mg/kg} = 3 \text{ mg/sq.m}$). Therefore you should be able to work out an appropriate dose if you know the mg/sq.m dose in man.

Hope this is helpful - others may disagree, it will be interesting to see if there any other comments.

Duncan Jodrell

Edinburgh

On 21 Oct 1996 at 09:50:45

It depends upon the rat and the person. The questions you ask are spelled out in:

Freireich EJ et al. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and man. *Cancer Chemo Reports* 1966; **50**:219-244.

Another paper to look for is:

Monro A, and Mordenti J. Expression of exposure in negative carcinogenicity studies: dose/body weight, dose/body surface area or plasma concentrations? *Toxicology Pathology* 1995;23:187-98.

which has a comprehensive table describing physiological differences between rats and humans to guide your allometric conversions.

Joan Korth-Bradley

On 21 Oct 1996 at 09:51:25

A good reference to start with is 'First-time-in-human dose selection: Allometric thoughts and perspectives, by Boxenbaum and Dilea, *J.Clin.Pharmacol.* 35:957-966(1995).

Johan Gabrielsson

On 22 Oct 1996 at 11:08:50

You could use pharmacokinetic-based approach to convert human dose to rat dose using AUC or PBPK methods. These are outlined in a review written by Voisin et al., entitled "Extrapolation of animal toxicity to humans: interspecies comparisons in drug development" that appeared in *Regulatory Toxicology and Pharmacology*. 12(2): 107-116, 1990 (October).

Rajesh Krishna

On 22 Oct 1996 at 11:10:01

Species	Body Wt. (Kg)	Body Surf. Area (m ²)	Km Factor
Mouse	0.2	0.0066	3.0
Rat	0.15	0.025	5.9
Monkey	3.0	0.24	12
Dog	8.0	0.40	20
Human			
Child	20.0	0.80	25
Adult	60.0	1.60	37

Ref: Freireich E.J. et.al. *Cancer Chemother. Reports* 1966, **50**(4) 219-244.

Body Surface area dependent Dose conversion

Rat (150g) to Man (60 Kg) is 1/7 the rat dose

Dog (8Kg) to Human (60 Kg) is 1/2 the dog dose.

Prasad Tata, Ph.D.

Otsuka America Pharmaceuticals Inc.

On 13 Nov 1996 at 11:37:07

Calculation of APPROXIMATE body surface area (BSA) uses simple allometric relationship based on body weight (W):

BSA = W to the 0.67 power.

The Freireich data are reanalyzed (by allometric approach) in "Dosage Regimen Design for Pharmaceutical Studies Conducted in Animals," J. Mordenti, *J. Pharm. Sci.*, **75**:852-57, 1986. A good discussion on allometry and tables of BSA data appear in "Extrapolation of Toxicological and Pharmacological Data from Animals to Humans," W. Chappell & J. Mordenti, *Advances in Drug Research*, Vol. **20**, 1-116, 1991 (published by Academic Press Ltd).

Joyce Mordenti

PS Joan, I was surprised by your plug for the Monro/Mordenti paper. I didn't expect many pharmacokineticists to discover it. Thanks!

On 14 Nov 1996 at 12:11:21

Calculation of APPROXIMATE body surface area (BSA) uses simple allometric relationship based on body weight (W):

BSA = W to the 0.67 power.

But why use BSA in preference to more empirically sound allometric models?

The only thing going for BSA is tradition. The usual Du Bois & Du Bois model for BSA is based on 10 individuals. An allometric exponent of 3/4 instead of 2/3 is based on a multitude of observations across several orders of magnitude of weight and varieties of animals.

See:

Peters RH. **The ecological implications of body size**. Cambridge: Cambridge University Press, 1983

This is THE reference work for a wider view of allometrics.

Holford NHG A Size Standard for Pharmacokinetics *Clin. Pharmacokin.* 1996;**30**:329-332

Compares common size models for clearance and shows the potential weakness especially at low body weights e.g. children in comparison to the 3/4 exponent model.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

Body weight

On 16 Feb 1996 at 10:01:58

Does anyone know if we can use the formula: $ClCr = (140 - \text{age}) * \text{weight} / 70$ or 85 for female to estimate body weight of a patient ?

Because I know the daily creatinine clearance and I know the age. So it could may be possible to estimate body weight. But this formula has may be some restrictions ? (severity of the renal function) My patients are staying in intensive care unit and it's not possible to weigh these patients.

The estimation by staff was not practicable.

Nicolas Van Brandt

Pharmacist, Lab. of Pharmacokinetics (Prof R.K. Verbeeck), University of Louvain, Av E. Mounier, 73-55, 1200 Brussels, Belgium

On 16 Feb 1996 at 10:01:59

$CLCr = [(140 - \text{age}) * (\text{body mass})] / [SrCr * 72]$

Multiply by 0.85 for females. This nomogram has a high correlation among the variables, so solving for body mass would give a good estimate. One would still have to consider the body *type*, ie, is the patient obese (larger proportion of fat) or particularly lean (larger proportion of muscle).

After estimating the mass, it would be a good idea to calculate lean body mass, which would require knowing the height (or length, in this case) of the patient, because one of the factors determining the rate of creatinine production is muscle mass--of two people weighing the same, the one with a larger proportion of skeletal muscle would produce more creatinine.

Randy Trinkle

Dept. of Pharmacy, Dawson Creek & District Hospital, Dawson Creek, BC, Canada

On 19 Feb 1996 at 10:23:13

It is certainly possible to obtain an ESTIMATE of weight (actually, something closer to ideal weight). Remember, however, that the coefficient of determination (R^2) for this relationship is not more than about 0.7 and there will be fairly large error in the estimate. To the best of my knowledge your question has not been answered experimentally. Good luck!!

Michael Mayersohn

College of Pharmacy, University of Arizona, Tucson, Arizona 85721

On 19 Feb 1996 at 10:23:16

I would think that formula relates to a normal population with normal renal function. I would be very cautious about using it to estimate the weight of patients in intensive care, many of whom have grossly impaired renal function. If you think about anuria as being one extreme (a regular situation in intensive care) the answer to the formula is a nonsense and a patient who was almost anuric would weigh almost nothing. I think you should look at some alternative ways to estimate weight.

Ken Newton.

On 19 Feb 1996 at 10:23:18

I am a Pharm D. student from Idaho State University. Recently I completed a class on clinical research and design. This class included lots of statistics and mathematical models. One thing the professor pounded into our heads is that when doing a linear regression, such as estimating CrCl from weight and serum creatine, or estimating kel for aminoglycosides from CrCl, YOU CANNOT GO BACKWARDS. Estimating CrCl from predictor variables like weight and serum creatinine is good, but what are good predictor variables for weight? Is the patient hypermetabolic, receiving adequate nutrition, third spacing, receiving adequate hydration. There are a lot of variables that go into why a patient's weight may fluctuate, not just CrCl.

I work at a 250 bed tertiary care facility with about 35 ICU beds. I am not sure what your facilities' resources are, but our beds are capable of weighing the contents of the bed. thus the patient. Each day the nurse pushes a button and the bed tells him/her the patients weight. I am sure there is more to it than that, but it is a very good way to monitor a patients weight.

SD Beyer

On 19 Feb 1996 at 10:23:22

I guess the estimations by staff would be not less accurate than those obtained via the formula.

Vladimir Piotrovskij

On 19 Feb 1996 at 10:23:24

I would be hesitant to use such an estimator to go back to establishing weight. It might be acceptable to establish a guess to correlate with guesses of the staff. The degree of variability might be as high as you could get from having two or three staff make an educated guess. Good luck.

John E. Murphy, Pharm.D.

Professor and Head, Department of Pharmacy Practice and Science

On 20 Feb 1996 at 10:46:51

A useful starting point to estimate the weight of non-ambulant patients may be the following paper

Atiea JA, Haboubi NY, Hudson PR, Sastry BD. 1994 Body weight estimation of elderly patients by nomogram. *Journal of the American Geriatrics Society*, **42**, 763-765.

Roger Rumble, PhD

Tasmanian School of Pharmacy, University of Tasmania, GPO Box 252C, Hobart, Tasmania, 7001 AUSTRALIA

Chiou Method

On 19 Nov 1996 at 17:08:49

I do grading for a pharmacokinetics course. One of our students has asked me about the Chiou (not sure of the spelling here) relationship used for determining clearance of dig and procainamide. They'd like to know if there's a paper or book out there that discusses proper usage of this equation. I've looked through all my resources and come up empty.

Any input from you folks would be greatly appreciated.

Catherine Heyneman, Pharm.D., ISU College of Pharmacy, Pocatello, ID 83209

On 20 Nov 1996 at 15:59:29

I think the reference you are seeking is: Chiou, W. L., Gadalla, M. A., and Peng, G. W. (1978). Method for the rapid estimation of the total body drug clearance and adjustment of dosage regimens in patients during a constant-rate intravenous infusion. *Journal of Pharmacokinetics and Biopharmaceutics*, **6**(2), 135-151.

Varun Garg

Otsuka America Pharmaceutical, Inc.

On 25 Nov 1996 at 10:09:09

The reference for the Chiou paper is:

Chiou, W. L., Gadalla, M. A., & Peng, G. W. (1978). Method for the rapid estimation of the total body drug clearance and adjustment of dosage regimens in patients during a constant-rate intravenous infusion. *Journal of Pharmacokinetics and Biopharmaceutics*, **6**(2), 135-151.

This method can be used for any drug that is given by continuous infusion. All that is needed to derive a clearance value is the rate of infusion, a population volume of distribu-

tion (L/kg*whichever weight is appropriate for the drug (IBW, DW, TBW)), and two serum concentrations drawn after the beginning of the continuous infusion preferably 1-2 half-lives apart, and the time difference between those concentrations.

The equation is:

$$CL = \frac{2Ro}{C_1 + C_2} + \frac{2Vd * (C_1 - C_2)}{(C_1 + C_2) * (t_2 - t_1)}$$

Where Ro = infusion rate in mg/h

Vd = population Volume of distribution in L

C₁ = first serum concentration drawn after beginning infusion

C₂ = second serum concentration drawn after beginning infusion

t₁ = time of C₁

t₂ = time of C₂

Although this equation is commonly used with theophylline, it can be used with intravenous procainamide. I don't believe it has an application with digoxin since it is administered either orally or IV push.

Michael Burton

Consensus documents

On 12 Jun 1996 at 11:16:09

Most of the messages and discussions going on in the list are interesting, although somewhat unconnected. Probably, this is the intention of a list on

the Internet. However, to show ourselves and others ('our skeptical colleagues') that the lists on the Internet are a useful and efficient tool for the progress of health care sciences, I suggest that we prepare 'Consensus Statements' on topics related to our list. We all have sound scientific knowledge and/or clinical experience in the field of pharmacokinetics to be able to prepare valuable documents for the benefit of our colleagues and the care of our patients.

Possible schedule:

1. A member of the list suggests a topic and a co-ordinator (himself?).
2. The co-ordinator prepares a basic document.
3. The basic document is sent through the list to all members (as an attachment).
4. For a given term (2 weeks?), those who wish to participate and contribute to the Consensus Statement should send their comments and amendments to the co-ordinator.
5. The co-ordinator produces a second document.
6. The second document is e-mailed to those who have significantly contributed to it for final consideration.
7. For a short term (1 week?), last comments and amendments may be sent to the co-ordinator.
8. The co-ordinator prepares a final document and sends it for publication to an adequate journal.

An example: Consensus statement on once-daily dosing of aminoglycoside antibiotics by the Internet PharmPK list contributors: A, B, C, ... X

Will we not be able to do it?

Cris Ronchera-Oms

Hospital Pharmacist, Valencia, Spain

On 13 Jun 1996 at 11:17:07

However, to show ourselves and others ('our skeptical colleagues') that the lists on the Internet are a useful and efficient tool for the progress of health care sciences,

I don't think this should be the primary reason i.e. to convince the sceptics. A better reason would be because we wish to advance our science by collaborating to produce a review document. I certainly support the concept. It does not have to be a consensus view. If there is controversy then this should be reviewed as well. I would also like to suggest that consideration is given to creating an HTML version of the document at an early stage.

8. The co-ordinator prepares a final document and sends it for publication to an adequate journal.

As Consulting Editor for 'Clinical Pharmacokinetics' I would be delighted to consider such a document for publication.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 13 Jun 1996 at 11:17:08

Cristanto!

Your idea concerning consensus documents is very good. I will no doubt add some element of organization to the group. It will, however, require some fine tuning before a "con-

sensus" is reached on the final format. I have a topic or two that I would be very interested in getting everybody's opinion about.

However, this new "activity" should not replace the current free-flow format because it has its advantages despite the apparent incoherence at times. I find your suggestion worthy of support and discussion.

N. Anaizi, PhD RPh

Univ. of Rochester Medical Center

On 13 Jun 1996 at 11:17:09

With all due respect, I VOTE NO to this suggestion. It is too structured and artificial and academic. It will result in a weekly pontificator and/or a myopic dialogia.

On 13 Jun 1996 at 15:45:24

Dear Chris,

Sounds like a good idea. The only problem I have is that I have to make time at the end of my day to read the mail I currently receive (5 lists). I would be interested in reading the kinetics material but am not sure how much time I could devote to contributing to the discussion, if indeed my contribution would be of merit. In any case, if there a sufficient number of pharmacist out there willing to help out, you can count me in. We will depend on your leadership or possibly the leadership of our fearless coordinator of this list for this project.

Robert Aucoin RPh

Peds Clincial Pharmacist, BRLA OLOLRMC

On 19 Jun 1996 at 13:33:42

Dear Colleagues,

I have received significant feed-back on the initial proposal to prepare consensus/review documents through the PharmPK list. Although one clearly negative opinion has been expressed, the proposal has received a warm acceptance (9 messages). Furthermore, Dr. David Bourne (co-ordinator of the PharmPK list) has also expressed a positive view. After gathering all the information, it seems possible to conduct this new activity through our list. It should not interfere much with the normal free-flow in the list, since only the initial/ intermediate/final documents will be circulated to all members, but not the amendments and comments, which must be e-mailed directly to the co-ordinator designated for each individual document. Consequently, much of the traffic will be off the list, and the group will be kept up-to-date and able to contribute.

Main objective: To prepare consensus/review documents on selected pharmacokinetic topics for the advance of scientific knowledge and health care. (Please note that these documents have not a predetermined format nor length).

Secondary objectives:

1. to activate and to promote the PharmPK list.
2. to show that lists on the Internet are a valuable and efficient tool for the advance of health care sciences.

Participants: members of the PharmPK list.

Sources: bibliographic material, own research and/or clinical experience.

Possible schedule (although it will probably be more flexible):

1. A member of the list identifies a topic worthy of review and/or consensus, suggests the topic and a co-ordinator.
2. The co-ordinator prepares a basic document.
3. The basic document is posted through the list to all members.
4. For a given term, those willing to participate and contribute to document should post their comments and amendments directly (e-mail) to the co-ordinator.

-
5. The co-ordinator produces a new document.
 6. These new document/s is/are again circulated through the list for re-consideration.
 7. Finally and for a short term, last amendments and comments may be posted (e-mail) to the co-ordinator.
 8. The co-ordinator prepares a final document and sends it for publication to an adequate journal. An WWW version will also be produced.

CALL FOR PROPOSALS: * topic (title): * co-ordinator (name and e-mail address): * term to have the basic document ready (date):

Cris Ronchera-Oms, Valencia, Spain.

On 27 Jun 1996 at 11:33:26

Dear Colleagues,

Four different issues have already been identified and proposed on which useful consensus/review documents could be prepared. These are:

1. Utility of monitoring vancomycin serum concentrations.
2. Continuous infusion of beta-lactam antibiotics.
3. Once-daily dosing of aminoglycoside antibiotics.
4. Cost-utility of bayesian methodology of pharmacokinetic analysis in the clinical setting.

This message is a call for individuals willing to act as co-ordinators for any of these topics (or others that they may propose).

Cris Ronchera-Oms, Valencia, Spain.

On 9 Jul 1996 at 09:29:31

Dear Colleagues,

These are the topics on which consensus documents will be prepared and the coordinators appointed for each topic:

1. Utility of monitoring vancomycin serum concentrations, Dr. Douglas C. Anderson, Department of Clinical Pharmacy Practice, University of Mississippi School of Pharmacy
2. Continuous infusion of beta-lactam antibiotics, Dr. Les White and Dr. Alasdair MacGowan, Department of Microbiology, Southmead Health Services NHS Trust, Bristol, UK
3. Once-daily dosing of aminoglycoside antibiotics, Dr. N. Anaizi, University of Rochester Medical Center

We would like to encourage you to e-mail any information (text, comments, references) that you may consider of value directly to the coordinator (not through the list).

For each topic, the coordinator will prepare a basic document to be posted to and reviewed by all members of the PharmPK list.

Cris Ronchera-Oms, Valencia, Spain.

On 9 Jul 1996 at 09:29:35

Dear Colleague,

We have recently introduce a new discussion format aimed at integrating the varied opinions of the participants concerning a given topic into a "consensus document", which may be published for the benefit of professionals, educators, and students.

The first topic has been chosen; it is the "once-daily dosing" of aminoglycosides, and I have been asked to be the coordinator of the discussion. To launch the discussion, the coordinator first prepares and posts a initial document to be thoroughly dissected and discussed by you to help the coordinator prepare the final consensus document for publication.

However, before I prepare the initial document, I would like us to better define our primary objectives, i.e., the main issues that should be emphasized. The reason is simple - we would like to bring the relevant issues into focus and contribute new and useful insights; I do not think that we should aim to write another review article. During the last five years, over a hundred articles addressed directly or indirectly this topic. These included reports on original randomized clinical trials, in vitro studies, animal studies, accounts of clinical experience, meta-analyses, review articles, book chapters, and newsletters. Here are a few good reviews:

1- Barclay ML, Begg EJ, Hinckling KG. 1994 What is the evidence for once daily aminoglycoside therapy? *Clin Pharmacokinetics* **27**, 32-48

2- Gilbert DN. Aminoglycosides. In Mandel GL, Bennett JE, Dolin R. **Principles and Practice of Infectious Diseases**. 4th ed. 1995 Churchill Livingstone, NY.

3- Preston SL, Briceland LL. 1995 Single Daily Dosing of Aminoglycosides. *Pharmacotherapy*, **15** 297-316.

The "once-daily" or "single-daily" or "pulse" dosing of aminoglycosides was first used by Labovitz in 1974 and rediscovered in the late 1980s. It gained popularity worldwide year after year. A survey conducted in the USA in 1994 by Schumock and co-workers (*Pharmacotherapy* 1995, **15** 201-209) estimated that in the USA over 25% of hospitals of 400 beds or larger used the qd dosing routinely. Currently many centers are adopting to the "once-daily aminoglycosides" as their standard practice. However, we have no solid, updated information concerning:

1. the relative number of institutions/ hospitals that have adopted this dosing method as their standard (preferred) method. In the USA, the adoption process usually involves the "Pharmacy and Therapeutics" committee. 2. the "official" guidelines for its use (dose, conditions excluded, monitoring criteria, etc.).

I believe that we should first make a good effort to gather this type of information. Our group (PharmPK) and our medium (the InterNet) are best suited for this task. So please check the hospitals in your town and forward the above information to me along with a very brief description of each hospital (size, type of care, etc).

In addition, please let me know what you think should be the main focus of our consensus document.

N. Anaizi

University of Rochester Medical Center

On 10 Jul 1996 at 11:17:22

The important questions which need to be answered are:

CAN once-daily dosing of aminoglycosides be done successfully?

SHOULD once-daily dosing of aminoglycosides be done?

How often will deviation from the methods (i.e., patients selected, duration of therapy, etc.) described in the primary literature be necessary when this method is adopted in a given institution?

What role does serum concentration monitoring play? What, if any, serum concentrations should be obtained? What are "therapeutic" concentrations?

In patients with reduced CrCl, should the daily dose be reduced, or the interval lengthened?

Should patients with infections of different severity ("mild", "moderate", "severe") receive different maximal daily doses?

Steve Ebert

On 11 Jul 1996 at 09:36:11

The important questions which need to be answered are:

CAN once-daily dosing of aminoglycosides be done successfully?

SHOULD once-daily dosing of aminoglycosides be done?

Some observations, perhaps an answer in the bunch... Once daily aminoglycoside dosing is currently being done successfully at several institutions in our state. The starting dose is 5mg/kg q24h. A trough is drawn 2 to 3 hours before the next dose. This gives time to the

attending MD or clinical pharmacist to access the timing of the next dose. Peaks are drawn 12 to 14 hours after the dose (mid-point).

Different bugs require different peaks to do the job. The literature is plentiful of high peaks (10-12) getting maximum penetration and the low troughs (0-.2) giving the bugs a false sense of security and dropping their guard. That's the easiest way to put it.

We don't do this in pediatrics. Docs won't hear of it and I agree. I have a hard time convincing them to give 2.5mg/kg as a loading dose. Also with kids who have a CrCl of >130ml/min we would have to give 7 to 9 mg/kg for the effect to even last 24 hours. A second hard sell. Not one I'm willing to engage in.

There is plenty of literature out there. Most of it was reviewed here and on the PharmPK list and a couple on the Hospital US list in the past six months.

ODAD is an idea that will either sell in your hospital now or sell later. Either way we still have to monitor to stop them from cooking kidneys.

Robert Aucoin RPh

Peds Clinical Pharmacist, OLOLRMC Baton Rouge, LA

Creatinine Clearance Calculation - Age

On 6 Feb 1996 at 12:55:47

I am trying to determine the effects of age and renal function on the clearance of a drug. The Jelliffe and Cockcroft and Gault methods to determine creatinine clearance from serum creatinine concentrations include the patients age in the calculations. The inclusion of age in the creatinine clearance calculation may be confounding the determination of the effects of age and renal function on drug clearance. Are there any other accurate methods for calculating creatinine clearance from serum creatinine concentrations that do not include subject age in the equations?

Ben Suttle

Zeneca Pharmaceuticals

On 7 Feb 1996 at 10:04:10

Because of the age related decline in renal function, I think that it will be difficult to separate the determination of renal function from a serum creatinine value in a predictive algorithm without considering age. I would suggest that 8 or 24 hour urine collections be performed in an experimental situation to separate the effects of age from renal function. Although the current gold standard is probably non-radioactive iothalamate clearance using a continuous infusion with three timed urine collections and mid-point serum concentrations over 3 hours.

Michael Burton

On 8 Feb 1996 at 12:26:09

Creatinine clearance estimates are based on the input/output principle. The role of age, weight, etc. in the equations are simply estimates of the rate of endogenous production of

creatinine which is the rate in (input). The rate out (output) is the creatinine clearance, and the ratio of the two is equal to the serum creatinine.

Creatinine production is known to decrease with age. If you leave it out of the estimation formula, you are neglecting a known variable. Why not measure drug clearance or elimination directly? I have published a couple of papers in which we measured drug clearance directly using limited sampling.

Art Harralson, Pharm.D., BCPS

Professor and Vice-Chairman, University of the Pacific, School of Pharmacy

On 8 Feb 1996 at 12:26:10

To Ben Suttle, Zeneca Pharmaceuticals:

I assume your drug of interest is >50% renally cleared, otherwise what follows is not very relevant. I don't think you can get around this problem easily since age is one of the major determinants of declining CrCL after the age of 25 or so. Furthermore (as you probably know) serum Cr levels can be notoriously misleading in estimating CrCL in elderly patients, in nutritional deficiency or metabolic disorders when decreased Cr production by muscle tissue can mask diminishing renal function. Therefore, why not be done with it and do a 24 hr urine collection, a 12 hr serum level and assay both for creatinine to directly estimate the "true" CrCL? Alternatively, some other direct way to estimate GFR would be OK, e.g. as suggested in the reply from Michael Burton.

Bruce Charles, PhD

Pharmacy Dept, Univ. Queensland, Brisbane, Australia

Creatinine Clearance Calculation - Weight, Age, Serum Creatinine

On 5 Dec 1996 at 10:32:43

I have a few questions about calculating CrCl that I hope someone can help me with. Currently my hospital has started a policy of monitoring CrCl by pharmacy, a good idea, but the problem is we cannot all agree on the 'correct' formula to use. Most of us use ideal body weight in the formula $[(140 - \text{age}) * \text{IBW}] / 72 * \text{SCr}$ (*0.85 for female).

1. Some have used dosing weight in place of IBW in pt's greater than 20% above IBW. Is this justified?
2. Some have suggested normalizing for BSA. Has this been shown to be more/less accurate?
3. Some have rounded SCr up to 1 for pt's older than 65. Is this appropriate?

We would like to standardize on one way of calculating CrCl so as not have conflicting recommendations, as have already happened. Thanks in advance for any information.

Chris Humble

Albert Einstein Med Ctr

On 6 Dec 1996 at 10:31:06

IBW. Is this justified?

Not really ! The so-called dosing weight is good for dosing aminoglycosides and similarly distributed drugs. In the case of creatinine clearance, you need Lean or Ideal Bdy Mass

(LBM or IBM) because it provides a more "accurate" parameter of muscle mass, and hence of the rate of creatinine production. However, for practical purposes whether you use LBM or DW what you get is still a ROUGH estimate of GFR, and hence of renal func-

tion. This "ROUGH ESTIMATE" is however still very useful for the purpose of dose adjustments.

2. Some have suggested normalizing for BSA. Has this been shown to be >more/less accurate?

Normalizing for BSA is great for comparison purposes, and for drawing general guidelines and nomograms. Drug elimination is effected by the actual (non-normalized) glomerular filtration rate and/or tubular secretion rate. For your purposes (and ours) normalizing is unnecessary.

3. Some have rounded SCr up to 1 for pt's older than 65. Is this appropriate?

I have seen arguments for it and against it. I happen to use this shortcut routinely for elderly female pts to get a "quick & dirty" estimate as opposed to a rough estimate of CLcr. The more important issue is how to estimate CLcr in elderly pts with low muscle mass (e.g., muscle atrophy or emaciated pts). In this case rounding to one is not enough. Estimating creatinine clearance in these pts has always been problematic. In these patients the serum creatinine is often deceptively low or "normal", and the Cockcroft equation (Nephron '76; 16: 31-41) yields inaccurate estimates of renal function. However, recently SANAKA and his co-workers (Nephron 1996; 73: 137-144) developed an equation that gives CLcr values that are close to those obtained by direct measurement of creatinine clearance using 24-hr urine collections.

For males: $CLcr = \frac{BW (19 Alb + 32)}{100 Scr}$ For females: $CLcr = \frac{BW (13 Alb + 29)}{100 Scr}$

Where: BW = actual body weight in kgs; Alb = serum albumin in grams / dL; and Scr = serum creatinine in mg/dL.

In conclusion, while it is good to try to obtain as accurate an estimate of CLcr as possible, the important issue is what to do with it once you get it. Let this be our thread for future discussions on this topic....

N. Anaizi, PhD RPh

Univ. of Rochester Med Center

On 6 Dec 1996 at 10:33:16

The Cockcroft & Gault formula quoted for estimating CrCl can and does require actual body weight. Ideal body weight may be OK in normal circumstances but in overweight persons this may be misleading. there is no harm in normalizing to BSA (1.73 sq m). I know that in diabetics the CrCl using this formula (using actual weight) has been tested by comparing it with radio-isotopic method with very good agreement (Sampson & Drury, 1992, Diabetes vol 15 p609-). In my experience this formula also gives correct estimates of CrCl in HIV subjects when using actual weight when compared to actual renal clearances of creatinine. You may find that renal clearance of creatinine overestimates true GFR by some 15-20% in healthy subjects and in HIV (Noormohamed et al. Br J Clin Pharmacol, (1997) vol 47 (in press). My limited experience with patients with a single kidney also shows that the formula can be used confidently and compares well with true GFR measured using ⁵¹Chrome-EDTA.

By the way the formula works just as well when using serum creatinine expressed in micromol/l. In such cases the formula is $(140 - \text{age}[y]) \times \text{body weight [kg]} \times K / \text{serum creatinine [micromol/l]}$ where $K = 1.23$ for male and 1.05 for female subjects.. Hope this is useful.

Faruq H Noormohamed

Department of Therapeutics, Chelsea and Westminster Hospital, 369 Fulham Road LONDON SW10 9NH

On 6 Dec 1996 at 10:33:33

There is a good discussion of creatinine clearance formulae in DiPiro's Pharmacotherapy. The discussion states that the Cockcroft-Gault equation was originally done with ABW not IBW or DBW.

See also Murphy JE, ed. Clinical Pharmacokinetics (pocket reference). ASHP, 1993, pages xxxv-xxxvii. These latter two references caution on STABLE vs CHANGING renal function, as well.

Also: Davis GA, Chandler MH. Comparison of creatinine clearance estimation methods in patients with trauma. American journal of health-system pharmacy 1996 May 1; 53(9):1028-32. This article helps point out some issues with adjustments, etc., also.

We have a similar problem here. Our decision (for purposes of a standardized and consistent way to REPORT an estimate of the patient's CrCl) was to use the Jelliffe formula ($114 - 0.8(\text{Age})/\text{SCr}$, females 85% of this). This is reported out in our institutions lab results (it is automatically calculated every time a SCr is done on a patient). It bypasses the need for weight (retrieving a height and weight on a patient is not always possible or done!), and has a disclaimer stating that the estimate is about 9% greater than actual.

Our Pharmacy order-entry computer (Cerner) automatically calculates using C-G (based on IBW) when we enter height and weight. The bottom line is for a screening process: which patients have bad renal function.

My personal approach is to look at the screening data (or just the patients age) and determine where to go next. I try and look at many factors, most specifically age, nutritional status (+ or -), and concurrent disease states. I try to find the factors about the patient that will affect how I look at their SCr, usually those that I feel who's SCr will NOT reflect their true renal function (i.e., malnourished patients, patients with liver disease, etc.) This latter aspect addresses the "rounding up" issue you mentioned. I do not do it, and I believe my colleagues do not either. (There was a recent article that addresses this within the past few years that escapes me at this writing, sorry!) I personally use C-G when I know the RF is stable, and then judge where I feel the patient will trend toward during my monitoring processes.

Bottom line: use whatever formula to screen and/or initial CrCl estimate, then use your clinical judgement and experience and talking with colleagues when faced with difficult (presumed or real) patients.

Marc Semprebon, RPh, MSLS

Dartmouth-Hitchcock Medical Center, Lebanon, NH

On 6 Dec 1996 at 10:36:00

I mis-represented information in my previous note regarding the Jelliffe formula and our reporting of CrCl. Our comments about the estimated clearance is "As a group, this estimate appears to be about 9 ml/min (not %) less than actual measured clearance. However, in an individual patient, the estimate is within +/- 20 ml/min 2/3rds of the time, when compared to actual measured value."

Marc Semperebon, RPh, MSLS

Dartmouth-Hitchcock Medical Center, Lebanon, NH

On 9 Dec 1996 at 16:30:20

IBW. Is this justified?

If you consider the fact that creatinine is produced in the muscle tissues, rather than adipose tissues, then the use of anything but IBW is not justified.

2. Some have suggested normalizing for BSA. Has this been shown to be more/less accurate?

In general, CrCl is not an accurate nor precise measure of renal function, but it is the easiest method we have available in clinical practice. Nonetheless, normalizing CrCl values for a BSA of 1.73 m² (roughly 70 kg) allows a fair comparison between individuals of different body habitus. I am assuming that pharmacy is in charge of calculating CrCl primarily for the purpose of dosing renally excreted/metabolized drugs. In that regard, one has to be careful in basing the dosing regimen on normalized CrCl, since the original PK study for a specific drug may not have normalized subject's CrCl (many do, however).

3. Some have rounded SCr up to 1 for pt's older than 65. Is this appropriate?

This does not seem appropriate since I can't figure out why a value of 1 is chosen. I am assuming it is because it is a round number. In such patients, a 24-hour collection is necessary.

Arasb Ateshkadi, Pharm.D.

Assistant Professor, Department of Pharmacy Practice, College of Pharmacy University of Utah, 258 Skaggs Hall, Salt Lake City, UT 84112

On 10 Dec 1996 at 10:59:18

If you consider the fact that creatinine is produced in the muscle tissues, rather than adipose tissues, then the use of anything but IBW is not justified.

Your statement about IBW is a bit too strong. The idea is to predict creatinine production rate and in part this can be done using a measure of body size to predict muscle mass. IBW is computed from gender and height. Total body weight in a person of "normal" body composition has been the basis for the standard CPR formulae and for this empirical reason it should be preferred over IBW. In people with abnormal composition especially obesity then IBW may be better than TBW when there is an excess of muscle free mass aka fat. I am not aware of any reported study that has examined IBW as a predictor of CPR. Does anyone know of one?

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 11 Dec 1996 at 12:34:14

If you consider the fact that creatinine is produced in the muscle tissues, rather than adipose tissues, then the use of anything but IBW is not justified.

Your statement about IBW is a bit too strong. I am not aware of any reported study that has examined IBW as a predictor of CPR. Does anyone know of one?

Those interested in a study of creatinine clearance estimators and the IBW v. TBW question may be interested in the following paper:

Hallynck T, Soep HH, Thomis J, Boelaert J, Daneels R, Fillastre JP, De Rosa F, Rubinstein E, Hatala M, Spousta J and Dettli L, Prediction of creatinine clearance from serum creatinine concentration based on lean body mass. *Clinical Pharmacology & Therapeutics* 30(3): 414-21, 1981.

Joseph Balthasar, PhD

SUNY at Buffalo, Pharmaceutics

On 12 Dec 1996 at 10:27:23

Your statement about IBW is a bit too strong. I am not aware of any reported study that has examined IBW as a predictor of CPR. Does anyone know of one?

Those interested in a study of creatinine clearance estimators and the IBW v. TBW question may be interested in the following paper: Hallynck T, Soep HH, Thomis J, Boelaert J, Daneels R, Fillastre JP, De Rosa F, Rubinstein E, Hatala M, Spousta J and Dettli L, Prediction of creatinine clearance from serum creatinine concentration based on lean body mass. *Clinical Pharmacology & Therapeutics* 30(3): 414-21, 1981.

Thanks for pointing out this interesting study of Lean Body Mass as a predictor of CPR. Note however that LBM is NOT the same as **IBW**. **LBM** (as described by Hallynck et al.) is based on the skinfold thickness (at subscapular and biceps sites) and total body weight. IBW on the other hand uses gender and height i.e. very different body properties.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

CVVH (Continuous Venovenus Hemofiltration)

CVVH

On 19 Mar 1996 at 09:32:05

Our PICU docs are about to start using **CVVH** (Continuous Venovenus Hemofiltration) in the unit. Our Pediatric Clinical staff consist of me and 1 part-time staff RPh. I have only seen the procedure once in a hospital 400+ miles away. Now the questions. 1) How many of you out there are familiar with CVVH in your present or immediate past institution? 2) How much is the pharmacist involved in the set-up and monitoring of CVVH? Our docs expect me and our "team" to monitor all drug levels and adjust doses as needed once CVVH is turned on. 3) Is there any literature out there concerning drug clearance in CVVH that is not covered by dialysis? Any additional advice/warning would be appreciated.

Robert Aucoin

Baton Rouge, La.

On 22 Mar 1996 at 11:32:38

There are several forms of this dialysis procedure. CVVH, CVVHD, CAVH, CAVHD. We have used CVVH, CVVHD most recently at our institution. The sieving coefficient can depend on the filter used. In general I will follow the start time, blood flow, dialysis filtration rate and ultrafiltration rate, and daily fluid removed. Depending on the patient's problems, empiric dosing is done on the limited available literature for CVVH or CAVH sieving coefficients. Most of the children requiring CVVHD would be individually unique, making it even more of a challenge. For those agents that drug levels are available, I will calculate a clearance rate during the CVVH and adjust accordingly with changes in the dialysis. For severe infections, aminoglycoside levels are kept between 3-7mg/l, and vancomycin above

10-15mg/l (depending on assay error secondary to CDP-I). Some references to help get you started are:

1. Bressole F et al. Clinical Pharmacokinetics During Continuous Haemofiltration. *Clin Pharmacokinet* 1994; **26** (6):457-471
2. Armstrong DK et al. Vancomycin and Tobramycin clearance in a n infant during continuous hemofiltration. *Annals of Pharmacotherapy* 1993; **27**:224-227
3. Thomson AH et al. Gentamicin and Vancomycin removal by continuous venovenous hemofiltration. *Annals of Pharmacotherapy* 1991; **25**:127-129.

Willaim Dager, Pharm.D.,FCSHP

Coordinator, Pharmacokinetic Consult Service, UC Davis Medical Center

On 25 Mar 1996 at 09:44:43

Thank you for the info. I'm putting together a packet of info on CVVH that has been sent to me from around the country. If I can help you with anything, give me a shout.

Robert Aucoin

On 25 Mar 1996 at 09:44:45

I would add:

Reetze-Boroden P, Bohler J, Keller E. Drug dosage in patients during continuous renal replacement therapy. *Clin Pharmacokin* 1993; **24**:367-379.

This article contains a lengthy table of suggestions for dosage adjustments, depending on the type of continuous therapy that is being used, and organizes the information by drug class.

Randy Trinkle, BScPharm, BA

Dept. of Pharmacy, Dawson Creek & District Hospital, Dawson Creek, BC

Debates in Pharmacokinetics

On 10 May 1996 at 10:15:32

As part of my advanced pharmacokinetics course for students here I require a formal debate of PK "controversies." The purpose is not to win or lose (though that tends to become part of it) but rather to examine papers carefully and come up with reasoned responses to the questions. Below are some of the topics used each year. My request is for IDEAS ON OTHER TOPICS that I might use. Any suggestions will be appreciated.

DEBATE TOPICS

1. Pharmacokinetic monitoring services are cost-effective!
2. Theophylline concentrations are useful predictors of effectiveness and safety!
3. Interpretation of phenytoin concentrations should be based on measurement of unbound drug!
4. Ideal body weight should be used to predict creatinine clearance from serum creatinine!
5. Large dose, extended interval (sometimes called "once-daily") dosing of aminoglycosides is better than traditional dosing!
6. All patients receiving gentamicin should have troughs less than 2 mg/L to prevent toxicity!
7. Peak concentrations of aminoglycosides are valuable predictors of efficacy!
8. Measuring concentrations of tricyclic antidepressants is necessary to ensure safe and effective therapy!
9. Vancomycin dosing and pharmacokinetic evaluation should be based on a one-compartment model (rather than two compartment)!
10. There is no need to measure vancomycin concentrations!

-
11. All patients receiving aminoglycosides for more than two days should have concentrations measured!
 12. Measuring digoxin concentrations is a waste of time and money!
 13. Bayesian analysis improves therapeutic drug monitoring!
 14. Neonates do not get toxic on aminoglycosides!
 15. Estimates of creatinine clearance from serum creatinine and patient factors is as accurate as measuring creatinine clearance with urine collection!
 16. Laboratory assays of drug concentrations are very accurate and can be trusted!
 17. The therapeutic range for procainamide is well established and well documented!
 18. Aminoglycoside "peak" concentrations should be drawn one-half hour after the end of a dose infusion and "trough" concentrations should be drawn one-half hour before the next dose!
 19. A panel (three or more) of aminoglycoside concentrations is more accurate than only measuring a peak/trough! (See Zaske et al.)
 20. Pharmacokinetic monitoring of phenytoin is unnecessary - "seat of the pants" dosing is just as effective!
 21. When monitoring lithium concentrations, the blood for measurement should always be taken approximately 12 hours after a dose!
 22. Therapeutic drug monitoring is underutilized for many drugs!
 23. Measuring saliva concentrations of drugs offers a reliable approach to therapeutic monitoring!
 24. Accurate phenytoin dosing requires measurement of two steady-state concentrations!
 25. Phenytoin dosing should be based on ideal body weight!
 26. Aminoglycoside dosing should be based on ideal body weight!
 27. Carbamazepine concentrations are useful predictors of effectiveness and safety!

John E. Murphy, Pharm.D.

Professor and Head, Department of Pharmacy Practice and Science

On 12 May 1996 at 14:10:11

John:

Let me throw in a suggestion for controversy subjects that will really get the discussion going:

Measurements of drugs in blood only provides data on what happens in the blood. Noninvasive methods are required to measure the time course of drugs at organ and tissue sites.

Professor Walter Wolf, Ph.D.

Director, Pharmacokinetic Imaging Program, Department of Pharmaceutical Sciences, University of Southern California, 1985 Zonal Ave., Los Angeles, CA 90033

On 13 May 1996 at 17:31:48

Are there any FDAers out there or experienced individuals running these types of trials?

If so, I need your opinion.

Is it necessary to analyze placebo samples in open-labeled or blinded studies for all phases of drug development? If so, would it be acceptable to analyze a fraction of them at random?

Prasad Tata

On 16 May 1996 at 21:57:50

How about debating the pros and cons of detailed multi-compartmental modeling of pharmacokinetic data as contrasted with classical PKPD modeling?

Another good one might be: Linear models are perfectly adequate for description of pharmacokinetics, and nonlinear models are always a

solution in search of a problem.

Bob Phair.

On 19 May 1996 at 21:11:24

How about :

Most kinetic Drug interactions are of theoretical rather than practical importance

Noel E Cranswick

Drug interaction study to role of Cytochrome P-450 2D6

On 18 Dec 1996 at 11:00:43

We all know for studying cytochrome P-450 2D6 role in drug metabolism it is customary to study Drug-Quinidine interaction. Due to fluorescent interference of quinidine with the study drug, I am considering to use Ajmalicine (reported $K_i = 0.014$) or prodipine ($K_i = 0.0048$). Can somebody share their clinical or analytical experiences with me.

Prasad Tata, Ph.D.

On 19 Dec 1996 at 11:00:15

In response to the 2D6 question- A lot of work has been done using dextromethorphan as a marker for 2D6. Perhaps that could be an alternative agent you could use.

Kristen Jones, PharmD, BCPS

Assistant Professor, Campbell University, Buies Creek, NC 27506

On 23 Dec 1996 at 14:11:13

There is a paper in the *Journal of Medicinal Chemistry* which appeared in 1993 (Vol.36, issue 9, pages 1136-45) entitled "development of a pharmacophore for inhibition of human liver cytochrome P450 2D6: molecular modeling and inhibition studies" by Strobl GR et al, that you may find informative (I know this does not answer your question directly!).

Rajesh Krishna

Effect of Dosing Vehicle on Pharmacokinetics

On 31 Aug 1996 at 22:43:21

I would like to know the effect of dosing vehicle used to intravenous administration on pharmacokinetics (plasma concentration). For example, when a drug is administered as saline or PEG-400 solution, whether would the pharmacokinetics of drug be same between the two vehicles.

Teruaki Okuda

On 2 Sep 1996 at 22:50:02

Since the route of administration is intravenous (avoiding the Absorption phase) my initial thought isn't so much kinetics vs. chemistry & toxicology. A drug that's stable in saline wouldn't really need to be administered in PEG-400 would it?

Richard Molitor, R.Ph.

Seattle, Wa

On 2 Sep 1996 at 22:50:07

The "safe" answer to your question is: if the vehicle does not (1) change the dissociation of the drug through pH effects, (2) does not effect binding of the drug (e.g., to excipients in the vehicle), (3) does not unduly alter the initial concentration of drug in the bolus, and (4) the vehicle has no vascular effects of its own, then the initial absorption and ultimate plasma concentration curves should not vary noticeably between vehicles, at least within the typical variance associated with dosing and sampling.

Dr. David S. Farrier

Summit Research Services, 1374 Hillcrest Drive, Ashland, OH 44805

Felbamate - gabapentin Interaction

On 24 Jul 1996 at 11:58:04

I Like to participate.

Therapeutic Window (TW) for Felbamate.

This is part of a large study evaluating dose-response curve for felbamate in mono-therapy and poly-pharmacy for the treatment of refractory seizure. TW was found to be 50-110mg/l. Data submitted for publication at the Neurology. Let me know if you are interested, so I can prepare to present it at the ACCP.

Gamal Hussein, Pharm.D. and Allan Troupin, M.D.

Northeast Louisiana University, College of Pharmacy and LSU-Medical School, Dept. of Neurology

On 25 Jul 1996 at 12:52:13

Felbamate is now used only in rare cases. I imagine there very little interest in it at present.. However, a poster and an abstract would be appropriate.

Dr.Anaizi

On 27 Jul 1996 at 11:46:23

Felbamate article "Therapeutic Windows" was accepted to the Epilepsy. Many Children still on felbamate. I just discovered a new drug interaction where Gabapentin decreases felbamate clearance by >50%. This was accepted at the "Neurology". Anyway, you'r right with regard to the little interest on the subject. I am just trying to HELP.

I have an excellent Seizure Clinic here in Charity hospital, A pharmacist and a physician see the patient&family in the same time, this may serve as role model for other individuals interested in providing progressive pharmaceutical service with a focus on antiepilepsy

drugs/pharmacokinetics and outpatient clinics. I can discuss our clinic, its evolution and impact on patient outcome.

Other potential project is Rasmussen Encephalitis. It is a rare disorder of uncontrolled seizure, A case report and literature review may be helpful, if you decide so. Most of these patients are in the pediatric age group. phenobarbital coma is the first step after the failure of available anticonvulsant which is commonly encountered. The treatment is still unknown, with plasmaphoresis, IVIG and immunosuppressants as options. this subject may generate a good debate for those interested in seizure control. let me know if I can be of any help.

Gamal Hussein, Pharm.D.

On 29 Jul 1996 at 11:48:30

Dear Hussain,

I find your observation regarding felbamate <-> gabapentin interaction very interesting. I would be very interested in any observations you might have regarding the nature of the interaction. My understanding of the pharmacokinetics of these two antiepileptic drugs is that while felbamate is metabolized by the liver, gabapentin is not. Indeed, gabapentin is entirely dependent on glomerular filtration for its elimination; its clearance appears to be directly proportional to the GFR. What I find curious about gabapentin is that it does not appear to be reabsorbed to any significant extent by the renal (proximal) tubules, although it is known to be absorbed from the small intestine by a Na-dependent co-transport system, which is normally responsible for the absorption of aminoacids. A similar aminoacids transport system is known to exist in the proximal tubule.

N Anaizi

On 30 Jul 1996 at 12:26:01, GHussein.at.aol.com sent the message

Notes in gabapentin-felbamate interaction:

Felbamate's elimination by the kidney is known, but not appreciated, since it is about 50%. My best speculation is that gabapentin competes at the molecular level for renal excretion of felbamate rather than competition/induction of hepatic metabolism. We have not yet evaluated other data that will define the potential effect of felbamate on the excretion of gabapentin, a possible correlate of the data discovered by my group. These data were accepted for publication at "Neurology".

Gamal Hussein, Pharm.D.

Fenoterol Pharmacokinetics

On 14 Mar 1996 at 11:00:38

I need information, data (oral resorption, plasma concentration, plasma protein bond, renal excretion,...) about "fenoterol", used for tocolysis/inhibition of premature labor.

Walter-R. Kaempf M.D.

On 15 Mar 1996 at 11:54:03

Some information (scanty, but with further citations) is in

McCombe J. 1995 Update on tocolytic therapy. *Ann Pharmacother* **29**, p515-22.

Randy Trinkle, BScPharm, BA

Dept. of Pharmacy, Creek & District Hospital, Dawson Creek, BC Canada

Flucytosine Pharmacokinetics

On 23 Oct 1996 at 10:41:10

Is there someone out there who has experience with dosing of flucytosine? From what I know and have read, peak levels >125 mg/L are toxic (bone marrow suppression and hepatotoxicity) and those <50 mg/L would be at risk of developing resistance. We see very few patients here at DHMC who receive 5-FC (and amphotericin) but always seem to have problems with their regimens, mostly because we mail out the drug samples and do not have results back until 48-72 hours later.

Marc Sempregon, RPh, MSLS

Clinical Pharmacist, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756

On 24 Oct 1996 at 10:41:31

The data linking serum concentrations of 5FC with efficacy or toxicity are, as for many drugs, anecdotal. Generally we try to maintain serum concentrations (we usually draw a random sample midway through the dosing interval) of around 70-80 mcg/mL.

One should continue to monitor platelet and WBC counts, even when concentrations are within the "normal" range. Some literature suggests that 5FC is converted to 5FU by intestinal bacteria/yeasts which contain cytosine deaminase, rather than this conversion occurring in plasma. Therefore, factors other than serum 5FC concentration (e.g., duration of therapy) may be more important vis a vis toxicity.

Steven C. Ebert, Pharm.D., FCCP

Clinical Specialist, Infectious Diseases, Clinical Associate Professor of Pharmacy, Department of Pharmacy, Meriter Hospital, 202 S. Park Street, Madison, WI 53715

General Pharmacodynamic Reference Book

On 5 Dec 1996 at 10:50:37

Does anyone has good references on principles, design, responses definition, modelling and statistical analyses of pharmacodynamic studies.

Francois Vandenhende

Statistician, Lilly Research Laboratories, MSG - Belgium

On 8 Dec 1996 at 18:29:19

There are several texts in pharmaceutical statistics. For clinical trials or otherwise, a couple of good books are:

1. Planning pharmaceutical clinical trials: basic statistical principles. William M. Wooding
2. Statistical methodology in the pharmaceutical sciences. Donald A. Berry.

Rajesh Krishna

On 8 Dec 1996 at 18:31:05

You might want to look at: Van Boxtel et al. "The In Vivo Study of Drug Action". Elsevier 1992. This book attempted to cover most of what you ask for but of course it is now 5 years old. Principles havent changed much however.

Nick Holford

Dept Pharmacology & Clinical Pharmacology. University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

Gentamicin in endocarditis

On 27 May 1996 16:31:53

Summary:

A colleague in hospital pharmacy has asked me to inquire whether others have experience/information on departures from recommended dosage adjustments for gentamicin in patients who are being treated for endocarditis.

Details:

In this case, a patient has renal failure and is being dosed with gentamicin 80 mg at 8 h intervals giving high trough values (2.7 mg/L) and low peak values (5 mg/L).

The standard procedure would be to lengthen the interval between doses, so that the desirable trough approaches zero and the peak is 12-15 mg/L.

However, the infectious disease medical specialist believes that a continuous low drug level will give the best result in endocarditis.

We would be pleased to hear of anything specific which either supports or refutes this view.

Stuart McLean, MPharm, PhD

School of Pharmacy, University of Tasmania, GPO Box 252C, Hobart 7001, Australia

On 28 May 1996 at 12:30:27

1. What is the organism?
2. What are the other antibiotics being used?
3. Is ampicillin (or another beta-lactam) being used, and is it being given by continuous infusion?

Randy Trinkle, BScPharm, BA

On 28 May 1996 at 12:30:33

Based on my past experience, high peaks are important to ensure penetration of gentamicin into the vegetation. One previous patient that I was involved in the treatment received tobramycin at a dose to produce peaks of 15 mg/L and troughs of <1 mg/L. for a *Pseudomonas aeruginosa* endocarditis. The patient was successfully treated, although 2 courses of therapy were required without nephrotoxicity. With the elevated trough levels, it is unlikely that the patient will be able to complete the required 6-8 weeks of therapy with gentamicin due to nephrotoxicity. Depending on the age of the patient, nephrotoxicity is likely to be seen starting at 5 days into the therapy. The question is one of is it more important to complete the duration of therapy without nephrotoxicity or have a short course due to high troughs with resultant nephrotoxicity with limited penetration into the vegetation. Since there is no blood flow to the valves except the surrounding blood in the heart, high peaks to facilitate diffusion into the vegetation seem more important to me.

Michael Burton

On 29 May 1996 at 10:29:17

As Mike Burton has noted, the type of bacterium causing the endocarditis may influence the importance of serum concentration monitoring. For *Pseudomonas* endocarditis, I agree that high concentrations (tobramycin peaks of 10-14 mcg/mL) are best, with troughs <1 mcg/mL. On the other hand, for staphylococcal, alpha-streptococcal, or enterococcal endocarditis, lower peaks (5 mcg/mL or less) with troughs <1 are probably sufficient. SCE

Steve Ebert

On 31 May 1996 at 10:59:38

In response to follow-up questions from Randy Trinkle:

1. What is the organism?

Unknown until valve is removed and cultured.

2. What are the other antibiotics being used?

Vancomycin, initially I.V. 500 mg 12 hourly, now 1 g daily.

3 Is ampicillin (or another beta-lactam) being used, and is it being given by continuous infusion?

No

Stuart McLean, MPharm, PhD

School of Pharmacy, University of Tasmania, GPO Box 252C, Hobart 7001 Australia

Guidelines for Furosemide IV push

On 21 Oct 1996 at 16:59:11

I am posting this for the Clinical Pharmacist at our hospital. I hope someone can provide us with some help.

Are there any guidelines published for furosemide IV push administration? The manufacturer states that 20-80 mg can be given IV push over 1 to 2 minutes and that "high dose" parenteral therapy should be administered as a controlled intravenous infusion at a rate of not greater than 4 mg/min. Is it safe to give furosemide undiluted in doses > 100mg IV push over 1- 2 minutes which would exceed 40 mg/min?

We have not found an answer in a search of the literature.

B. Miers

Health Science Librarian, Methodist Medical Ctr., Peoria, IL

On 22 Oct 1996 at 12:07:51

The main problem associated with furosemide when given IV push is ototoxicity. This appears to occur particularly as a result of high serum peaks of loop diuretics (ethacrynic acid >> furosemide > bumetinide). Here are some "rules" that I try observe when using furosemide: 1- Maximum rate of iv push = 40 mg/min (no need for dilution) 2- Dose may be doubled every 2 hrs until adequate response is achieved. 3- The individual dose should not exceed 160 mg. 4- Total daily (iv) load should not exceed 800 mg (that is five 160-mg doses). 5- Oral dose = 2 x iv dose (bioavailability is about 60%)

Furosemide is sometimes given as a bolus followed by continuous iv infusion (diluted appropriately) at the rate of 0.05 - 0.5 mg/kg/hr (to achieve and maintain a serum level of 1-2 mg/L). This method of administration may reduce the risk of ototoxicity, but it does not appear to enhance the diuretic response.

I hope this information is useful!

Needless to say that I assume no legal responsibility.

N. Anaizi, PhD RPh, Univ of Rochester Med Center

On 23 Oct 1996 at 10:41:32

Thanks very much for the useful information on furosemide guidelines. It was greatly appreciated!

B.Miers, Methodist Med. Ctr., Peoria, IL

On 23 Oct 1996 at 10:41:59

I tend to disagree with Dr. N. Anaizi that the individual dose should not exceed 160 mg. Many patients with severe renal failure may not adequately respond to this dose, in which case the dose needs to be doubled. For a wonderful discussion of diuretic resistance, I highly recommend:

Brater DC. 1993 Resistance to diuretics: mechanisms and clinical implications. *Adv Nephrol Necker Hosp* **22**, p349-69.

Arasb Ateshkadi, Pharm.D.

Assistant Professor, Department of Pharmacy Practice, College of Pharmacy, University of Utah, 258 Skaggs Hall, Salt Lake City, UT 84112

On 24 Oct 1996 at 10:40:39

The issue of diuretic resistance raised by Dr. Ateshkadi is a more specific one. I was addressing general guidelines for the more common, inpatient use of loop diuretics. On a few occasions we have used furo doses in excess of 200 mg in pts with oliguric RF. In most of these cases furo was used in combination with chlorthiazide to block Na reabsorption at the more distal sites of the nephron.

A comprehensive discussion of the clinical pharmacology of diuretics may be found in section V of Messerli's **Cardiovascular Drug Therapy** published by Saunders (2nd edition, '96)

N. Anaizi

Ketoconazole - Cytochrome P-450 Inhibition

On 25 Jul 1996 at 14:13:43

My understanding is Ketoconazole is a Non Specific inhibitor of Cytochrome P-450 (according to the original papers published by Janssen Pharmaceutica). It is a non specific inhibitor with somewhat more affinity towards, CYP-450 3A4. In recent times I started seeing several papers probing the metabolic pathway of drug candidates stating because the metabolism of Drug X is inhibited by ketoconazole so Drug X metabolism is mediated by CYP-450 3A4. In my opinion this type of observations are ACCEPTING A FALSE HYPOTHESIS (TYPE II ERROR ??).

If we want to test whether a particular drug is metabolized by 3A4 or not the best way is to see the effect of induction by Dexamethasone and also looking for Inhibition of metabolism by Gestodene or Norethindrone which are known to be Very specific inhibitors for CYP-450 3A4.

Can someone throw some light on this aspect.

Prasad Tata, Ph.D.

Department of Pharmacokinetics, Otsuka America Pharmaceutical, Inc., 2440, Research Blvd., Rockville, MD 20850

On 26 Jul 1996 at 10:43:42

Just wanted to add that Rifampicin is believed to be a most potent inducer of CYP_{3A4} subfamily mRNA. Other inducers include phenobarbital and Pregnenolone 16alpha-carbonitrile.

Both Ketoconazole and gestodene, albeit very potent, are a non-selective inhibitor of CYP_{3A4}. Troleandomycin is presumed to be a very specific inhibitor of CYP_{3A4}.

So, Rifampicin and Troleandomycin can be used to identify the cytochrome P₄₅₀3A₄ isoform.

Additionally, the purified CYP_{3A4} (not easily available) can also be used.

FYI, I maintain a PK/PD/Biopharmaceutics Home Page that also has a table of different P₄₅₀ isoforms, some substrates, inducers and inhibitors. The URL is given in my attached signature file.

G Krishna

<http://griffin.vcu.edu/~gkrishna/PK/pk.html>

On 30 Jul 1996 at 12:26:02

Using induced microsomes to determine the primary cytochrome P₄₅₀ responsible for metabolizing a substrate is questionable. Upon induction, you can markedly change the relative composition of specific P₄₅₀s in the liver - some non-constitutive enzymes will be expressed after induction, while some constitutive P₄₅₀s will be suppressed. Hence, using induced microsomes may lead to an inaccurate conclusion as to the primary P₄₅₀ responsible for metabolizing a substrate. We found this to be the case with dapsone (see Vage C & Svensson CK. Drug Metab Dispos 22:572, 1994.). It is also important to recognize that substrate concentration can influence which P₄₅₀ predominates in the metabolism of a substrate. Hence, the best way to make this assessment is via a battery of experiments.

Craig K. Svensson, Pharm.D., Ph.D.

Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI 48202
USA

<http://wizard.pharm.wayne.edu/svenss.html>

On 31 Jul 1996 at 12:31:04

Dr. Swanson,

Your observation that it is better to test inhibition reactions in constituent stage is a good time tested idea. However to quickly pin point what isoform is responsible for the metabo-

lism of Drug X many people used induction of selective isoform and looking for corresponding increase in a particular metabolite formation (metabolic pathway) and subsequent inhibition by a selective inhibitor. This strategy provides quick way of getting a feel on the major metabolic pathways based on these initial experiments further experiments can be planned for further probing the metabolic profile of a drug candidate.

My question is whether we can classify Ketoconazole as a Specific inhibitor of CYP 3A4 or it is a non specific inhibitor of CYP-450.

Prasad Tata

Once Daily Administration - Aminoglycoside

On 8 May 1996 at 10:40:49

Our hospital has been using od aminoglycosides for several months. The dosage range is 5-7mg/kg/day (for gent and tobra).

Comparison studies with conventional q8h administration found similar efficacy /c no greater toxicity. (This stuff is on MEDLINE.)

The putative clinical advantage relies on a sequence of events when susceptible bacteria are exposed to an aminoglycoside. Since the drug has an intracellular mechanism, it requires some sort of transport into a bacterium. A conventional trough concentration appears to be high enough to down regulate this transport, making bacteria less susceptible. Allowing the concentration to drop over 8 half-lives (effectively to zero), which is what a dose/24h amounts to, allows bacteria to "recover" the transport mechanism. In addition, some drug binds to extra-membrane bacterial structures, and as extra-bacterial drug concentration drops, bound drug becomes unbound (it's a reversible binding event with a low enough affinity constant to make this possible). This unbound drug is then taken up by bacteria to effect a kill. This last bit is also an explanation proposed for the 'post-antibiotic effect' exhibited by the aminoglycosides.

Even if there doesn't turn out to be a greater clinical effectiveness with od dosing, there are other advantages. We now see more patients being treated on an out-patient basis in our ER, since they only have to come in once a day. There's also the reduced cost of administration for in-patients, with nurses preparing and hanging one dose a day rather than three, plus no more gent assays. After all, what would you be measuring--that there's nothing there after 24 hours? The assay that *is* done is serum Cr, just so you know how the patient's kidneys are holding up, and if their renal function is such that you can assume a normal half-life. If their Cr is high, give the gent every 36 or 48 hours.

Randy Trinkle, BScPharm, BA

Dept. of Pharmacy, Dawson Creek & District Hospital, Dawson Creek, BC

On 8 May 1996 at 10:40:47

For Once-daily aminoglycoside dosing:

Two references are:

Nicolau, DP, Freeman, CD, Belleveau, PB, et al. 1995 Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients.

Antimicrobial Agents and Chemotherapy, **39**(3), 650-655.

Gilbert, DN. 1991 Once-Daily aminoglycoside therapy. *Antimicrobial Agents and Chemotherapy*, **35**(3), 399-405.

The dose given is usually 6 to 7 mg/kg for Gentamicin or Tobramycin, and the frequency is adjusted based on a random level as shown in the nomogram in Nicolau's paper. I am not aware of a paper describing once daily dosing in pediatrics, and we use conventional dosing (adjusted by levels) for patients with renal failure or deep tissue infections (osteomyelitis, or endocarditis).

On 8 May 1996 at 10:40:54

I have just recently seen a posting to this group referring to ODA. There seemed some concern over the references and pharmacists that use this protocol. The definitive article describing this practice was written by Hartford Hospital and is available in several journals. At the hospital I work at the pharmacists monitor the aminoglycoside therapy for patients on the ODA protocol. Those pharmacists have demonstrated their capability by passing a stringent pharmacokinetic examination and demonstrating the clinical ability. In short the ODA protocol is as follows. Gent or Tobra are doses as 7 mg / kg on ideal body weight (given over 1 hr) (ideal weight = 50kg + 2.3kg x height in inches over 5 foot for males (females are 45kg + 2.3kg/inch > 5foot)) obese individuals (30% > ideal wt) are dosed as ideal body weight + 0.4 x excess wt over ideal). After this initial dose a random level is obtained from 6 - 14 hrs after the start of the infusion. This level is plotted on the aminoglycoside nomogram to determine the dosing frequency (q24, q36, or q48 hrs). This level is repeated in 5 days or if clinically necessary. Some patients are excluded from the protocol i.e. preg-

nancy, renal dialysis, burn patients, severe ascites, cystic fibrosis, and endocarditis. Some of the doses I have seen are from 280mg to 680mg ivb q24 hrs. The reasoning behind the protocol is to have the trough level fall below 0.4mcg/ml about 4 hrs before the next dose. (remember aminoglycosides exhibit a post antibiotic effect) Clinical experience shows that the aminoglycoside level that provides poor outcomes is the trough level > 2.0 mcg/ml. The higher peak levels allow for aminoglycosides to achieve a better antimicrobial effect than traditional dosing. Pseudomonas infections can be treated with this regimen. Hope this helps

TGUSCHEL

On 9 May 1996 at 10:06:56

In addition, some drug binds to extra-membrane bacterial structures, and as extra-bacterial drug concentration drops, bound drug becomes unbound (it's a reversible binding event with a low enough affinity constant to make this possible). This unbound drug is then taken up by bacteria to effect a kill.

What is an extra-membrane bacterial structure? Is this part of the bacterium? Those hairy bits that some bacteria have?

So are you saying that the kinetics of unbound drug close to the effect site are determined by binding to the bacterium itself? Is there any direct experimental support for this or is hypothesis only?

... plus no more gent assays. After all, what would you be measuring--that there's nothing there after 24 hours? The assay that *is* done is serum Cr, just so you know how the patient's kidneys are holding up, and if their renal function is such that you can assume a normal half-life. If their Cr is high, give the gent every 36 or 48 hours.

Nothing like closing the stable door after the horse has bolted!

PLEASE consider measuring the gent concs. They are a more sensitive marker of renal function changes (Thalf of gent is half that of creatinine). Plus you can use the gent concs to adjust the dose BEFORE the patient's renal function deteriorates.

Measuring gent concs at 1 and 8 hours after the od dose will give readily measurable concs and if your lab is up to scratch you will have the results back before the next dose is due.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019,
Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 9 May 1996 at 10:06:58

On the Once-daily aminoglycoside story

The blokes at Clinical Pharmacology in Christchurch (NZ) have been the southern hemisphere players in this game for some time.

This team have published some clear guidelines and a suggested approach

Evan Begg, Murray Barclay, Steve Dufful. 1995 A suggested approach to once-daily aminoglycoside dosing *Brit J Clin Pharmacol*, **39**, 605-609

Barclay, Dufful, Begg & Buttimore. 1995 Experience of once-daily aminoglycoside dosing using a target area under the concentration-time curve. *Aust NZ J Med* **25**, 230-235

There has also been a meta-analysis looking at some of the published data

Galloe et al. 1995 Aminoglycosides: single or multiple daily dosing? A meta-analysis on efficacy and safety *Eur J Clin Pharmacol*, **48**, 39-43

Andrew McLachlan

Dept Pharmacy, Uni of Sydney, NSW 2006 Australia

On 9 May 1996 at 13:58:32

I'd like to respond and echo some of Nick's comments re: ODA.

Actually three meta-analyses have been published- one in Lancet (BMJ?), another in Ann Intern Med, and another in J Antimicrob Chemother. What is interesting is that the papers all have slightly different conclusions.

The "definitive paper" written by the Hartford group is largely anecdotal, i.e., "this is what we did, and it seemed to work". The mean duration of therapy was 2-3 days. The authors cannot, when prompted, defend the method(s) used to determine the serum concentration nomogram used. Others who have adopted this method have had problems

with toxicity. 7 mg/kg dose is designed to achieve higher peak:MIC for Pseudomonas---
why not use tobramycin?

Integration of concentration-effect (bactericidal rate) relationship for aminoglycosides implies that net kill should reflect AUC, not peak. This is why most studies show no difference (the Prins paper was not a randomized study). ODA will likely be more effective if only bacteria with high (>2 mcg/mL) MICs are included.

I agree one serum concentration would be appropriate in patients who would traditionally be dosed q 8-12h. We use a 5 hr post dose to estimate AUC (least biased time point based on optimal sampling theory). In patients with poor renal function, we obtain peak/trough as traditionally is done.

We rarely used ODA outside of ICU and home/ambulatory patients. We stratify maximal daily dose (3-6 mg/kg/d) by estimated CrCl and disease severity. On the other hand, we do not use 8h interval, but instead go right to q 12h. We average 0.7 serum concentrations/course (mean 5d) and our nephrotoxicity rate is 2.8%.

Steve Ebert

On 28 May 1996 at 12:30:30

I apologize for raising an issue which has been discussed extensively in the not too distant past.

My question is whether there are literature data (or personal experiences) to support the use of ODA in patients with chemotherapy induced neutropenic sepsis, where overwhelming gram -ve septicaemia can develop rapidly in the absence of appropriate antibiotic therapy.

Duncan Jodrell

Senior Lecturer in Medical Oncology

On 29 May 1996 at 10:29:14

There wasn't any literature on once daily aminoglycosides in febrile neutropenia when I recently searched. We've been utilizing it in our chemotherapy-induced neutropenia patients (both inpatient and outpatient management), but counts return quickly to normal (we also use filgrastim) so I'm not sure this is a true test. Our physicians and nurses like it. We have relatively limited experience in AML patients s/p chemotherapy, however, it appears to be no different from conventional dosing. Our experience with impaired renal function (ie dosing q48 hours) is also very limited. Usually, we do not use it as monotherapy against gram negative organisms, and we have very few resistant gram negative organisms.

Dianne M. Brundage, Pharm.D., BCPS

Methodist Hospital Pharmacy, 6500 Excelsior Blvd, Minneapolis, MN 55426

On 29 May 1996 at 10:29:16

The largest published study was authored by the EORTC and published in *Annals of Internal Medicine*, around 1992-3 or so. It compared ODA plus once-daily ceftriaxone with 8-hourly amikacin and ceftazidime. No differences in efficacy noted. A delay in onset of nephrotoxicity was observed in ODA group. Steve Ebert

On 31 May 1996 at 10:59:39

Hi Duncan,

The following very recent paper might be of some interest - perhaps you have seen it already.

R Hatala, T Dinh, DJ Cook Once-daily aminoglycoside dosing in immunocompetent adults: A meta-analysis, *Annals of Internal Medicine* **124**, 8 (APR 15 1996) 717

Gregory Peterson

Senior Lecturer, Tasmanian School of Pharmacy, University of Tasmania GPO Box 252C, Hobart, TAS, 7001 AUSTRALIA

On 29 May 1996 at 10:29:15

The use of pulse dosing of aminoglycosides in neutropenic patients has yet to be investigated in humans. Studies on neutropenic rats suggest that the "post antibiotic effect" may be considerably shorter in neutropenia. The implication is that with pulse dosing neutropenic pts would be "unprotected" during the terminal portion of the dosing interval.

These findings led to the notion that neutropenic patients should be excluded from ODA dosing programs. To date I know of no clinical study that addressed this issue specifically. However, it is very likely that at least one is going on now. By the way, these same formal dosing programs exclude pts with endocarditis and all instances in which the aminoglycoside is used for its synergistic effect together with a beta-lactam.

Nasr Anaizi, PhD, RPh

Univ. of Rochester Medical Center

Oleic acid and Lymph

On 7 Feb 1996 at 11:28:28

I am a research student at the University of Bradford (UK), and intend to investigate how oleic acid alters the bioavailability of drugs that have a high hepatic first pass metabolism, e.g. propranolol, metoprolol, felodipine. I am in the pharmaceutical technology dept., so am concentrating on the formulation aspect of drug delivery.

Work with propranolol and oleic acid suggests increased lymphatic transport of the drug (e.g. Barnwell, *Int J Pharm* 1992) but considering propranolols' moderate lipophilicity ($\log P_{o/w} = 3$) this seems doubtful. Any thoughts?

I would be grateful for any comments, advice, constructive criticism concerning oleic acids possible effects on bioavailability.

Kieran Crowley

On 12 Feb 1996 at 11:25:19

What was the evidence presented in that article for lymphatic transport?

J Paul

On 13 Feb 1996 at 09:58:08

What was the evidence presented in that article for lymphatic transport?

Lymphatic cannulation.

Chetan Lathiac

Preclinical Pharmacokinetics

On 7 Oct 1996 at 11:18:31

I have just arrived to PK field, working in preclinical studies. I am trying to manage data and statistics when comparing bioavailability data obtained from independent animals (one point, one animal). I have only found a method of calculating and comparing AUC obtained in this way from Shoenwald et al. I'd appreciate any help in how to deal with statistics in bioequivalence studies when a curve is obtained from different animals ending with a curve made of medium values but not a 'medium curve'

Carmen

On 7 Oct 1996 at 18:01:55

calculation of bioavailability one point per animal...

Was each animal given the same dose and was that dose expressed per kg body weight? Were data collected after both intravenous and oral doses or did you use some relative standard? What are the units of measurement of your individual data samples? Do you have body weights or plasma volumes for the individual animals? Unless all the animals are the same or nearly the same size, it may be useful to normalize the data set before calculating the AUC. If the dose was given per kg, this normalization may already be built into your data set.

You can assign statistical weight to the data based on your knowledge of the measurement error. Then you can fit the data to a sum of exponentials, or to a compartmental model, or use a "non-compartmental" approach as described by (for example) Gibaldi, M., **Biopharmaceutics and Clinical Pharmacokinetics**, 4th ed., Lea and Feibiger, 1991.

As with all AUC measurements, you will have to choose some estimate of the slowest exponential to extrapolate to $t = \infty$. For this reason, it is always desirable to have data as far out in time as possible.

Now, when you do your least squares fit you will get point estimates for your AUCs and you will get coefficients of variation based on your estimate of measurement error. For this part of the work, my favorite software is SAAM II, but there are many other capable packages.

Robert D Phair

BioInformatics Services

On 8 Oct 1996 at 12:11:09

Recent article by Ette et al. (*J. Pharmacokinet. Biopharm.* 1995, **23**, 551) may help.

Vladimir Piotrovskij, Ph.D.

Janssen Research Foundation, Clinical Pharmacokinetics, B-2340 Beerse Belgium

Pharmacokinetic Software

On 2 Dec 1996 at 10:35:37

Several people have posted asking me to list the references I received and the programs on my evaluation list. Here they are.

Please note that the list is in no particular order, and not all programs are necessarily equivalent - this is just what I got back from the group. I'm not sure if it's kosher to include Email addresses, but have assumed that if someone is providing a product they don't mind being contacted... [my apologies if this is not the case]

The best all-around source for this information is still

<http://www.pharmpk.com/soft.html>

but I was only interested in IBM-PC-WIN_{3.x}-MSExcel-compatible programs, which is a much smaller window.

1. T.D.M.S.
2. MultiForte & Boomer from David Bourne [david@boomer.org][love that kangaroo!]
3. "Fit-Regression" from WindowChem Software [www.windowchem.com], a product which we purchased as an Excel add-on]
4. NCOMP from Paul Laub [plaub@draco.rm.fccc.edu]
5. PKAnalyst from Micromath [www.micromath.com] - they also have a product called Scientist with PK add-ons, but it doesn't look too different from PKAnalyst based on the demos I downloaded from their site
6. WinNonlin from Pharsight [http://www.pharsight.com/products/prod_winnonlin_home.php]. This product follows on from PCNONLIN, which I have used before.
7. SAAM from NIH [www-saam.nci.nih.gov/saam.htm]

There are a few other leads I haven't followed up on yet:

ACSL BioMed and Optimize at www.mga.com

Kinetica [by Simed] at www.bioscience.com

PCMODFIT [contact Alan Thawley, alan.-a-.artpac.demon.co.uk]

METABASE & PK SOLUTIONS at www.bright.net/~dfarrier/index.html

Prices of the above range from zero to ridiculous! I have not yet looked at them all, so I have no comments to make on any. Once again, my thanks to everyone who responded, and I hope all of my transcriptions and citations are accurate.

Adrienne Stevenson

Ottawa, Canada

On 3 Dec 1996 at 15:27:06

Thanks for the list of PK programs you are evaluating. Since you specifically mention Excel, you might consider looking at PKPD Tools for Excel with XLMEM. This is a public domain Excel spreadsheet by Charles Minto and Thomas Schnider. You can find it on my WWW site: <http://pkpd.icon.palo-alto.med.va.gov>

One interesting aspect to this is the implementation of mixed effect modeling, using the NONMEM objective function (first order approximation), in a dynamic link library accessible to Excel. The function returns the same values as all of the NONMEM test sets, with comparable execution times (the code is compiled). However, it is limited to the series of models implemented in PKPD tools, and thus has neither the flexibility nor the more recent objective functions (e.g., conditional estimation) implemented in NONMEM. At present, it is a prototype of a more complete population analysis tool with Excel that Drs. Minto and Schnider hope to build.

PKPD Tools should be interesting. It is still evolving, with major updates every 6-8 months, as Drs. Minto and Schnider have time to make additions.

Steve Shafer

On 3 Dec 1996 at 15:37:34

SAAM from the NIH is a good package that has been in use for decades, but my actual kinetics software recommendation to Adrienne Stevenson was for SAAM II with an intuitive graphical user interface and a bunch of hotshot peer-reviewed optimizer algorithms and flexible weighting schemes. You can find out more about SAAM II from the Epsilon Group [<http://tegvirginia.com/solutions/saam-ii/>]

Robert D Phair PhD

BioInformatics Services

<http://www.webcom.com/rphair>

On 5 Dec 1996 at 10:33:39

Dear all,

I am interested in getting a moderately priced PK analysis package which is Windows compatible. I have seen the demo versions of Scientist and PKanalyst from Micromath. They appear slightly similar although my understanding is that in Scientist there is greater flexibility for the model equations (simultaneous differential, Laplace etc) as well as the possibility of fitting simultaneously data of other metabolites or concentrations in other compartments which would be useful for my work. I would like to know if anyone out there has purchased and used either of these packages and whether they found significant hick-ups. Any comparisons of these and better/worse PK packages would be welcome. In the past, I have done my fitting with a combination of Sigmaplot, the free listing of Yamaoka K et al J. Pharmacobio-Dynam 4:879-885, 1981, and the method of using EXCEL for non-linear curve fitting described by Bowen and Jerman, TIPS 16:413-417, 1995.

Sigmaplot is OK for simple equations, the Yamaoka program is extremely versatile and with some re-writing can load/save info to disc (however it is a B/W dinosaur) and the EXCEL method is good for enzyme, cytotoxicity and PD work but is out of the question for serious PK work. Time to go upmarket and get something more presentable.

Laurent P Rivory

Department of Medicine, University of Queensland, Princess Alexandra Hospital, Ipswich Rd, Woolloongabba 4102, QLD, Australia

On 6 Dec 1996 at 10:32:30

All the programs you mentioned are a variation on the theme of curve fitting. The short coming as I see it (and I hope others might share their own viewpoints on this) is that programs such as these give good equations and curve fits but provide little in the way of useful PK parameters. Typically they give little more than the AUC, half-life and lag-time. On the other hand, when one surveys, for example, Drug Metabolism and Disposition, the vast majority of papers dealing with pharmacokinetics provide tables which include these and other PK parameters (such as the V_d , Cl , MRT , $AUMC$, etc.) as their primary results. Typically, these results are all based on non-compartmental assumptions. I tabulated the contents of 2 years of DMP issues to arrive at this fact. It appears that compartmentalists need equations, but practitioners need parameters. To fill the void in software, I developed a program called PK Solutions. It runs in Excel and is automated with VBA procedures. It calculates about 25 parameters for blood levels obtained after single oral or iv bolus and predicts an additional 25 steady state parameters based on multiple dosing. It provides curve stripping and/or Excel Solver-based curve fitting of time-concentration data, or one can supply exponential terms derived from other software (i.e., curve fitting software).

Dr. David S. Farrier

Summit Research Services, 1374 Hillcrest Drive, Ashland, OH 44805 USA

On 6 Dec 1996 at 10:34:28

About Laurent Rivory's question about PK analysis packages:

I suggest considering ADAPT II, the PKPD simulation and fitting program written by DZ D'Argenio and A Schumitzky and available at little or no cost from the Biomedical Simulations Resource at the University of Southern California. I have heard that a Windows version of ADAPT II is nearing completion; in the meantime an excellent DOS version exists and has a devoted following (myself included).

Advantages of ADAPT II:

1. Enormous flexibility, in that you write the equations or differential equations describing the system as well as the variance function describing the presence of noise or error.

-
2. Statistical features not found in other packages such as fitting using Bayesian priors as well as support for designing optimal sampling.
 3. The program comes as well documented FORTRAN 77 source code, so that if you absolutely have to, you can "look under the hood" and find out how the program works.
 4. Track record - the program has been around since 1979 and has many users worldwide; the authors at USC regularly hold conferences or training courses on ADAPT (as they did last May).

Disadvantages of ADAPT II:

1. Enormous flexibility - maybe too much for someone learning pharmacokinetics. Additionally, flexibility assumes basic knowledge of writing FORTRAN code as well as compiling and linking FORTRAN programs.
2. Requires a FORTRAN compiler, so that while ADAPT II is free (at least to academic users), the compiler is not. But in a lab where lots of number crunching is going on, a FORTRAN compiler may find many other uses.
3. Lack of a slick interface (the DOS version; the Windows version may be different). Programs that are point and click are nice UNTIL you want to do something even slightly different from what the program's authors had in mind. Then your hands are tied ... but not with ADAPT II.

Paul (Sisyphus) B. Laub

Dept. of Medical Oncology, Fox Chase Cancer Center, PA 19111 USA

On 6 Dec 1996 at 11:40:25

We use SCIENTIST a lot and are very happy with it. It is easy to use and has nice graphics.

Prof. Dr. Hartmut Derendorf

University of Florida, 100494, College of Pharmacy, Gainesville, FL 32610

On 8 Dec 1996 at 18:30:32

Laurent-

As I have said in response to two recent queries like yours, you owe it to yourself to check out SAAM II.

I've been in the kinetics business for almost 30 years and I'm now doing all my work in SAAM II. It's got a neat graphical user interface, runs under Win95, WinNT, or MacOS, has a bunch of hot-shot integration and parameter estimation algorithms, and it's not very expensive. I've used the software to teach kinetics to more than 100 people in the last three years, and they have been unanimous in their praise for how easy it is to learn.

Robert D Phair PhD: rphair.aaa.ix.netcom.com

BioInformatics Services

<http://www.webcom.com/rphair>

On 8 Dec 1996 at 18:31:50

All the programs you mentioned are a variation on the theme of curve fitting. The short coming as I see it (and I hope others might share their own viewpoints on this) is that programs such as these give good equations and curve fits but provide little in the way of useful PK parameters. Typically they give little more than the AUC, half-life and lag-time. On the other hand, when one surveys, for example, Drug Metabolism and Disposition, the vast majority of papers dealing with pharmacokinetics provide tables which include these and other PK parameters (such as the Vd, Cl, MRT, AUMC, etc.) as their primary results. Typically, these results are all based on non-compartmental assumptions.

I have to disagree with your conclusion as a general shortcoming about 'curve fitting' programs. Any general non-linear regression program that allows the user to define the model will also allow any parameterisation the user wants. There is nothing to stop you parameterising a model in terms of Vd and CL (as opposed to elimination rate constants [like alpha and beta] and 'intercepts' [like A and B]). Unfortunately I suspect many of the programs you mention were not developed or maintained by pharmacokineticists and so they offer a general 'mathematical' parameterisation without understanding the nature of the application of PK models as a tool to understand biology.

AUC and AUMC have no intrinsic merit as PK parameters. They are simply intermediate values which are usually obtained via non-compartmental methods and then applied to obtain the PK parameters of real interest i.e. CL and Vss.

I would say that most PK analysts today have moved away from the old A, alpha, B, beta, and the K_{10} , K_{12} , K_{21} , V parameterisations of the two compartment model and now favour parameters that are more closely related to structure and function i.e CL, V_{ss} , CL_{ic} (inter-compartmental clearance) and V (central cpt volume).

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

Pulse dosing of aminoglycosides

On 8 May 1996 at 10:40:53

Concerning the current trends in the dosing of aminoglycoside antibiotics (AGAs) consider the following:

1. Pulse dosing of AGAs means high doses (5-7 mg/Kg) with long dosing intervals (usually once every 24 to 48 hrs, depending the drug's half-life).
2. After a peak of 10 - 20 mg/L, the serum AGA level should ideally drop to undetectable (<0.3 mg/L) several hours before the next dose is due.
3. The higher peaks should enhance the antimicrobial efficacy; AGAs have concentration-dependent kill rate. Although there are no controlled clinical studies that show higher therapeutic efficacy with pulse dosing compared to the traditional multiple daily dosing regimen, the available data indicate that pulse dosing is at least as effective as the traditional method.
4. Pulse dosing may be safer; lower nephrotoxicity was demonstrated in at least one clinical study (Prins et al. Lancet 1993; 341: 335-339). Our own experience at the University of Rochester Medical Center tends to support the same conclusion.
5. AGAs have the so-called post-antibiotic effect (PAE) (continued suppression of bacterial growth even after the drug level has fallen below the MIC). The duration of the PAE depends on the organism and on the preceding peak (within limits, higher peaks give longer PAEs).
6. In general, for antimicrobial agents that have concentration dependent bactericidal action and a PAE, higher single doses with longer intervals are preferred.
7. For more information please e-mail me at nanaizi.-at-.frontiernet.net

You will find many references in the following:

1. Am J Hosp Pharm 1994; 51:2016-2021

2. Pharmacotherapy 1995; 15:297-316

Dr. Anaizi, PhD RPh

Associate Prof of Pharmacology and Physiology, Univ. of Rochester (NY)

On 12 May 1996 at 14:10:09

We are currently dosing aminoglycosides qd per protocol which is an amalgamation of Gilbert's method and Quintalani's.

We routinely measure levels 12h after the first dose. This occasionally yields useful information. Just this week we had a 15 yo patient with severe abdominal trauma and liver injuries. The 12h level was unexpectedly elevated. We were able to modify the dose prior to seeing an increase in SCr.

Does anyone have information in qd dosing in pediatrics? We are hesitant to use it in younger children and infants.

Carl Heisel

References on WWW

On 31 May 1996 at 10:59:41

To PK/PD Discussion group. I would be grateful for any information relating to the approved way of referring to articles or references taken from the www.

Janet Mifsud

Department of Pharmacy, Univeristy of Malta

On 3 Jun 1996 at 11:56:08

I doubt that there is a standard, formally approved format for citing material published on the net. Most of the valuable material on the net has already been either published in the "paper media" or present in scientific meetings. The important point is that we give due credit by citing the original source; the exact format is of secondary importance. I would be surprised if a formal format actually exists.

N. Anaizi

On 3 Jun 1996 at 11:56:12

On a separate note, is it *acceptable* to cite from the WWW knowing what an uncontrolled place it is (certainly judging by some WWW sites.)

Paul Baker

Pharmacy, Heartlands Hospital, Birmingham, UK

On 4 Jun 1996 at 11:44:17

However, every piece of information passed on should reference where it was obtained and the source.

Remember there is no check of accuracy or credibility on any information posted via electronic means. Anyone with access may post data and we are dependent on the individual for accuracy and viability. Many items are strictly the opinions of the sender not necessarily fact.

In short, beware of anything obtained unless it can be verified or checked for accuracy.

Joe Bishop

On 4 Jun 1996 at 11:44:18

On a separate note, is it *acceptable* to cite from the WWW knowing what an uncontrolled place it is (certainly judging by some WWW sites.)

Paul Baker

I wholeheartedly agree with Paul here. I recall seeing a recent report (from a poster submitted at an ASHP meeting I believe) that made the observation that up to 40% of the postings on sci.med.pharmacy were "bad information." I would feel much more comfortable using peer reviewed material to prove a point (especially if it had to be good enough to survive in court). If one did use material on the Web for a report you would probably want to annotate the reference as to whether it was peer reviewed or not.

Richard Molitor, R.Ph.

Editor, "Molitor Monitor"

On 5 Jun 1996 at 11:05:49

On a separate note, is it *acceptable* to cite from the WWW knowing what an uncontrolled place it is (certainly judging by some WWW sites.)?

From the perspective of the journal 'Clinical Pharmacokinetics' I would be prepared to accept citations to WWW pages as a source of further information. There is no requirement for any citation in a paper that it must be a peer reviewed paper journal.

Nick Holford

Consulting Editor Clinical Pharmacokinetics

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 29 Dec 2012

Two comments (in 2012).

1. Check references on the WWW **and** in this archive collection.
2. One method of citing WWW pages might be to list the URL, date accessed and maybe the page title and source description. It could be useful to keep a pdf file or printed copy of the page cited for your reference.

Sigmoid Emax and the logistic CDF

On 18 Mar 1996 at 09:50:24

I wish to get a better understanding of the development and relationship of sigmoid emax modeling of quantal responses to the standard form logistic CDF. Can anyone suggest a paper in a statistics journal?

Nathan Pace, M.D.

On 19 Mar 1996 at 09:32:08

For quantal responses, logistic regression (using generalized linear models) clearly has theoretical advantage. The standard reference on generalized linear models is McCullagh, P. and Nelder, J.A., **Generalized linear models**, 2nd ed., Chapman & Hall, New York, 1989.

I heard that some people may find it difficult to read, but I do not know of anything easier.

Chuanpu Hu

On 22 Mar 1996 at 11:32:44

I have perused McCullagh and Nelder, **Analysis of Quantal Response Data** by BJT Morgan (Chapman & Hall, New York, 1992), and **Continuous Univariate Distributions**, Vol 2, 2nd edition by Johnson, Kotz, & Balakrishnan (John Wiley & Sons, New York 1995) and can find no mention of sigmoid emax models or any related CDFs.

In the new monograph **Nonlinear Models for Repeated Measurement Data** by Davidian & Giltinan (Chapman & Hall, New York, 1995) it is mentioned on page 241 in a chapter about PK and PD analysis: "Derivation of a suitable PD model: unlike PK

modeling, this is usually done in a somewhat empirical fashion. By far the most commonly used model is the so-called 'Emax' model, or some variation thereof..."

In my specialty (Anesthesiology) most PD papers report use of sigmoid emax models.

With the extensive developments in logistic regression, why do PD researchers continue to use the sigmoid emax model - a technique which appears to not have the same rigorous theoretical foundation as logistic models?

Nathan Pace

University of Utah

On 25 Mar 1996 at 09:44:46

With the extensive developments in logistic regression, why do PD researchers continue to use the sigmoid emax model - a technique which appears to not have the same rigorous theoretical foundation as logistic models?

For the usual purposes of pharmacodynamic models the logistic function and the sigmoid emax model are simply different parameterisations of the same model. IMHO the parameterisation of the sigmoid emax model (esp. EC₅₀) is more helpful in understanding what is being described. I understand logistic regression to mean the use of the logistic function aka the sigmoid emax model to predict the probability of an event what e.g. as a function of conc or dose. There is no reason to prefer the sigmoid emax model over the logistic function because they are the same. Logistic regression is statistical shorthand for a particular application of these models.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 25 Mar 1996 at 09:44:52

There may be theoretical advantages of logistic function over a sigmoid Emax model, however, from the practical point of view no significant difference can be seen, since, after elementary transformations the sigmoid Emax equation

$$E = E_{\max} \cdot C^n / (C_{50}^n + C^n)$$

is converted into:

$$\ln(E / (E_{\max} - E)) = n \cdot \ln(C) - n \cdot \ln(C_{50})$$

Vladimir Piotrovskij

Software for Tracking Clinical Pharmacy Services

On 4 Dec 1996 at 10:42:47

Does anyone have the name of a good software package that we could use in our clinical service to track interventions, kinetic consults, and their subsequent impact on dollars saved or cost avoided? We are being asked to give hard data to support our existence. We do regular kinetic consults and bill them as we would a drug. I would like something that would be separate from the patient bill to track clinical activities.

I realize that much of our work results in cost avoidance but there is a substantial amount that results in actual savings. We have all of these computers, now we need to put them to work.

Robert G. Aucoin RPh

Peds Clinical Pharmacist. The Children's Center, Our Lady of the Lake RMC. Baton Rouge, LA

On 5 Dec 1996 at 10:50:13

It is my impression that the Capcil program from Simkin in Gainesville, Florida provides this capacity

John E. Murphy, Pharm.D., Professor and Head, Department of Pharmacy Practice and Science

Theophylline clearance

On 5 Feb 1996 at 11:00:17

I am seeking information concerning theophylline clearance (population kinetics). I am building a kinetic module for use at the hospital I work. Any information would be greatly appreciated.

Doug Kidder R.Ph.

On 6 Feb 1996 at 12:55:45

There are several factors that can influence the calculation of a patient's theophylline clearance in clinical practice. Drug interactions can have abrupt (ie cimetidine after 24 hours) or delayed (e-mycin, starting or stopping tobacco) onset. Factors such as liver disease or heart failure depend on the severity and presence of symptoms. This can some times change on a daily basis. If the patient received a flu vaccination or has been recently under or over compliant (Some patients will double up prior to arriving to the ER to avoid being tubed). Severe COPD/Asthma requiring ventilation may depend on the presence of PEEP >10mmhg (or presence of autoPEEP)(decreased cardiac output secondary to depressed venous return) or changes in ABG's. Infusion rates (was the rate equivalent to the total amount given in the past 24 hours) due to incompatibilities or administration error. Time of level draw and the method used, especially if not at steady-state, to calculate the clearance can also influence your predictions (ie Koup vs Chu vs PK Bayesian software).

I hope this gives you a starting point and some things to consider

William Dager, Pharm.D.,FCSHP

Coordinator, Pharmacokinetic Consult Service, UC Davis Medical Center

On 7 Feb 1996 at 11:28:25

Due to the many factors which affect theophylline clearance, it is very difficult to develop a population model which can include all cofactors and accurately predict the effect of each cofactor on theophylline clearance. The best method is to just measure a serum concentration. However, numerous articles are published on the effect of various factors on theophylline clearance. They are:

Jusko WJ, et al. 1979 Factors affecting theophylline clearances: Age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepine, barbiturates, and ethanol. *J Pharm Sci*, **68** (11), 1358-66.

This article is widely quoted and used in development of several already available pharmacokinetic dosing software programs.

Reigelman S., et al. 1980 Factors affecting the pharmacokinetics of theophylline. *Eur J Respir Dis.*, **61** (Suppl 109), 67-82.

Richer M, et al. Hypoxia, arterial pH and theophylline disposition. 1993 *Clin Pharmacokin.*, **25**, 283-99.

How well do these models work?

Casner PR, et al. A randomized controlled trial of computerized pharmacokinetics theophylline dosing versus empiric physician dosing. 1993 *Clin Pharmacol Ther.*, **53**, 684-90.

My experience with a similar unpublished study was the same; a population kinetic model combined with dosage individualization based on serum concentrations does not improve outcome of patients receiving theophylline as measured by length of hospitalization and toxicity.

There are numerous studies in the literature on population theophylline pharmacokinetics, primarily in the late 1970's and 1980's. Good luck!!

Michael Burton

On 7 Feb 1996

It seems to me that any estimate of renal function without age in the equation would discount the fairly well established effect of age on renal function. You might wish to focus on studies that have measured creatinine clearance and a drug's clearance and separated out the age factor in that manner. That is, is there any difference in clearance of a drug in a 20 year old and an 80 year old who both have measured creatinine clearance of 90 ml/min? I know there are such studies but don't have them readily available.

John E. Murphy, Pharm.D., Professor and Head, Department of Pharmacy Practice and Science

On 8 Feb 1996 at 12:26:11

We have experience with a population based Bayesian forecasting model that does a pretty good job taking in to account the various factors that alter theophylline clearance. The advantage of using this type of model is that it utilizes available serum concentrations as well as population data. In the absence of serum concentration data, it gives a very good first estimate of the likely clearance value.

Applied Pharmacokinetics, (Evans, Schentag, and Jusko, eds.) has a very complete compilation of theophylline pharmacokinetic values in various populations. The tables are all completely referenced so you can review the original literature and make up your own mind. The discussion of various parameters in the text is also interesting.

Art Harralson

Professor and Vice-Chairman, University of the Pacific, School of Pharmacy

On 23 Feb 1996 at 10:59:52

Dear Doug,

From the sound of your question, the responses you've gotten are pretty abstract. I, too, am a pharmacist in a hospital which routinely screens all patients on theo for estimated levels and confirm them via actual levels. We use very simple equations to determine estimates because like most hospitals we have a lot of patients. This simple straight forward estimate may be used if you like:

-
1. Estimate Clearance in L/hr by: using Ideal Body Wt x .05 x disease states

Here you'd factor in specific disease adjustments

Examples: asthma = 1.0 smokers use 1.4 see applied therapeutics for a complete list of factors associated w/variation in theophylline elimination.

2. Next calculate Vd using $ABW * 0.5$
3. Knowing the relationship b/w VD and cl we can determine $t_{1/2} = vd/cl * 0.693$ (usu 8hrs)
4. Estimate Cpss using: $Cpss = (dose/24hr) \text{ divided by } CL = mg/l$

Hope this is what your after. It's fairly accurate and quick. Applied therapeutics also discusses expected changes in levels when certain drugs which interfere w/clearance are added.

Anna

Tissue Homogenizers

On 22 Mar 1996 at 11:32:46

I am interested in hearing about your experiences with tissue homogenizers - especially the pros and cons of Potter-Elvehjem (teflon coated rods?) versus the handheld electric "tissue grinders". The goal is to prepare liver microsomes.

J. Vora

Butler University, Indianapolis, IN, USA

On 25 Mar 1996 at 09:44:48

It has been my experience that the PE tissue homogenizers work very well for liver. Liver tends to be a soft tissue and grinds easily. Other tissues, for example gut tissues, tend to get wrapped up in the grinder and may jam it, thus breaking the homogenizer (and they are expensive to replace). The problem that we have encountered with the electric homogenizers for microsomal work is that they tend to generate a lot of heat and may inactivate microsomes. Even the PE tends to generate some heat, and we place the grinder in an ice bath while we grind. The other problem with the electric homogenizers is that it is sometimes difficult to get all the tissue back out of them without excessive rinsing. It is easier to rinse the PE homogenizer. Hope that wasn't too graphic for anyone !!

Brian Corrigan

Toxicokinetic Data and LOQs

On 19 Dec 1996 at 10:59:58

I have recently been asked to analyze some toxicokinetic data (involving the pooling of data from a number of animals to generate a series of mean conc v. time values, which are then subsequently analyzed in a non-compartmental fashion) and have been faced with triplicate determinations of which one or even two of the triplicates are below the **LOQ** for the assay, without being "not-detected" per se. It has been suggested to me that, rather than leaving the mean value for these points undetermined (thereby losing that point from the graph altogether, and analysing the remaining points only) I instead assign a value of half the LOQ to these determinations, and thus derive a mean for inclusion in the graph and analysis. I am instinctively uneasy about this, but in the context of TK analysis, where sampling is very limited, it would be of enormous benefit to be able to ascribe a value to all the time points available.

Does anyone have any comments on this approach?

Ray French.

On 20 Dec 1996 at 14:02:55

It depends on what the LOQ of the assay is? Personally I prefer to use that one particular concentration for which you have a value rather than guessing for the samples with LOQ. Other words use one value that have a real number and don't use take the value two LOQ samples LOQ = ? of the lower limit of quantitation (assuming two out of three determinations are LOQ).

Prasad Tata, Ph.D.

Otsuka America Pharmaceuticals, Inc.

On 20 Dec 1996 at 14:03:09

Certainly these points provide some information, an approximate upper-bound if nothing else. Some statistical software will allow their use as constraints. If you choose to assign a specific value, recognize that the statistical weighting given this value must reflect the uncertainty.

Richard Scheyer, M.D.

Dept. Neurology, Yale School of Med., P.O. Box 208018, New Haven, CT 06520-8018 USA

On 20 Dec 1996 at 14:03:24

In similar situations with clinical PK studies, I have ascribed zero to those values.

Lester Gibbs

Penederm, Inc., Foster City, CA

On 20 Dec 1996 at 14:04:20

An old problem. Our arbitrary solution is if at least one data point in the set is above the LOD, we use the **LOD** for the remaining points. If the data falls between the LOD and the LOQ we use the data. In either case it must be clear that these points are estimates.

Ed Garner

Vancomycin Clearance from Dialysis Membranes

On 9 Jul 1996 at 09:29:33

I read an article recently about some newer membranes used in dialysis removing vanco to a higher degree than what older dialysis equipment did. I can't seem to locate where I read this article. Does anyone else recall recently reading of this and if so could you give the the reference info?

Randy

On 10 Jul 1996 at 11:17:21

Matzke GR 1994 Pharmacotherapeutic consequences of recent advances in hemodialysis therapy. 1994 *Annals of Pharmacotherapy* **28**, 512-14. contains a reference of this type.

Joan Korth-Bradley

On 11 Jul 1996 at 09:36:08

Here are some useful references I have on the topic:

Bastani B, Spyker DA, Minocha A, Cummings R, Westervelt FB 1988 In vivo comparison of three different hemodialysis membranes for vancomycin clearance: cuprophane, cellulose acetate and polyacrylonitrile. *Dialysis Transplantation*, **17**, 527-543

Lanese DM, Alfrey PS, Molitoris BA 1989 Markedly increased clearance of vancomycin during hemodialysis using polysulfone dialyzers. *Kidney Int*, **35**, 1409-1412

Torras J, Cao C, Rivas MC, Cano M, Fernandez E, Montuliu J 1991 Pharmacokinetics of vancomycin in patients undergoing hemodialysis with polyacrylonitrile. *Clin Nephrol*, **36**, 35-41

DeSoi CA, Sahm DF, Umans JG 1992 Vancomycin in elimination during high-flux hemodialysis; kinetic model and comparison of four membranes. *Am J Kidney Dis* **20**, 354-360

Barth RH, DeVincenzo N, Zara AC, Berlyne GM 1990 Vancomycin pharmacokinetics in high-flux hemodialysis. *J Am Soc Nephrol*, **1**(4), 387. Abstract

Schoumacher R, Chevalier RL, Gomez RA, Rogol AD, Cummings R, Spyker DA 1989 Enhanced clearance of vancomycin by hemodialysis in a child. *Pediatr Nephrol*, **3**, 83-85

Quale JM, O'Halloran JJ, DeVincenzo N, Barth RH 1992 Removal of vancomycin by high-flux hemodialysis membranes. *Antimicrob Agents Chemother*, **36**, 1424-1426

Pollard TA, Lampasona V, Akkerman S, et al 1994 Vancomycin redistribution: dosing recommendations following high-flux hemodialysis. *Kidney Int*, **45**, 232-237

Touchette MA, Patel RV, Anandan JV, Dumler F, Zarowitz BJ 1995 Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. *Am J Kidney Dis*, **26**, 469-474

Bohler J, Reetze-Bonorden P, Keller E, Kramer A, Schollmeyer PJ 1992 Rebound of plasma vancomycin levels after haemodialysis with highly permeable membranes. *Eur J Clin Pharmacol*, **42**, 635-640

Welage LS, Mason NA, Hoffman EJ 1995 Influence of cellulose triacetate hemodialyzers on vancomycin pharmacokinetics. *J Am Soc Nephrol*, **6**, 1284-1290

Reggie Frye

On 11 Jul 1996 at 09:36:10

See June 1, 1996 *AJHP*, p 1339, Letter: More information on vancomycin clearance by new hemodialysis membranes.

Bill Budris

Vancomycin Question

On 3 Dec 1996 at 14:18:33

1. Regarding vanco kinetics, our instructor gives the following equation:

$$K_{el} = 0.0044 + 0.00083(CrCl)$$

I can't find this in any of my kinetics resources, and it gives a very different answer from the more commonly used $K_{el} = \ln(Cp_1/Cp_2)/\text{time}$. So my question is, is this a valid equation, and if so, is CrCl expressed in ml/min?

2. Is it necessary to wait 1.5 half-lives before drawing the first vanco blood level?
3. If your vanco infusion is given over 2 hours instead of 1 hour, do you still need to wait a full 3 hours to account for the distribution phase before drawing a peak?

Thanks again in advance. I hope everyone had a most excellent Thanksgiving.

Catherine Heyneman, Pharm.D.

ISU College of Pharmacy, Pocatello, ID 83209

On 4 Dec 1996 at 09:59:05

1. Regarding vanco kinetics, our instructor gives the following equation:

$$K_{el} = 0.0044 + 0.00083(CrCl)$$

I can't find this in any of my kinetics resources, and it gives a very different answer from the more commonly used $K_{el} = \ln(Cp_1/Cp_2)/\text{time}$. So my question is, is this a valid equation, and if so, is CrCl expressed in ml/min?

I expect CrCl is in ml/min here, i.e., a CrCl of 100 ml/min would yield K_{el} of 0.0874, which probably gives you a half-life of about 8 hr.

2. Is it necessary to wait 1.5 half-lives before drawing the first vanco blood level? Define "first level"- first level after a loading dose? If so, probably not (see later).

3. If your vanco infusion is given over 2 hours instead of 1 hour, do you still need to wait a full 3 hours to account for the distribution phase before drawing a peak?

Why draw a peak any way? Vanco peaks have no real impact on outcome, and are difficult to interpret due to the issues you are pointing out here. I'd suggest either monitoring concentrations using troughs only (goal: 10-13 mg/L) or using a midpoint concentration (goal: 15-19 mg/L) to estimate AUC and hence daily dose.

Steve Ebert

On 4 Dec 1996 at 10:41:40

1. The equation $K_{el} = 0.0044 + 0.00083(Cr)$ is derived from work done in the late 70's and early 80's by Mollering using Bayesian modeling from POPULATION kinetics of Healthy adults. Therefore, clinicians must evaluate the patient in question prior to invoking a particular nomogram or equation to a specific patient. An equation I use in clinical practice to estimate the initial patient elimination rate constant is, $CL = (Vd) (K_{el})$. This equation is more patient specific in that one integrates the patient specific serum creatinine to calculate Cl. Many arguments can be posed such as aminoglycoside as well as glycopeptides clearance is not 100% proportionate to creatinine clearance; however, the equation is more individualized to the patient in question and allows for error on conservative if clearance is high (note if serum creatinine is $< 1 \text{ mg}\%$ use 1) something the other equation does not do.

2. Vancomycin has been shown to distribute via more than one compartment model (Applied Pharmacokinetics, 1992) and precise time for distribution has not been clearly established; however, this poses no problem clinically because definitive vancomycin peak levels have not been established and toxicity associated with 2hour post infusion (initiation) levels $< 60 \text{ mg/l}$ have not been substantiated. The longer you wait the better, as the sole purpose of drawing levels is to obtain patient specific pharmacokinetic parameters so you can attain desired levels. 3. One should wait at least 1hour after administration to allow for distribution of any given dose regardless of infusion time. Patients with rapid clearance are will eliminate the drug if "peak" (because it really is not a peak) is drawn too soon.

I hope this is helpful to you and hope look forward to your evaluation of the information!

Ruben Atencio R.Ph., B.C.N.S.P.

On 4 Dec 1996 at 10:42:15

1. Reference is Matzke GR, et al. 1984 Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrobial Agents and Chemotherapy*, **25**, 433-7

Creatinine clearance is expressed as ml/min.

There are many reasons why a population prediction of k (and $t_{1/2}$) may not match calculations from actual patient values.

* Population predictors such as these are based on regression of k vs CLcr in a number of patients. The are value is often not too high.

* Vancomycin concentration measurements often a problem if drawn early after an infusion

* etc, etc, etc - see standard texts for such explanations

The equation is probably as "valid" as any other similar type predictor taken from a sample of patients that may or may not be reflective of the patient you are treating.

P.S. Population predictors for a number of drugs can be found in my book (cheap advertising, eh) Murphy JE (ed). **Clinical Pharmacokinetics Pocket Reference**. American Society of Health-System Pharmacists, Inc., Bethesda, MD, 1993.

2. The usual recommendation is one to two HOURS (I assume this is what you meant) after a one hour infusion in order to avoid distribution phase when using one-compartment model approaches to analysis. P.S., the equation above is for one-compartment approaches.

3. The longer infusion time will mask more of the distribution phase. However, many still recommend waiting the hour. As long as you aren't using a short interval waiting the extra time should not be a problem and may be a benefit in insuring the infusion is actually completed.

John E. Murphy, Pharm.D.

Professor and Head, Department of Pharmacy Practice and Science

On 5 Dec 1996 at 10:28:35

Why draw a peak any way? Vanco peaks have no real impact on outcome, and are difficult to interpret due to the issues you are pointing out here. I'd suggest either monitoring concentrations using troughs only (goal: 10-13 mg/L) or using a midpoint concentration (goal: 15-19 mg/L) to estimate AUC and hence daily dose.

I generally agree with the above but have a minor philosophical quibble. IMHO the point of measuring one or more concs is to estimate clearance so that the maintenance dose rate can be individualised to achieve a specific target conc. A single conc cannot estimate an AUC. It can estimate clearance (and you can derive AUC if you wish but that is unnecessary because MDR comes directly from Clearance and Target Conc). If you have several concs then you can calculate an AUC and use that to estimate clearance.

Measuring two concs e.g. 'peak' and 'trough' allows a more precise estimate of PK parameters. The point of measuring the concs is to estimate clearance NOT because the MEASURED concs at particular times are themselves related to outcome.

Outcome should to be related to the target conc. For almost all drugs the target conc is still something of a guess but outcome for vanco may be related more closely to average steady state conc [or AUC if you wish - they are equivalent] and thus Clearance is the parameter you need to estimate to individualise dose.

If you only measure one conc then a mid-dosing interval conc will be closer to the average conc and thus more readily related to clearance. A trough conc implicitly relies more on assumptions about volume of distribution than the mid-point conc.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 5 Dec 1996 at 10:32:13

The first equation relates vancomycin elimination rate (in 1/h) to >creatinine clearance in ml/min, and originates from Figure 2 of a paper by Matzke and coworkers (Matzke et al 1984).

We have successfully utilized this equation in a pharmacy based program designed to individualize initial doses of vancomycin for patients at the Buffalo General Hospital.

The second equation requires administration of the drug and the acquisition of appropriately timed plasma concentrations. However, this approach has the obvious advantage of allowing the direct estimation of the elimination of vanco (or any other drug) in the patient. We also make use of this equation to aid in the adjustment of vanco doses to achieve desired plasma concentrations (i.e., follow-up).

The relationship of vancomycin concentrations to therapeutic effects and the pharmacoeconomic benefits and of vancomycin therapeutic drug monitoring have been questioned in the literature (Cantu et al 1994; Pryka et al 1991). However, two papers have been published which suggest that PK-based dosing has pharmacoeconomic benefits. The first paper, by Lake and Peterson in 1988, claims that PK-based initiation of vanco therapy may lead to dramatic reductions in drug acquisition costs (Lake & Peterson 1988) (this has been our experience at BGH). The second paper, which has just been published, indicates that vancomycin TDM may reduce overall therapy costs by decreasing the incidence of vancomycin nephrotoxicity (Fernandez de Gatta et al 1996).

At BGH, we obtain peak vancomycin concentrations 1 hour after the end of a 1 or 2 hour infusion of vanco (we use 2 hour infusions for patients receiving doses greater than 1g or for patients who develop red neck syndrome).

Joseph Balthasar, Ph.D., Rph

Clinical Assistant Professor, SUNY at Buffalo, Department of Pharmaceutics

Cited papers:

Cantu, T. G., Yamanaka-Yuen, N. A., Lietman, P. S. 1994 Serum vancomycin concentrations: reappraisal of their clinical value. [Review]. *Clinical Infectious Diseases* **18**, 533-43

Hernandez de Gatta, M. M., Calvo, M. V., Hernandez, J. M., Caballero, D., San Miguel, J. H., Dominguez-Gil, A. 1996 Cost-effectiveness analysis of serum vancomycin concentration monitoring in patients with hematologic malignancies. *Clinical Pharmacology Therapeutics*, **60**, 332-340

Lake, K. D., Peterson, C. D. 1988 Evaluation of a method for initiating vancomycin therapy: experience in 205 patients. *Pharmacotherapy*, **8**, 284-6

Matzke, G. R., McGory, R. W., Halstenson, C. E., Keane, W. F. 1984 Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrobial Agents Chemotherapy*, **25**, 433-7

Pryka, R. D., Rodvold, K. A., Erdman, S. M. 1991 An updated comparison of drug dosing methods. Part IV: Vancomycin. [Review]. *Clinical Pharmacokinetics*, **20**, 463-76

On 6 Dec 1996 at 10:34:57

I have always thought that a peak taken after the distribution phase and in the elimination phase (i.e. at least 2 h post vanco infusion) could be used with a trough to get a fairly good idea of $T_{1/2}$ elim.

Dr Les White

Department of Microbiology, Southmead Health Services NHS Trust

Bristol BS10 5NB, UK.

<http://www.ibmpcug.co.uk/~lwhite/index.html>

On 6 Dec 1996 at 10:35:31

Nick, I think we're in agreement. We obtain a single concentration midway in the dosing interval because 1) it provides some estimate of Cl; and 2) it's the most cost-effective way to obtain some useful information. Obviously more concentration points will allow for better estimates of AUC/Cl, but I doubt this helps clinically.

Steve Ebert

On 8 Dec 1996 at 18:32:19

I have always thought that a peak taken after the distribution phase and in the elimination phase (i.e. at least 2 h post vanco infusion) could be used with a trough to get a fairly good idea of $T_{1/2}$ elim.

That is correct. And with a little bit of extra work you can estimate what you really need to know to adjust dosing i.e. the clearance.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019,
Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>



4

1997

Adjusted weight-based dosing for LMWHs

On 23 Jun 1997 at 12:04:11

I have a therapeutic dilemma for which I can find no good information.

Our hospital has begun using dalteparin both for **DVT** prophylaxis following orthoped surgery and for the initial treatment of an existing DVT. We have recently added enoxeparin to trial for DVT prophylaxis following knee prosthesis surgery.

I am concerned about using a straightforward 100 U/kg (for dalteparin) bid schedule for treatment of established DVT. In an obese patient (and this has recently been a real case) weight-based dosing results in a calculated dose that seems very high to me. My concern involves the volume of distribution of this drug. My thinking is that an obese patient would not have a proportionately higher volume of distribution but a dose calculated strictly by kilogram of real body weight would result in a huge dose (in the case at hand 15000 units bid).

I cannot find **any** good info on the partition/distribution of dalteparin or any other **LMWH**.

If someone is heavy and well-muscled then I would expect a proportionately greater vascular volume, which is the volume these agents appear to distribute to. However, if someone's greater weight is due to lipid tissue, then I would not, and a straightforward unit/kg dose would, I'm afraid, result in dangerous over-coagulation.

I haven't gotten very useful info from the manufacturer, just that the V_d is between 40-60 mL/kg. The range for V_d that I've found in the literature for dalteparin is 3-11 L.

Bottom line--should dalteparin (and other LMWHs) be dosed based on ideal/lean body mass?

Randy Trinkle, BScPharm, BA

Dept. of Pharmacy, Dawson Creek & District Hospital, Dawson Creek, BC

On 25 Jun 1997 at 10:29:39

We have just performed a study at our hospital looking at the pharmacokinetics of dalteparin in obese and normal weight individuals. The study was undertaken by one of our pharmacists (Julie Yee) in conjunction with myself. We are about to submit for publication, but here are a few interim findings.

I have a therapeutic dilemma for which I can find no good information.

So did we...

I am concerned about using a straightforward 100 U/kg (for dalteparin) bid schedule for treatment of established DVT. In an obese patient (and this has recently been a real case) weight-based dosing results in a calculated dose that seems very high to me. My concern involves the volume of distribution of this drug. My thinking is that an obese patient would not have a proportionately higher volume of distribution but a dose calculated strictly by kilogram of real body weight would result in a huge dose (in the case at hand 15000 units bid).

Our recommendations for dosing dalteparin, prior to our study, appear similar to yours (200 iu/kg sc once daily [DVT] or 120 iu/kg sc bid [massive DVT or PE]). Given this an average patient, 70kg, would receive either 14000 iu or 16800 iu daily.

I cannot find *any* good info on the partition/distribution of dalteparin or any other LMWH.

Neither could we.

I haven't gotten very useful info from the manufacturer, just that the Vd is between 40-60 mL/kg. The range for Vd that I've found in the literature for dalteparin is 3-11 L.

This is about what we found in the literature.

Bottom line--should dalteparin (and other LMWHs) be dosed based on ideal/lean body mass?

The answer is not all that clear. To date we believe that the risk of bleeding seems to be related to the peak concentration, and hence Vd would be important. Some obese patients that we have treated with high doses (200 iu/kg/d) have had minor bleeding complications. However the trough is also important to maintain clinical effect, and hence Cl is important. In our study Vd correlated poorly with lean body weight {as determined by: $LBW (kg) = (height (cm) - 150 cm) * 0.9 + 45 kg [+ 5 kg(Male)]$ } with an r2 of 0.05. Vd correlated better with weight adjusted body weight r2=0.56 and total body weight r2=0.52 (total body weight ranged from 55 to 155 kg). (Weight adjusted body weight was determined as $LBW + 40\%$ of the difference of total body weight and LBW.) Obviously given the moderate r2 not all obese patients had large Vds and therefore there is some risk of bleeding when obese individuals are dosed based on their total body weight.

We currently recommend either:

1. Dose on total body weight up to a patient weight of 90 kg. Heavier patients are dosed as if they weighed 90kg (maxm dose/day is therefore either 18000 iu or 21600 iu), or
2. Dose on weight adjusted body weight (this isn't popular with the house staff!).

Steve Duffull

Dept of Clinical Pharmacology, Christchurch Hospital, Private Bag 4710, CHCH, New Zealand

Adsorption of Lipophilic Drug to Polycarbonate Membrane

On 19 Jun 1997 at 13:29:34

I have been evaluating drug absorption by using Caco-2 cell monolayer. In the case of high lipophilic compound, I cannot often reject the influence of adsorption of drug to the polycarbonate membrane which supports Caco-2 cell monolayer. So, accurate permeability coefficient of the drug cannot be evaluated

I would appreciate if any members of PharmPK can advise me on what experimental conditions should be applied in order to avoid the drug adsorption.

Teruaki Okuda

On 23 Jun 1997 at 12:03:03

Excellent question, however, I do not have any clear answer at this point. I am also using Caco-2 as a screen in drug discovery and have essentially experienced same problem of adsorption/absorption of "grease balls" (a term used by Stella for highly lipophilic compounds) to In Vitro system (transwell and membrane). This problem severely limits the use of existing In Vitro systems (both transwell and vertical diffusion chamber system by Costar) as far as lipophilic compounds are concerned. In a two compartment system such as these, doing an additional experiment with a blank set (one without Caco-2 monolayers) also presents mathematical challenges as far as correction due to adsorption/absorption is concerned.

Some other approaches such as the use of solvents to minimize this problem can affect the integrity of the monolayers. The use of solvents for recovery from the receiver side at the end of sampling (basal or serosal side) can be tried but the amount bound to the donor side (apical of mucosal for forward transport) will still pose a problem. Again, donor samples can be taken at the beginning and at the end of experiments to calculate total recovery, but that still does not completely solve the problem.

I hope I have described the problem in detail and would appreciate more thoughts on this matter.

Gopal Krishna

On 23 Jun 1997 at 12:12:45

This is a classic problem in cell physiology. One important class of experiments that could help is characterization of the kinetics of drug adsorption to the polycarbonate membrane. A good place to start is to load the membrane (with no cells) with the drug for several fixed loading periods and several doses, then evaluate the efflux kinetics by removing the loading solution, washing quickly, and then sampling the efflux medium as frequently as practical thereafter. A kinetic model of the adsorption process can then be constructed based on the loading and efflux data. You can then fit the transport data with a model of both the polycarbonate membrane and the cell monolayer. The major difficulty you will face is that the total binding capacity of the PC membrane may not be the same with and without cells. Nevertheless, you should be able to place an upper bound on the influence of adsorption. You will want to fit the data from cell experiments and the data from no-cell experiments simultaneously. This is relatively straightforward with modern software tools.

Alternatively, you may want to test other growth surfaces, but my experience is that adsorption is never negligible, and the best approach is to include the support membrane in your PB-PK model. Analysis is always cheaper than more experiments. Indeed, this is one of the principal motivations for moving to complex kinetic models.

Robert D. Phair, Ph.D.

BioInformatics Services

<http://webcom.com/rphair>

Altered Pharmacokinetics by Solid Tumor

On 6 May 1997 at 11:53:11

We are evaluating alterations in pharmacokinetics of the anticancer drug when co-administered with chemo-sensitizers for overcoming P-glycoprotein mediated multi-drug resistance in solid tumors. As controls, we are using normal (tumor-free), and MDR knock-out mice. It is likely that the tumor itself can alter anticancer drug PK. If anybody in this group has experience in this area (alteration of PK caused by tumors), their input into the design of such experiments would be most welcome and looked forward to.

Regards,

Rajesh Krishna

BC Cancer Agency

On 12 May 1997 at 15:55:39

Dear Dr. Krishna:

We have been studying and documenting the effect of modulators on the PK of 5-FU in solid tumors (especially breast and colon in humans), and in several rat.

Let me begin by referring you to a paper we presented in 1995 at the AACR meeting entitled: "Pharmacokinetic Guidance of Drug Modulation: Initial studies with 5-fluorouracil" (#2141). We have a number of such studies, which we hope to publish shortly in full detail.

The main thrust of our approach is the use of noninvasive methods (NMR spectroscopy and nuclear imaging) to monitor drug pharmacokinetics at their target sites, rather than inferring what might happen based on blood data. The latter do not yield reliable information on the time course of drugs at their target sites, and we had shown (*J. Pharm. Sci.* **53**:873-877, 1986) that inter-animal variations (and obviously, inter-patient variations) will

cover subtle changes unless the same individual can be used as his/her own control. Hence, noninvasive methods are absolutely required.

Professor Walter Wolf, Ph.D.

Director, Pharmacokinetic Imaging Program, Department of Pharmaceutical Sciences,
University of Southern California, 1985 Zonal Ave., Los Angeles, CA 90033

|

On 12 May 1997 15:56:52 -0500

A few years ago I did some studies on etoposide in children with Cyclosporin A as a modifier of PGP, and found significant changes in clearance. I gather this is a fairly well described effect. I am unclear why you think tumors in mice might be altering drug PK themselves, unless you are allowing them to reach enormous proportions.

Stephen Lowis

Department of Paediatric Oncology, Bristol Royal Hospital for Sick Children

On 13 May 1997 at 11:22:18

Stephen:

Thanks for your note. Yes, it is a well described effect that inhibitors or more appropriately, modulators of PGP alter significantly the anticancer drug PK, particularly clearance, when co-administered for MDR reversal. However, it is possible that the tumor by itself can alter the PK of the anticancer drug (healthy vs tumor bearing animals) by altering drug metabolism. We are studying the effects of PSC 833 on doxorubicin PK and the possible effects of PSC 833 on the metabolites of DOX in solid tumor bearing experimental animals (~100-200 mg tumors) - and would need to delineate the effects of the tumor itself (effects of the tumor vasculature, angiogenesis, microvascular environment on drug uptake and disposition as well as to address the issue of metabolism in tumors).

Rajesh Krishna

Aminoglycoside Dosing in Critical Care

On 7 Nov 1997 at 11:27:50

I work in a multidisciplinary ICU and I was wondering if anyone has heard of software to aid management of aminoglycoside dosing and dose interval in critically ill patients...taking into account their level of renal dysfunction etc. We normally use a once-daily dose regime adjusted according to trough levels. Also is anyone aware of specific data on the pharmacokinetics of gentamicin in this patient population (ie sepsis etc)

Dr. A. Ferguson

On 11 Nov 1997 at 13:28:02

You may consider trying Adapt II or USC Pak software. The former will require more programming experience. There is a website of Adapt II (Biomedical Simulations Resource - Univ of CA - LA). Information about USC Pak can be obtained from Roger Jellife. There are other programs with less versatility such as the Abbott Program, but I have not used this. If you plan to use a program for dosing - one capable of Bayesian estimation would be best. With Bayesian estimation, obtain serum concentrations about 1.5 to 2.5 times the expected half-life.

Trough levels are not the best for once daily dosing. If dosed correctly, the aminoglycoside concentration should be not-detectable at the trough.

David Nix

On 18 Nov 1997 at 13:42:11

There are several software packages that are designed to be helpful in aminoglycoside dosing in critically ill patients. The Abbottbase one is good, and also the MW/Pharm software from Groningen, the Netherlands, and OPT, from Glasgow. Our own USC*PACK software has been around for the longest of any software package I know, and is specifi-

cally designed to model the behavior of AG's and other drugs so that the pk model of the drug can keep up with rapid changes in a patient's renal function from dose to dose, for example, and also with changing body weight from dose to dose. CCr can be computed from a pair of serum creatinine samples and age, gender, height, and weight, so that serum creatinine can be changing widely from sample to sample, and the model can keep up with these changes.

There are population AG models for general medical patients, ICU patients, otherwise healthy young patients (teens and early 20's), those with spinal cord injuries, and newborns. You can also enter and store any other PK pop model for any drug you wish, as long as it has an absorptive, a central, and (if needed) a peripheral compartment. Elimination can be specifically expressed as an increment of K_{el} per unit of CCr, with a nonrenal intercept.

These PK models use Bayesian approaches to make individual, patient-specific PK models. These can also be linked to models of diffusion into porous spherical objects such as endocardial vegetations of a stated diameter, using diffusion coefficients obtained from animal studies, to compute possible drug concentrations in its various layers, and in the center of such a vegetation, and also to simulate the contribution of the post-antibiotic effect.

The PK and the diffusion models can also be linked to models of bacterial growth and kill which can be used to evaluate the ability of a certain regimen to kill well or not under defined circumstances. These Zhi models, developed with Drs. Pascal Maire and Xavier Barbaut, use data of the rate constant for growth in the logarithmic phase and the most rapid kill rate found with in vitro studies. This can be combined with data of each patient's known or estimated MIC to then model the possible growth and kill of organisms under such defined circumstances, to better understand the ability of various regimens and serum concentration profiles to be effective or not.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA
90033

On 18 Nov 1997 at 13:44:17

In terms of software for dose individualization of A_gs and indeed many other drugs there are a number of programs available. A review by Buffington et al (Clin Pharmacokinet 1993; 25:205-216) specifically discusses this issue. In essence Bayesian methodology seems to be widely used and appears to be very useful. To my knowledge all programs that use Bayesian methods use the maximum *a posteriori* (MAP) objective function, originally described by Sheiner et al (Clin Pharmacol Ther 1979;26:294-305). Minimization of this objective function will locate the mode values of the parameters. Therefore any computer program that uses the MAP objective function and uses an accepted method of minimization of this function, eg simplex, Marquardt Levenberg (etc) will essentially yield *identical* results. A good program will also allow you to input your own prior model for a new or existing drug (which would be useful for your own patient group).

In summary therefore it shouldn't matter which software you choose that meet this criteria, and therefore choice should be based on cost, availability and backup service.

Also is anyone aware of specific data on the pharmacokinetics of gentamicin in this patient population (ie sepsis etc)

There are some publications on this already. A useful initial reference is given by: Dager (*Ann Pharmacother* 1994, **28**, 944-951).

Steve Duffull

Christchurch, New Zealand

Amiodarone Pharmacokinetics

On 1 Apr 1997 at 13:58:02

Hello, I am a Clinical Pharmacist from Greece and I would like to know more about pharmacokinetics of amiodarone (about compartment modeling, equations etc.) Furthermore I would appreciate if you inform me about software or books about clinical pharmacokinetics of amiodarone.

Stavroula Theophanous

Clinical pharmacist

On 2 Apr 1997 at 13:16:23

There is a wealth of information on the PK of amiodarone. Paul Nolan (Pharmacotherapy 1997; 17 (2 Pt 2): 65S-75S recently reviewed the PK/PD of intravenous agents for ventricular arrhythmias that lists the most recent amiodarone PK papers.

Joan Korth-Bradley

Clin PK, Wyeth-Ayerst Research

ANOVA for Comparison of Bioavailability

On 11 Dec 1997 at 14:04:56

I think it is possible to use Anova for the purpose of comparison of AUC (after log transformation) and MRT and MAT as well. Could that be confirmed and does anyone knows a textbook or an article which describes it?

Professor P. Maincent

Laboratoire de Pharmacie Galenique

On 18 Dec 1997 at 10:37:12

You can use ANOVA to compare everything. The major problem is that AUC itself as calculated by trapezoidal summation (a common approach in bioavailability/bioequivalence studies) is a biased estimate of the true AUC. Since MRT and MAT include a higher moment, they are even more biased. Thus, any conclusion you get after applying ANOVA is doubtful.

Vladimir Piotrovskij

Antimicrobial Pharmacokinetics in the Eye

On 14 Apr 1997 at 12:28:24

I am an ophthalmologist and part of my teaching responsibilities is teaching residents the pharmacokinetics, pharmacodynamics etc of antimicrobial agents (anti-bacterial, viral, fungal, etc.) as related to the eye (e.g. corneal, scleral penetration, etc.) including topical therapy, local injection, and systemic administration. Any and all help regarding a syllabus and other teaching aids would be greatly appreciated. Thank you.

Martin Mayers, MD

Director, Department of Ophthalmology, Bronx Lebanon Hospital Center, Albert Einstein College of Medicine

On 15 Apr 1997 at 16:55:10

Any bibliography should include papers by Mike Barza, MD. You should also check the textbook, *Antibiotics in Laboratory Medicine*, by Victor Lorian, ed.

Steve Ebert

On 15 Apr 1997 at 16:58:51

Although they do not address antimicrobials specifically, here some excellent extensive general reviews of ocular pharmacokinetics:

In: **Ophthalmic Drug Delivery Systems** edited by Ashim K. Mitra

Ch. 4. Ocular Pharmacokinetics/Pharmacodynamics (by Schoenwald)

Ch. 8 Mathematical Models of Ocular Drug Transport and Disposition (by Himmelstein)

In: **Pharmacology of the Eye** edited by M.L. Sears (Handbook of Experimental Pharmacology Series vol. 69)

Ch. 2 Ocular Pharmacokinetics (by Maurice and Mishima)

Paul Damian PhD, MPH

Program Coordinator, Western Region, Food Animal Residue Avoidance Databank, Dept. of Environmental Toxicology, University of California, Davis, CA 95616

On 23 Apr 1997 at 11:07:06

Suggestions for course syllabus:

A. Drug tear film kinetics

1. initial tear concentrations
2. drainage/spillage
3. tear turnover
4. systemic absorption

B. Formulation effects

1. viscosity
2. suspensions
3. ointments/gels
4. ocuserts
5. drug concentration
6. osmolarity
7. contact lenses

C. Corneal Penetration

1. 3 layers

D. Drug characteristics and ocular penetration

1. molecular size
2. water solubility
3. protein binding
4. susceptibility to active transport processes

E. Periocular admin

1. Subconjunctival inj
2. Subtenons inj
3. Retrobulbar inj

F. Intravitreal inj

Here are excellent articles you may find helpful:

Timothy S. Lesar and Richard G. Fiscella, 1985 Antimicrobial Drug Delivery to the Eye, *Drug Intelligence and Clinical Pharmacy* **19** 642

Ronald D. Schoenwald 1990 Ocular Drug Delivery, *Clin. Pharmacokinet*, **18** (4), 255-269

I just finished a course section on ocular pharmacokinetics and have many more references. The most important factors I feel should be taught to future prescribers are:

1. the cornea saturates so while 1 drop is good, 2 drops is a waste of time and money for some drugs eg. timolol
2. tear film kinetics: the eye can only hold 30 μL transiently and the tear film takes up 10 μL ----a drop contains 50 μL ----do the math! Pretty expensive to have drug on the cheek.
3. practical dosing concerns: Write on the RX to space drops by 5-15 mins. and use NLO.

Carol Noreen Carson, R.Ph.

Apparent Bioavailability in Excess of 100 Percent

On 11 Dec 1997 at 10:57:12

In analyzing some data recently, we ran across a number of test molecules which appeared to possess systemic oral bioavailability (F) substantially in excess of 100% (i.e., 150-220%). Our study design was as follows: administer a 30-min i.v. infusion on study day one, and calculate standard non-compartmental PK parameters from the resulting concentration-time data. On study day two, administer the same compound by oral gavage, in solution, and again get PK parameters from the conc.-time data. To estimate F, we used the ratio of the dose-normalized AUCs for each dosing regimen. (i.e., $\text{DNAUC}_{\text{po}}/\text{DNAUC}_{\text{iv}} * 100$).

After observing this phenomenon, we re-did several studies with one of the compounds of interest, lowering the p.o. dose such that it was identical to the i.v. dose. Each time, our apparent F was on the order of 150-180%.

We have considered several possibilities, including route-dependent enterohepatic recirculation (if absorption is rapid, the liver could see a much larger dose after po dosing, and more compound could be excreted in bile, leading to increased recirculation) and (less likely) pulmonary elimination of the compound following i.v. dosing.

Input from the group would be most appreciated. Does anyone else know of examples of compounds with apparent F this large? We can find no such references in the literature, but would appreciate any references you may have. Also, are our explanations of the phenomenon reasonable? Are there others we are missing? If so, how would one design an experiment to test the alternative hypotheses? Any input would be helpful - I look forward to reading your discussion postings on this topic.

Keith Ward

Investigator, DMPK, SmithKline Beecham Pharmaceuticals R&D, King of Prussia, PA

[Any (other) suggestion of non-linear pharmacokinetics? Saturable metabolism or saturable protein binding have the potential to distort the determination of F from AUC ratio calculations - probably in opposite directions. Non compartmental methods including F from AUC ratio become much less convenient when there is non linear kinetics. Have you performed dose ranging studies? I would recommend simultaneous fitting of IV and oral data with if appropriate non-linear (saturable) components. Enterohepatic recycling etc. will also make the 'simple' non compartmental analysis invalid - db]

On 12 Dec 1997 at 15:20:28

I think David Bourne's comments are very good. The only other thing I would suggest is another way of modeling the data. For example, you might make an iterative Bayesian and also an NPEM model, in which both regimens can be combined into a single consecutive regimen. You can also get F from such a mixed IV-PO regimen with this software.

In addition to the basic linear model having an absorptive, central, and (if needed) a peripheral compartment, we are now starting to make nonlinear and larger NPEM models using the Cray T3E at the San Diego Supercomputer Center. There you can make your model by typing the ODE's, etc, and running it.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA 90033

[Roger has added the dimension of population analysis along with simultaneous iv/po modeling. The model would need to 'also' include a nonlinear component. Modeling individual subject data may not require a Cray - db]

On 12 Dec 1997 15:42:04

I recall that F values greater than 100% also have been seen with oral administration of ethanol if the rate of administration is rapid enough.

Bruce Charles, PhD

School of Pharmacy, The University of Queensland, Brisbane, Qld, Australia 4072

On 12 Dec 1997 12:46:19

isn't it possible that there is a new metabolite, which is only built following the peroral route of administration, and that this metabolite interferes with the analytic ?

Ralph Quadflieg

Pharmazeutische Technologie und Biopharmazie, Universitaet Bonn, An der Immenburg
4, 53121 Bonn

On Fri, 12 Dec 1997 09:49:09

I agree with David's suggestion to think of non-linearities in first-pass extraction after oral administration. If the rate of absorption after the oral dose is faster than the IV rate of input and the drug has saturable elimination then the AUC after the oral dose can be greater than after IV. This has caused much confusion from the naive interpreters of AUC when comparing IV and oral doses of ethanol.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019,
Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.htm>

On 15 Dec 1997 at 10:49:45

Another way to increase the oral AUC in the experiment described (one iv dose and oral dosing the next day) is to inhibit metabolism with the exposure on the first day. Dichloroacetate, for instance, is known to inhibit its own metabolism following a single dose to humans. I think that is described in Curry, S. H., Lorenz, A., Chu, P., Limacher, M. and Stacpoole, P.W. (1991). Disposition and pharmacodynamics of dichloroacetate (DCA) and oxalate following oral DCA doses *Biopharm. Drug Disp.* **12**, 375-390.

Obviously there are many experiments that would easily check this hypothesis, like reversing the order of dosing or only using naive animals.

Hugh Barton

PBPK Modeling, ICF Kaiser

On 15 Dec 1997 at 10:50:00

I agree with some hypothesis about enterohepatic recirculation, but I think that maybe you need to consider changes in half-lives and in MTR. You do not specify if they change, but modelling combined IV-PO could be an interesting way to consider.

One more thing: All population came from same sex?

Carlos Ramos Mundo MS, MEXICO.

On 16 Dec 1997 at 10:54:54

There is one other thought about how this may have occurred. Years ago when we were doing our curve fitting we noticed that occasionally we calculated a negative mean residence time when we used a polyexponential to fit our blood level curve. Graphically it looked like we had a good fit (Figure 1 in the reference listed below), however, when we plotted our curve beyond our last data point, we noticed the curve did not asymptotically approach zero from above the axis, but dipped below and then came back up to zero (Figure 2). This can happen if the pre-exponential coefficient (A) of the smallest exponential coefficient (alpha) becomes negative. If the curve fitting program does not appropriately parameterize the values being fit, you can have those types of results. See our short communication in *Biopharm & Drug Disposition* 9:579-586 (1988).

Ronald A. Herman, Ph.D.

On 18 Dec 1997 at 10:38:13

It would help much if you would give more details on your experimental settings including sampling scheme and the limit of quantification of your assay method. Also important is how did you calculate AUCs. The only examples of abnormally high F I know were not related to any pharmacokinetics, but rather to experimental methods and data analysis.

Vladimir Piotrovskij

On 18 Dec 1997 at 10:40:40

Dear Keith

You comment:

In analyzing some data recently, we ran across a number of test molecules which appeared to possess systemic oral bioavailability (F) substantially in excess of 100% (i.e., 150-220%). Our study design was as follows: administer a 30-min i.v. infusion on study day one, and calculate standard noncompartmental PK parameters from the resulting concentration-time data.

Have you considered adsorption or absorption of the substance onto/into the infusion tubing. Adsorption can be important for biological molecules (eg proteins like insulin), and absorption can be important for lipophilic compounds. This would result in a lower dose being administered and hence an apparent lower F from iv than PO.

After observing this phenomenon, we re-did several studies with one of the compounds of interest, lowering the p.o. dose such that it was identical to the i.v. dose. Each time, our apparent F was on the order of 150-180%.

This is the right sort of order of magnitude for sorption interactions.

Steve Duffull

Christchurch, New Zealand

Apparent Volume of Distribution with One Capacity Limited Process

On 6 Aug 1997 at 11:13:40

Recently, I have come across a situation involving nonlinear clearance of a drug in which the volume of distribution is not well defined. Any clarification will be greatly appreciated.

The rate of elimination for a drug eliminated by only one capacity-limited process is given by:

$$\frac{dC_p}{dt} = \frac{V_{max} \cdot C_p}{K_m + C_p}$$

$$\text{or } \frac{dX_e}{dt} = \frac{V_{max} \cdot V \cdot C_p}{K_m + C_p}$$

It is apparent from this relationship that the Cls of a drug is dependent on V. The question then is: What is the definition of V? Is it the volume of distribution in the central compartment, volume of distribution during the terminal phase or some other combination of terms especially if multi-compartment processes are involved?

Roseline Pardue

On 11 Aug 1997 at 13:54:48

It is apparent from this relationship that the Cls of a drug is dependent on V.

If you choose this parameterization the volume you want is the central compartment volume. Most people who have used this kind of model in PK have preferred to define V_{max} in units of mass/time rather than conc/time as you have done.

If you define X as the amount of drug in the central compartment and V_{max} in mass/time units then:

$$\frac{dX}{dt} = \left(RateIn - \frac{Vmax \cdot Cp}{Km + Cp} \right)$$

then define Cp as X/V you can write:

$$\frac{dCp}{dt} = \left(RateIn - \frac{Vmax \cdot Cp}{Km + Cp} \right) / V$$

In this case it is obvious that V must refer to the central compartment volume because the DE is describing the central compartment rates.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 11 Aug 1997 at 13:58:30

I have tried to clarify this problem on a recent paper: "Clearance, Turnover Time, and Volume of Distribution" published by *Pharmacological Research*, **35**, 189-193, 1997.

Aldo Rescigno

On 13 Aug 1997 at 10:03:43

Your post reminds me of a productive debate that I had with Nick Holford in a thread that is still available on the BIS Computational Biology Forum at

<http://www.BioInformaticsServices.com/rphair/bis/resources/forum>.

The thread is called "Compartmental model parameterisation" and deals primarily with the relative merits of Clearances and rate constants for characterization of PK systems. You might find it informative. I know I learned a lot from Nick in the course of that discussion.

To answer your question, though, appears to require only that you think about the source of the V in your equation. You start with dCp/dt on the left hand side, where Cp is the

plasma concentration of the drug. You set this equal to the Michaelis-Menten capacity-limited elimination, $V_m \times C_p / (K_m + C_p)$.

You do not give a definition for X_e , and I think you might find a clear answer to your question by being precise in your definitions. One way to approach this is to recognize that mass is conserved, so $V_p(dC_p/dt)$ elimination flux (units of , say, $\mu\text{mole}/\text{hour}$), where V_p is the plasma volume. The elimination clearance, CL_e , is then the ratio of this flux to the plasma concentration:

$$CL_e = (\text{Elimination Flux})/C_p$$

Your post implies that the left hand side of your second equation represents the CL_e , so

$$\frac{dX_e}{dt}/C_p = CL_e = (\text{Elimination Flux})/C_p = V_p \cdot \frac{dC_p}{dt}/C_p = \frac{V_p \cdot V_m}{K_m + C_p}$$

Consequently, the V in your equations appears to be equal to V_p , the plasma volume.

Robert D. Phair, Ph.D.

BioInformatics Services

<http://www.bioinformaticsservices.com>

AUC_t Greater than AUC_{infinity}

On 7 Apr 1997 at 22:04:00

A question for anyone with the patience for a newcomer to pk/pd. In a standard study comparing blood levels of a brand name and generic drug, is it possible to get values for $\text{auc}_{\text{infinity}}$ that are less than the values obtained for auc_t ?

Bill McNaughton

On 9 Apr 1997 at 12:47:11

No, it is not possible to have values of $\text{AUC}(0\text{-inf}) < \text{AUC}(0\text{-}t)$.

$\text{AUC}(0\text{-inf}) = \text{AUC}(0\text{-}t^*) + C^*/k_e$ where C^* is the last measured concentration at time (t^*) and k_e is the terminal elimination rate constant. My guess is that k_e was entered as a negative value. k_e is determined from the slope of the terminal linear portion of the LN (Conc) vs time curve. The slope will always be negative since concentrations are declining. It is sometimes an art in determining which points to use in determining the terminal slope. The terminal elimination rate constant term implies decreasing concentrations and therefore the negative is not required (k_e is always positive, $-(\text{slope})$)

David Nix

On 9 Apr 1997 at 12:47:30

The partial area under the curve (AUC_t) is the area from $t=0$ to $t=t$. $\text{AUC}_{\text{infinity}}$ is the area from $t=0$ to $t=\text{infinity}$. Since there can be no negative contributions to the AUC at any time after t (or before t , for that matter) $\text{AUC}_{\text{infinity}}$ is always greater than AUC_t.

Of course, one might make the mistake of plotting the data on linear, instead of semi-log, paper, and then extrapolating a fast (apparently terminal) exponential through the horizontal axis and thus appear to start accumulating negative contributions to $\text{AUC}_{\text{infinity}}$. It

should be clear however that the real blood concentration can never be a negative number, so the AUC can only increase as the integration is carried out toward infinity.

Bob Phair, Ph.D.

BioInformatics Services

<http://www.webcom.com/rphair>

On 9 Apr 1997 at 12:47:45

It is possible and is also incorrect. Check your rules for determining half life and extrapolation to infinity.

Steve Bramer

On 9 Apr 1997 at 12:48:37

You have raised a very interesting point. I too have come across occasions when AUC(inf) values were lower than AUC(t). We need to clearly define the AUC(t) values. Is this the AUC up to the last validated measurable plasma concentration [C(last), I call the corresponding AUC, AUC(last)] or is it the AUC up to the last point which is below the limit of quantitation [considered zero in AUC calculation] which I call AUC(all).

It would be highly unusual to have AUC(last) larger than AUC(inf). However, it is possible for AUC(all) to be larger than AUC(inf). This occurs when time span is large between the last validated plasma concentration in the disposition phase and the next sample with concentration below quantitation.

The above is difficult to explain in words. You will get a better appreciation if you draw a figure. I would be happy to fax you one.

As a note, I don't particularly like to use AUC(inf) for drugs with short half lives ($T_{1/2} = < 12$ hours). The reason for this is one single concentration [C(last)] in the beta phase has a high influence on the AUC(inf) values since $AUC(inf) = AUC(last) + [C(last)/(0.693/T_{1/2})]$. It is simply better to determine AUC(last) with most sensitive assay and taking blood samples for a time period exceeding $4 * T_{1/2}$.

AUC(inf) is more appropriate for drugs with long $T_{1/2}$ (>24 hours) provided that the ratio of AUC(last)/AUC(inf) exceeds) 0.80.

I hope the above will stimulate discussion on AUC determinations since this parameter is critical in bioavailability assessment.

Aziz Karim

On 10 Apr 1997 at 13:31:57

Bill,

While it is true that the actual AUC(inf) cannot be less than the actual AUC(t), it is possible to calculate an AUC(t) value that is larger than the calculated AUC(inf) value depending on the sampling scheme relative to the half-life, as Dr. Karim discussed.

As a follow-up to his note on the potential inaccuracies of the calculation of AUC(inf) for compounds with short half-lives, if variability of the low concentrations is an issue, AUC(inf) could be extrapolated from a predicted C(last) at the time of the last measurable concentration based on the half-life (beta) regression. With this method, the data used to estimate half-life would be weighted equally in the extrapolation to infinity. This method assumes that there are adequate data to estimate the half-life relatively accurately.

Jo Cato

On 10 Apr 1997 at 13:34:03

AUC_t cannot exceed AUC_{infinity} since $AUC_{inf} = AUC_t + C(t)/\lambda_z$. However, it is possible to get $AUC_{infinity} < AUC_{(0-24)}$ or $AUC_{(0-48)}$, AUC_{Call}, etc.

If your sampling points in the terminal phase are far apart and your last sample is BQL (and your program treats BQL samples as zero), then λ_z may be larger than the slope connecting the last 2 points which are C(t) and 0. This will cause AUC_{inf} to be less than AUC₀₋₂₄ because in the calculation of AUC_{inf}, zero is not used.

Brinda K Tammara

Otsuka America Pharm. Inc., Rockville, MD-20850

On 10 Apr 1997 at 13:34:26

As indicated by several replies generated from the inquiry as to whether one can get values of $AUC(0-\infty)$ which are less than $AUC(0-t)$, the answer is that in theory NO. However in practice you may come across data which suggests that this is the case. Apart from the obvious error in calculating AUCs. I assume you have used the correct formula for calculating the area of trapezoids, or as David Nix pointed out you may have used $-k_e$ rather than the absolute value of k_e to calculate $AUC(t-\infty)$. that is if you have devised your own routine for calculating the parameters. Alternatively the problem may reside in the software package you are using in that some software may calculate $AUC(0-\infty)$ either using the exponential fitting parameters or alternatively use the expected concentration at time 't-last', derived from the terminal rate constant as opposed to observed value whilst $AUC(0-t)$ have been calculated using observed values. Bit complicated but I hope it is clear.

Faruq H Noormohamed

Department of Therapeutics, Chelsea and Westminster Hospital, 369 Fulham Road, LONDON SW10 9NH

Blood flow or Perfusion

On 24 Apr 1997 at 11:10:16

I would like to pose a different question to the entire group for brainstorming and learning:

In relation to drug delivery and particularly to pharmacokinetics, what would be the definition of "Blood flow" versus "perfusion"? Are they the same? Or are they different? If different what is their relationship or interdependence?

Alfredo R. Sancho,

USC PK-Imaging Ctr., Los Angeles, CA

On 25 Apr 1997 at 11:56:57

From a clinical point of view, you could have blood flowing through a vessel which is distally obstructed and therefore have no perfusion beyond the obstruction. So, you can have blood flow without perfusion. The converse however is not possible.

Oscar Linares

On 28 Apr 1997 at 11:06:29

About the question on blood flow and perfusion it should be noted that are two different concepts. One is related to the passage of blood through a vessel, that is a necessary condition, but not sufficient to have perfusion, since an adequate pressure is needed to achieve perfusion. So both are physical terms related to cardiovascular physiology, but by no means have clinical or physiological equivalence

Fermin Valenzuela, Dept. of Pharmacology, Faculty of Medicine, Universidad Nacional Autonoma de Mexico

On 28 Apr 1997 at 11:18:27

In relation to drug delivery and particularly to pharmacokinetics, what would be the definition of "Blood flow" versus "perfusion"?

Blood flow: The movement of blood within the blood system as a direct result of cardiac output.

Perfusion: The movement of blood from the CV system into and through organs or tissues.

Are they the same? Or are they different?

They are different.

If different what is their relationship or interdependence?

Perfusion is dependent upon blood flow supplying the perfusate (blood, plasma, leukocytes, etc.) to the organ or tissue being perfused.

Louis P. Blatzheim

On 28 Apr 1997 at 11:19:04

Hi, I am very interested in these questions as I am working on a study of peripheral vascular disease using fluorescent dyes.

In relation to drug delivery, I think blood flow and perfusion can be very different. Perfusion is dependent on factors such as permeability, diffusion, and the surface area of the capillaries, in addition to the flow to the region. Blood flow would be dependent on cardiac output and heart rate, and local autonomic control of vasoconstriction.

I am now interested in whether combined pharmacokinetic information from an intravascular indicator dye and a permeable dye can give information on both flow and permeability. Any comments on this idea would be appreciated. Specifically I am working with sodium fluorescein (permeable) and indocyanine green (intravascular).

Deborah Oh

University of Illinois at Urbana-Champaign

On 28 Apr 1997 at 11:18:40

From the perspective of a cardiovascular physiologist, blood flow is well-defined. It is a measure of the volume of blood passing a given point in the circulation per unit time. It has units of, say, ml/min. When a "perfused organ" preparation is used, we mean simply that we are (or an anesthetized animal is) pumping blood into the arterial side of an organ's or tissue's vascular system.

So I would ask, when used in the context of pharmacokinetics, what are the units of "perfusion"? Or even, what is the definition of perfusion?

Oscar's point is well-taken in that some portion of a tissue may not be perfused because of an upstream obstruction, but I'd argue that that portion of the tissue is also without blood flow.

So you cannot deliver a drug (at least by a vascular route) to a tissue that receives no blood flow and is thus "unperfused".

Robert D. Phair, Ph.D.

BioInformatics Services

<http://www.webcom.com/rphair>

On 28 Apr 1997 at 11:20:41

Webster definition of perfusion: the act of pouring over or through, especially the passage of a fluid through the vessels of a specific organ.

Not being a pharmacokineticist but a radiologist working on perfusion measurement from images, I do not know the field enough to answer your question-the pharmacokinetic sense of perfusion. The concept of perfusion has become controversial, especially with the growing application of MR and CT for perfusion measurement.

Perfusion to an organ is determined by complex physiologic/anatomic processes: blood pressure, velocity, capillary morphology, capillary permeability, oxygen and nutrient demands. The definition of perfusion has varied depending on the field of interest: physiologist, radiologist, pathologists, cardiologist, etc. Perfusion in the classical physiological sense is blood circulation: it is measured by total blood flow per a unit mass or volume of

tissue (e.g. ml/min/100g). For example, a single organ such as the kidney with a single blood supply, the blood flow into the kidney is measured and divided by its mass. In this definition, blood flow may be synonymous with perfusion. But we must remember that classical perfusion measurement techniques are based on terminal deposition (microsphere) or washout (radionuclide) of tracers and hence only considering the component of blood flowing in the capillary bed. This approach excludes the blood which transits without exchanging with the organ.

This definition also should exclude physiologic blood-tissue exchange which is frequently confused with perfusion. In practice, however, the blood-tissue exchange is an important part of drug transport to an organ and very difficult to separate from overall drug transport measurements.

K. Ty Bae, MD, PhD

On 28 Apr 1997 at 11:21:45

My understanding is that perfusion relates to flow of blood to exchanging capillary beds and total blood flow is exactly that. The difference is particularly important in tissues such as the skin where there are considerable numbers of a-v shunting vessels.

Laurent Rivory

On 29 Apr 1997 at 09:55:11

There is an extensive literature on using permeable and inpermeable markers to get information on blood flow and permeability (as well as markers that enter parenchymal cells). You could start with names like Carl Goresky, Ken Zierler, and Jim Bassingthwaighte. As you might imagine it is easy to spell Jim's last name incorrectly, and I probably have done so here. You could also look at an old book by Niels Lassen and William Perl titled *Tracer Kinetic Methods in Medical Physiology*, Raven, 1979.

Regarding your distinction between blood flow and perfusion, I would argue you are using perfusion to signify extraction. I personally don't think perfusion is well-defined, but if it were it ought to have the same units as blood flow and might represent the fraction of cardiac output that is delivered to a particular tissue or organ.

I suspect, however, that this debate is going to generate more heat than light.

Robert D. Phair, Ph.D.

BioInformatics Services

<http://www.webcom.com/rphair>

On 29 Apr 1997 at 09:55:27

Dr TyBae says, in part:

Perfusion to an organ is determined by complex physiologic/anatomic processes: blood pressure, velocity, capillary morphology, capillary permeability, oxygen and nutrient demands. The definition of perfusion has varied depending on the field of interest: physiologist, radiologist, pathologists, cardiologist, etc. Perfusion in the classical physiological sense is blood circulation: it is measured by total blood flow per a unit mass or volume of tissue (e.g. ml/min/100g). For example, a single organ such as the kidney with a single blood supply, the blood flow into the kidney is measured and divided by its mass. In this definition, blood flow may be synonymous with perfusion. But we must remember that classical perfusion measurement techniques are based on terminal deposition (microsphere) or washout (radionuclide) of tracers and hence only considering the component of blood flowing in the capillary bed. This approach excludes the blood which transits without exchanging with the organ. This definition also should exclude physiologic blood-tissue exchange which is frequently confused with perfusion. In practice, however, the blood-tissue exchange is an important part of drug transport to an organ and very difficult to separate from overall drug transport measurements.

Two points can be made here. First, if perfusion is defined as "organ blood flow", then it's determined by arterial pressure, venous pressure, and the organ's vascular resistance. Resistance is usually dominated by the arterioles. Under this definition, perfusion is independent of velocity, capillary morphology, capillary permeability, and oxygen and nutrient demands. Second, classical perfusion measurement techniques are not entirely limited to microspheres, or radionuclide washout. It would be reasonable to agree that perfusion could also be measured by a flowmeter on the incoming artery.

So, it seems to me that perfusion is organ blood flow, perhaps corrected for a-v shunts as was pointed out by another post in this thread. As such it has little (I would say nothing) to do with blood-tissue exchange. This may be what Dr TyBae means by, "This definition also should exclude physiologic blood-tissue exchange which is frequently confused with perfusion." Organ blood flow or perfusion is, of course, a crucial determinant of drug delivery to the capillary beds. Once there, however, the drug's chemical properties and the available transport mechanisms will determine its extraction. At a very detailed level, one must

also be concerned with the issues of flow-limitation, but once in the interstitial space, cellular uptake, too, is independent of blood flow. Thus Dr TyBae is correct that blood tissue exchange is an important element of drug delivery, but mixing the concepts of perfusion and extraction can only lead to unending semantic wars, as is apparently the case in radiological usage currently.

Robert D. Phair, Ph.D.

BioInformatics Services

<http://www.webcom.com/rphair>

Blood Volume

On 9 Oct 1997 at 10:39:32

Would anyone be able to supply me with a formula (and hopefully a reference) for determining blood volume> Perhaps based on height and weight/ body surface area, lean body mass? Any help is greatly appreciated. Thanks in advance.

Bob Dunn

On 09 Oct 1997 20:15:50

I usually use 65-70 ml/kg but it depends on the species

Andrew Fowlie

On 10 Oct 1997 08:14:33

You will find blood volume (man: 7.5% of body mass) and other physiological parameters for man, rodents, rabbit, dog, and monkey in: DAVIES,B. and T.MORRIS: Physiological parameters in laboratory animals and humans, Pharm. Res. 10, 1093-1095, 1993.

Hans Markus

On 10 Oct 1997 10:31:06

The general rule is 8% of body weight. Thus 80 mL of blood per kg body weight

Rob Hunter

On 20 Oct 1997 at 12:26:06

I've found the Geigy Scientific Tables (were published by Ciba Geigy before the merger; now?) useful for human blood volume as functions of the sort of parameters you mention. I think offhand it's one of the later volumes which treats the subject in some detail, with a choice of formulae and secondary references.

DuncanMFE

Calculation of F and PK/PD Modeling

On 5 Sep 1997 at 10:54:12

I would like to get your opinions on the following questions.

First one is on the calculation of relative bioavailability.

To calculate the relative bioavailability of a oral formulation in individual subject, we can use (1) the ratio of individual AUC from oral dosing to average AUC from IV dosing to a group of subjects or (2) the ratio of individual AUC from oral dosing to individual AUC from IV dosing. I call second method self-comparison method. I would like to know which method is more accurate? Any statistical or physiological justification?

Second question is on PK/PD correlation.

I would to know how to deal with PK/PD correlation problems in the situations such as plasma concentration measurement and efficacy determination on different time intervals (PK in hours and PD in days) or different dosage regimen for PK and PD (PK-single dosing and PD-multiple dosing). Your answers or suggestions for references will be greatly appreciated.

Tony Lee

On 8 Sep 1997 at 10:20:45

The topic is more complicated than is suggested in this question. There can be hardly any debate about the question which method should be used to calculate the relative (or absolute) bioavailability FOR AN INDIVIDUAL: method (2). The reason is simple: AUC comparison is based on the assumption that clearance is constant. Since clearance is, in general, a pharmacokinetic parameter with relatively high inter-individual variability, it is essential that AUC of the same individual are compared.

However, the question is more complicated if you are interested in the 'best' (unbiased) estimate of 'average' bioavailability of a group of subjects (or, in terms of population PK, a typical value of bioavailability of the population), and its variance. In this case, some assumption on the statistical distribution are necessary. In my opinion, it is both realistic and practical to assume a log normal distribution of the pharmacokinetic parameters. The calculation is easy: (a) calculate the bioavailability of each individual subject (ratio of dose-adjusted individual AUCs) (b) calculate the mean and sd of the log(base e)-transformed ratio's (c) mean bioavailability is inversed of log-mean (d) coefficient of variation (CV, expressed as fraction) is the sd of the log(base e)-transformed ratio's (e) sd of bioavailability is product of mean bioavailability and CV.

If AUCs from the same individual are not available, the aforementioned procedures don't work correctly! In this case a different approach is necessary.

Johannes H. Proost

Dept. of Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, Groningen, The Netherlands

On 9 Sep 1997 at 10:46:11

What you refer to as the "self-comparison method" is the better way to assess the bioavailability (F) of a drug in an "individual subject". The ratio of AUC_{po} / AUC_{iv} both obtained from the same individual (under all the same conditions, other that route of administration) would control for between-subject sources of variance which would have an equivalent influence on the AUCs regardless of the route of administration. Such sources of variance would include for example, the apparent distribution volume of the drug and it's rate of clearance.

The only instance this might not be true is when the error of measurement is much greater than individual differences in the post-absorptive determinants of AUC. But if that were true, the whole question of "the relative bioavailability of a oral formulation in individual subject" would be compromised. If it's not already obvious, the best method is to assess the AUC_{po} / AUC_{iv} for each individual in a group of subjects and then describe bioavailability by descriptive statistics.

By the way, there is at least one important drug for which the comparison of $AUC_{po} / AU-Civ$ is not appropriate for assessment of its bioavailability. (hint: it accounts for > 5% of the total American caloric intake).

R. Thomas Gentry, Ph.D.

Office of Collaborative Research Activities, National Institute on Alcohol Abuse and Alcoholism, Willco Bldg., Suite 400, 6000 Executive Blvd., Bethesda, MD, 20892-7003

On 15 Sep 1997 at 15:12:58

Again, the situation is more complicated than in my first answer!

My first answer to the PharmPK group was an approximation, which will be sufficiently accurate in most cases. Here is a more complete answer, with the exact solution.

The only, almost complete reference to log normal distributions can be found in:

Biostatistics in Pharmacology (volume I, pp. 544-) by AL Delaunois, LJ Martin, E Olbrich, AA Weber Pergamon Press - Oxford 1973 (ISBN 0 08 016556 7) (series 'International encyclopedia of pharmacology and therapeutics')

According to this reference, the relationship mentioned in my note to the PharmPK group is only valid for the case CV is small.

For variance, the following relationship is given in the aforementioned reference (symbols modified to text):

$$\text{var} = s^2 = \ln(1+CV^2)$$

where var is the variance of the ln-transformed data, s is the standard deviation of the ln-transformed data, and CV is the coefficient of variation ($^2 = \text{square}$)

If CV is small, var is almost equal to CV^2 .

E.g.,

if $s = 0.1$, it follows that $CV = 0.10025$,

if $s = 0.25$, then $CV = 0.25396$

if $s = 0.4$ (rather large!), $CV = 0.41655$

Note: always use 'ln', natural logarithm, base e (using logarithms with base 10 requires co factors; I don't like them, and they should be banned from the whole field of pharmacokinetics).

Johannes H. Proost

Dept. of Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, Groningen, The Netherlands

On 17 Sep 1997 at 10:57:56

About bioavailability. The fraction absorbed can also be computed directly from a mixed dosage regimen containing both IV and PO dosage in individual patient regimens. This can be done in both parametric and nonparametric population models, using iterative Bayesian and nonparametric EM software for such modeling. This avoids comparison of AUC's, obtained possibly under differing clinical circumstances, and permits it to be done in the patients of interest, in their often changing clinical circumstances.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA 90033

http://www.usc.edu/hsc/lab_apk/

Collinearity and Mixed Effect Models

On 30 Sep 1997 at 11:04:55

Does anyone have any references on what is the impact of collinearity among predictor variables in a mixed effect model (either linear or nonlinear)?

Peter L. Bonate, Ph.D.

Hoechst Marion Roussel, Clinical Pharmacokinetics, P.O. Box 9627 (F4-M3112), Kansas City, MO 64134

On 20 Oct 1997 at 12:25:52

I think that this is a good question that I would also like to see further discussion about. I have not read any literature specifically addressing the effects of collinearity in nonlinear systems. For the linear system, almost any good stats textbook will provide an adequate description.

For the linear model:

Multicollinearity

Where explanatory variables are highly correlated the following may occur:

1. Coefficients may have large standard errors, since large changes in one coefficient can be compensated for by equally large changes in another. Hence very different coefficient values may result in nearly the same sum of sq.
2. May result in product moment correlation coefficients (r or r^2 values) that are inappropriate (often constricted). For example regressing two covariates, that have significant correlation with each other, against a dependent variable, often results in higher r^2 values when each is considered alone but the resultant model will often have a lower r^2 value when both are considered together.

3. Significant rounding errors may be introduced into the system.

In terms of non linear models r^2 values are not usually considered and hence point 2 will be seen in other ways. Obviously the correlation between coefficients can be addressed prior to undertaking non-linear regression.

I don't think the mixed effect model will alter the effect of multicollinearity. I do not see how accounting for random effects will change the influence of multicollinearity (or perhaps "multi-co-non-linearity"). However, it seems probable that estimation of the random effect component will be in error if there is significant correlation between the covariates. There will obviously, also be error in the coefficients that describe these covariates.

I hope these comments are useful. I look forward to the comments of others.

Steve Duffull

On 21 Oct 1997 at 10:10:07

Even when documented effect of collinearity in nonlinear models is quite a few, there is a point of view that may help:

"Collinearity in nonlinear models could cause that parameters estimates in iterative methods (like Marquardt), present an "apparent" low ss, however it is possible that ss surface is deformed by covariates, then predictors could be far from real values. Maybe a procedure to try to avoid this effect is to use partial correlation and other analytical procedure such as quadratical or transform covariates to get ride of collinearity"

As far as we concern, we try to several transformations to avoid collinearity, but the final effect is a strong tendency in residuals, at least in data that shows two- or one- compartment behavior. The effect is more evident when you try with flip-flop data.

Nowadays, we are trying with dud's method and it presents an error in simulation approximation of 5 -12 % in final estimates. Hopefully we will try this method with real data in next week.

It is important to point out that the main idea is to get a procedure to reduce collinearity effects, even when is probably to derive in handling experimental factors.

Carlos Ramos Mundo. M.S.

Compartmental Modeling and Population PK

On 20 Oct 1997 at 12:26:55

Lately, there has been a lot of traffic in this discussion group about compartmental models, i.e., how multi-exponential fitting relates to compartmental models, the advantages of compartmental modeling, its disadvantages, etc.

In general, compartmental models get a lot of bad press and kineticists are reluctant to use them in drug development. People talk about the issue of the number of compartments, non-identifiability, trying to interpret parameter constants, etc and because of this, most pharmacokinetic analyses in drug development center on non-compartmental analyses assuming that non-compartmental models are model-independent (a wrong assumption).

Population pharmacokinetics has the same disadvantages of classical compartmental models (assumption of a specific model which may be non-identifiability) in addition to others that are often not discussed (collinearity among predictor variables being the most egregious). Yet no one questions a pop pk analysis to the same extent as classical compartmental modeling, even though pop pk analyses often have fewer samples per subject albeit with greater numbers of subjects. It is as though having greater numbers of subjects gives a pop pk model greater validity than doing compartmental analysis on a data-rich data set with fewer subjects.

Any comments on this? Just food for thought for the AAPS focus group next month.

Peter L. Bonate, Ph.D.

Hoechst Marion Roussel, Clinical Pharmacokinetics, P.O. Box 9627 (F4-M3112), Kansas City, MO 64134

On 21 Oct 1997 at 10:09:53

I really don't think there is much difference in philosophy among "classic" (multi-sampling) and population (sparse sampling) approaches in the caution that needs to be ex-

exercised against applying the "wrong" model (with or without covariates). If the compartmental model is inadequate, the intrapatient variance (SIGMA) estimated in parametric population modeling is greatly inflated (although other sources obviously contribute such as assay error, inaccurate dosing and sampling times, etc). For ours, when we do population modeling we are very aware of the pitfalls of implementing an inappropriate model, e.g. when there are a total of 2 or 3 samples taken at different post-dosing times perhaps over several dosing intervals. We usually screen 1 and 2 (or, occasionally, 3) compartment models and examine weighted residuals and parameter estimates and SEs of estimation. The latter is important when looking at possible multicollinearity of covariates. If an appropriate model-building strategy is used, e.g. individual screening of covariates, stepwise addition of "significant" ($P < 0.01$) factors followed by backwards elimination, then the possibility of variables "masking" one another is greatly reduced (but it can still happen). We have no problem with the use of compartment models, as compared with other representations of the data since they do have a degree of physiological relevance. In NONMEM estimates of the more relevant primary parameters of interest (clearances and volumes) can be sought directly by reparameterising those dreadful compartmental rate constants.

Bruce CHARLES, PhD

School of Pharmacy, The University of Queensland, Brisbane, Qld, Australia 4072

On 21 Oct 1997 at 10:11:36

In general, compartmental models get a lot of bad press and kineticists are reluctant to use them in drug development.

Population pharmacokinetics has the same disadvantages of classical compartmental models (assumption of a specific model which may be non-identifiability) in addition to others that are often not discussed (collinearity among predictor variables being the most egregious). Yet no one questions a pop pk analysis to the same extent

IMHO those who discard compartmental approaches have a different philosophy of where the real problems lie. It seems to me that they think there is some kind of "true" and "objective" answer uncontaminated by assumptions which can be achieved by invoking the "non-compartmental" mantra.

Population modellers have sidestepped/overcome this particular intellectual hurdle and seem to find additional insight from applying models (whether individual or population) and can live with the assumptions and uncertainties.

I can assure you that the population modelers I know frequently discuss the problems with the technology and are continually seeking better solutions. From a limited perspective as an author, referee and editor of papers dealing with population models I would say that population models come in for a lot of peer criticism during the manuscript review process. This is valuable for authors and referees but readers of published articles may not appreciate what has gone on before the MS appears in print.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.htm>

Creatinine Clearance and IBW in Small Patients

On 25 Feb 1997 at 12:35:54

I am always running into non-pediatric patients, usually elderly, but could be any age group, who do not fit (naturally!) the standard 5 feet tall + scenario OR have **ABW** (actual body weight) that are <45.5 kg or 50 kg for male or female, respectively. Someone recently (and of course I can't find the formula!) had a CrCl calculation incorporating serum albumin for patients with low values, but this is NOT the patient population I am looking for (though some may fit into this category). Any suggestions?

Marc Sempregon, RPh

DHMC, Lebanon, NH 03756

On 26 Feb 1997 at 16:20:32

At least part of the problem you appear to be having may be helped by using a suitable model for size. This may help particularly with smaller than average people e.g.

$$CL = CL_{std} \times (Wt/Wt_{std})^{3/4}$$

where CL_{std} is the CL in a 'standard' size person with weight Wt_{std}. You can use total body weight, ideal body weight.

See this for details:

Holford NHG. 1996 A size standard for pharmacokinetics. *Clin Pharmacokin*, **30**, 329-332

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

Determining CYP_{3A4} activity *in vitro*

On 3 Sep 1997 at 10:15:09

We are looking for an index reaction to determine the activity of cytochrome P₄₅₀ isoform 3A_{3/4} in human liver microsomes (in vitro). Currently we used dextromethorfan N-demethylase as index reaction for CYP_{3A4}. However, a current article suggests that also CYP_{2E1} is involved in the formation of 3-methoxymorphinan and therefore dextromethorfan N-demethylase is not a good index reaction.

Does anybody have a GOOD suggestion how to determine the CYP_{3A4} activity in vitro?

Alex Hemeryck

Pharmacist, Heymans Institute of Pharmacology, University of Ghent, Medical School

De Pintelaan 185, B-9000 Ghent

On 4 Sep 1997 at 10:21:03

Hydroxylation of testosterone to 6-hydroxytestosterone is commonly used as an index reaction for CYP_{3A4/5} in human liver microsomes. Also, recently it has been reported that alprazolam 4-hydroxylation is predominantly metabolized by CYP_{3A3/4}. Erythromycin N-demethylation and midazolam hydroxylation are other common probe reactions. Nipeditpine is another substrate for CYP_{3A4}. Following references might give more information.

Alprazolam metabolism in vitro: studies of human, monkey, mouse and rat liver microsomes, von Moltke, LL, Greenblatt, DJ, Harmatz, JS, Shader, RI; *Pharmacology*, 1993, **47**, 268-276

Characterization of six in vitro reactions mediated by human cytochrome P₄₅₀: Application to the testing of cytochrome P₄₅₀-directed antibodies, schmider, J.; Greenblatt DJ,

von Moltke, LL; Harmatz JS, Duan Sx, Karsov D, Shader RI, *Pharmacology*, 1996, **52**, 125-134

Cytochrome P₄₅₀ isoform inhibitors as a tool for the investigation of metabolic reactions catalyzed by human liver microsomes, Bourrie M, Meunier V, Berger Y, Fabre G, *J. Pharm. Exp. Ther.* 1996, **277**, 321-332

Also, you can get some information at the Glaxo Wellcome drug metabolism guide on the web at <http://www.glaxowellcome.co.uk/science/drugmet/index.html>

Chandrani Gunaratna, Ph.D.

Senior Research Chemist, Bioanalytical Systems, 2701 Kent Avenue, West Lafayette, IN 47906

On 4 Sep 1997 at 10:22:10

I think you should read the article of Buening et al. "Activation and inhibition of benzo(a)pyrene and aflatoxine B₁ metabolism in human liver microsomes" *Cancer research* 1981 **41**: 67-72

Or maybe the article of de Waiziers et al. "Cytochrome P₄₅₀ isoenzymes, epoxide hydroxylase and glutathion transferase in rat and human hepatic and extrahepatic tissues" *J Pharmacol Exp Ther* 1990 **253**: 387-394

As far as I know the Cytochrome P₄₅₀ IIIA₄ activity is correlated well with the Erythromycin demethylase (ED) activity ($r=0.84$, $p=0.001$).

In addition the midazolam hydroxylation activity was used to measure the Cyt P₄₅₀ II-IA₄ activity.

Ralph Quadflieg, Pharm D

Department of Pharmaceutical Technology and Biopharmacy, University of Bonn, An der Immenburg 4, D-53121 Bonn, Germany

Digoxin Guidelines

On 9 Feb 1997 at 10:12:51

Our pharmacists would like to find guidelines for digoxin dosing and creatinine clearance. We would appreciate it if anyone can tell us where we can find this.

B. Miers

Methodist Med Ctr., Peoria, Il

On 10 Feb 1997 at 14:54:17

Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, Bennett WM, Aronoff GR, Golper TA, et al. Third Edition. American College of Physicians. Philadelphia, PA. 1994.

Drug Dosage in Renal Insufficiency, Seyffart G. Kluwer Academic Publishers. Norwell, MA. 1991.

Both sources have specific references.

G. Aronoff, M.D.

Kidney Disease Program, University of Louisville School of Medicine

On 10 Feb 1997 at 14:54:34

The dosing of digoxin in renal pts and those with liver disease or CHF is not straight forward. However, some useful information maybe found in a little book by JR White and MW Garrison entitled **Basic Clinical Pharmacokinetics Handbook** (it sounds bigger than it really is) (by Applied Therapeutics, inc)

Here are some basic steps:

1. Determine the size of the loading dose.

$V_d \times \text{desired level} \times \text{bioavailability (F)}$

(V_d and F vary depending on pt condition) (therp level depends on whether we are treating CHF or arrhythmia)

The loading dose is usually 10 to 15 U_g/kg.

The total loading dose is usually divided into 50%, 25%, 25% parts given 6 hrs apart.

2. Estimate the percent daily elimination (%E). This may be done using the Jelliffe method: $\%E = 0.2 \text{ CL}_{cr} + 14$; where CL_{cr} =estimated creatinine clearance in mL/min.
3. Daily maintenance dose = %E x Loading Dose

However, in practice dosing is adjusted according to clinical response (therapeutic and adverse effects) and serum level.

Nasr Anaizi, PhD RPh

Univ. of Rochester Medical Center

On 11 Feb 1997 at 16:19:13

Try the Third Edition of Michael Winter's Basic Clinical Pharmacokinetics. You should find it very helpful

John Eddy

Diltiazem HPLC Assay

On 1 May 1997 at 17:58:39

We are working in pk/pd diltiazem in acute atrial fibrillation patients. Could anyone inform me about a validated HPLC technique to determine diltiazem in human serum?

Juan Pablo Ordov=Es Baines

Pharmacy Service. PK Lab., Hospital Dr. Peset

On 2 May 1997 at 12:35:56

You may wish to consult the following reference with regard to a validated method for diltiazem:

Drug Metabolism & Disposition. 24(1):28-33, 1996 Jan.

Richard A. Sams, PhD

Professor and Laboratory Director, Analytical Toxicology Laboratory, College of Veterinary Medicine, The Ohio State University

On 2 May 1997 at 12:36:17

We developed a validated HPLC method to determine diltiazem and its metabolites in human plasma. The article can be found in *Journal of Chromatography (Biomedical applications)*, **582** (1992) 203-209. It also has the reference for other HPLC methods.

M. Delwar Hussain

School of Pharmacy, University of Wyoming, Laramie, WY 82071-3375

On 2 May 1997 at 12:36:26

Here is a reference for diltiazem assay;

High-performance liquid chromatographic assay for diltiazem in small-volume blood specimens and application to pharmacokinetic studies in rats Scully, P., Meehan, E. and Kelly, J.G. *Journal of Chromatography A* Volume **A729**, Issue 1-2, 5 April 1996 page 297-300

Chandrani Gunaratna, Ph.D.

Senior Research Chemist, Bioanalytical Systems, 2701 Kent Avenue, West Lafayette, IN 47906

On 5 May 1997 at 14:28:20

Virgil Dias at Hoechst Marion (when it was Marion Merrill Dow) published a PK/PD series about IV diltiazem in 1992. He would seem like a reasonable place to start. His article was in *Circulation* 1992; **86**:1421-8.

Dr. Vince Pearson

Drug Information Pharmacist, The Johns Hopkins Hospital, Baltimore, Maryland USA

Dissolution Test for Nicardipine HCl Tablets

On 14 Mar 1997 at 10:58:31

Does anyone out there know how to conduct the dissolution test for nicardipine HCl TABLET (not capsule, not SR) with official method? I have been looking for UPS XXIII, EP (1997), and JP (1991, English version), BPC (1995? 1996?) but can not find it. The information should include as follows:

Medium; Volume; Apparatus; Time; Procedure and Tolerance

Yung-jin (Frank) Lee, Ph.D.

Clinical/Hospital Pharmacy Dep., Tri-Services General Hospital, #8, Sec. 3, Ting-chow Rd, Taipei, TAIWAN 100, ROC

On 21 Mar 1997 at 10:34:02

The solubilities of these dihydropyridines tend to be very low so it is unlikely you will find a traditional dissolution method for nicardipine- ie. you could never maintain a sink condition for USP methods I or II. You may want to look in to a flow-through design or an extraction (two-phase) method. Sometimes surfactants help (SLS or Tween) however, they will only increase the solubility 2-4X at best and this is still not enough for compounds of this nature.

Keith Anderson

Drug Use in CVVH and CVVHD

On 19 Mar 1997 at 22:09:49

Does anyone know where I can get hold of information on the use of drugs in CVVH and **CVVHD**? i.e. which drugs need their doses to be compensated for because of removal into the ultra-filtrate etc? I especially need information re allopurinol.

Thanks

Estelle Smith, Paediatric Pharmacist, Shaare Zedek Hospital, Jerusalem, Israel

On 20 Mar 1997 at 09:28:16

Here are some general reviews on the topic:

Reetze-Bonorden et al, Drug dosage in patients during continuous renal replacement therapy. *Clinical Pharmacokinetics* **24** (5) 362 - 379, 1995

Bressolle et al, Clinical pharmacokinetics during continuous haemofiltration. *Clinical Pharmacokinetics* **26** (6) 457 - 471, 1994.

Bickley SK, Drug dosing during continuous arteriovenous hemofiltration. *Clinical Pharmacy* **7**: 198 - 206, 1988.

Schetz et al, Pharmacokinetics of continuous renal replacement therapy. *Intensive Care Medicine* **21**: 612 - 620, 1995.

Cotterill S, Antimicrobial prescribing in patients on haemofiltration. *Journal of Antimicrobial Chemotherapy* **36**: 773 - 780, 1995.

I'm not sure you will find anything on allopurinol but they might help you predict the likely effects.

Alison Thomson

Clinical Pharmacokinetics & Biometrics Unit, Dept of Medicine & Therapeutics, West Glasgow Hospitals Trust, Glasgow G11 6NT

On 21 Mar 1997 at 10:34:36

Reetze-Boroden P, Bohler J, Keller E. Drug dosage in patients during continuous renal replacement therapy: pharmacokinetic and therapeutic considerations. *Clin Pharmacokinet* 1993; **24**:362-379.

This is an extensive review of published data includes a table of suggested dosage adjustments for a large number of drugs.

Randy Trinkle, BScPharm, BA

Dept. of Pharmacy, Dawson Creek & District Hospital, Dawson Creek, BC

On 23 Mar 1997 at 11:09:41

We recently had a patient post chemotherapy who developed acute renal failure. The allopurinol dose was 600mg/day. In our CVVH patients, we use a f-40 filter with convection rates of 1 l/hr and blood flows of 170 ml/min. We have measured aminoglycoside clearance rates of approx 25 ml/min. Using this as a guide, and that allopurinol is dialyzable, we made an empiric dose reduction of 50 % and followed uric acid levels. The uric acid had dropped from 15.2 to 10.5 at the time cvvh was started. 300mg/day was given during cvvh for 2 days. The uric acid was 3.7 at that time. Both cvvh and allopurinol were stopped after 2 days and the uric acid level 3 days later stabilized at 8.7.

William Dager, Pharm.D.,FCSHP

Coordinator, Pharmacokinetic Consult Service, UC Davis Medical Center

EC₅₀ Software

On 14 Aug 1997 at 13:47:54

I am seeking for a computer program which is able to fit concentration-effect curves of several experiments with the same drug (e.g. n=6) and to determine an $EC_{50} \pm$ s.e.m., slope and maximum and to compare it with a different experiment (different drug or presence of an antagonist; e.g. also n=6) and to determine whether the parameters are significantly different or not. Until now, we use a program modified from a program of Waud which works with a logistic function:

$$e = \frac{K_1 \cdot A^{K_2}}{A^{K_2} + K_3^{K_2}}$$

where e = Effect, A = Concentration, K_1 = maximum value, K_2 = slope and K_3 = **EC₅₀**

However, the determined s.e.m. is very small, probably because it is determined only by the deviation of all single points from the curve which is fitted through these points. My suggestion would be that each individual experiment should reveal an individual concentration-effect curve (with some error regarding the deviation of the points from the curve) and then the EC_{50} and the other parameters (for n=6) with s.e.m. should be computed.

Wolfgang Vierling

Institute for Pharmacology, Technical University Munich

On 15 Aug 1997 at 10:35:30

We use SigmaPlot by Jandel Software it has a good curve fitting module that provides a standard error.

Curt Mazur

IDUN Pharmaceuticals, Inc.

On 15 Aug 1997 at 10:36:50

There are many programs which will do this but very few that will take into account the differences between individuals. If the latter is important to you then I would recommend NONMEM. Installation and training in the use of this program will require some effort but once you have mastered it you will find it has many applications in pharmacological analysis.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 18 Aug 1997 at 15:49:29

You may be interested by the work of Davidian et al. :

Davidian M, Giltinan DM, 1993, *Biometrics*, **49**, 59-73

Giltinan DM, Davidian M, 1994, *Statistics in Medicine*, **13**, 1165-1179

They use a maximum likelihood method to fit each curve, and then an EM-algorithm to estimate the distribution of the model parameters.

A Turbo Pascal program which implements a variant of this method (applied to the more simple Michaelis-Menten equation, and without the EM step) is available on my web page.

Jean Debord

Laboratoire de Pharmacologie, Faculte de Medecine, 2 Rue du Docteur Marcland, 87025 Limoges (France)

Effects of Dilution on PK/PD of Nondepolarizing Neuromuscular Blocker

On 4 Mar 1997 at 13:07:07

I will be conducting a study of the effects of giving a dilute concentration versus a standard concentration of a NMB. We will be comparing onset times and duration. My question is, in theory, should there be a difference, and if so what should it be? Keep in mind that equal doses will be given. Is anyone aware of any studies pertaining to any class of drug where differing concentrations but equal doses were given?

Scott Farley

On 5 Mar 1997 at 11:38:41

If you already know the parameters for absorption, distribution, binding, metabolism, and elimination of your drug, it would be a simple matter to calculate (using any of a number of simulation packages) the expected plasma concentrations for the two different dosing protocols (1-short infusion, high concentration, 2-longer infusion, lesser concentration; both delivering the same total dose). If the drug was designed for a particular dosing scheme, a smaller concentration infused for a longer time runs the risk of never reaching the target therapeutic concentration. This could occur, for example, if drug metabolism or elimination outpaced absorption.

If your situation is more complex, please repost to the list. Good luck.

Robert D. Phair, Ph.D

BioInformatics Services

<http://www.webcom.com/rphair>

On 5 Mar 1997 at 11:39:54

To answer your question: I don't expect any difference in onset time and duration between a standard concentration and a dilute concentration. If there is any effect, it will be small, and unlikely to be revealed experimentally.

If a drug is administered intravenously, it will be diluted to a considerable extent before it is transported via the arteria to the muscles. This dilution will be more pronounced if a small volume is injected, and less pronounced if a larger volume is injected. As a result, the concentration profile in the arteria will be less affected by the concentration of the injected solution. Although the steep rise and fall of the concentration during the first minute may be less pronounced than after injection of more concentrated solutions, the average concentration in the arteria will be hardly affected, and therefore also the net transport to the biophase.

However, this is theory, and it would be interesting to test this in practice. I am not aware of studies performed in this topic, so I also are interested in reactions by others.

It is not clear from your message why you want to perform such a study. Is this a question relevant to anesthesiological practice, or is it a purely scientific interest. Please give us more information about the rationale behind your question.

Johannes H. Proost

Dept. of Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, Groningen, The Netherlands

Experience with MATLAB

On 28 Nov 1997

Can anyone tell me if MATLAB is a good tool for modeling using systems of differential equations based on their experience with the program?

Paul Damian PhD,MPH

Rust Environment & Infrastructure

On 28 Nov 1997 14:27:48

I have been using Matlab for PBPK modeling. Using the GUI add-on Simulink, differential equations can be modeled and linked easily. They can be represented in transfer function or state space form, or you can model the equations yourself.

Two stiff system algorithms are available with Simulink, Gear and Linsim. Runge Kutte23 and 45, Adams and Euler algorithms are also available.

There is a Systems Identification toolbox for parameter estimation and a Statistics Toolbox that provides methods for parameter sensitivity analysis and optimization. There are a couple of IEEE papers that will give you some idea of Matlabs capabilities.

Wada, D.R., Ward, D.D. (1994), "The hybrid model: a new pharmacokinetic model for computer-controlled infusion pumps," *IEEE Transactions on Biomedical Engineering.*, vol. **41**, No. 2.

Wada, D.R., Stanski, D.R., Ebling, W.F. (1995), "A PC-based graphical simulator for physiological pharmacokinetic models", *Computer Methods and Programs in Biomedicine.*, vol. **46**, pp. 245-255.

Alex MacDonald

Graduate Student, Dept of Medicine and Pharmacology and Dept of Automatic Control and Systems Engineering, University of Sheffield UK

On 28 Nov 1997 15:14:43

I have used MATLAB/SIMULINK for many things, have found it an easy tool to use for modeling and simulation, and have not felt limited by the software. Some examples: (1) population PKPD estimation - linearization methods, global two-stage (2) optimal sampling (3) PBPK modeling and simulation (4) nonlinear feedback control (5) ANOVA (6) EEG signal processing

MATLAB is a command-line, interpretive, matrix-based language with scripts. It has good graphics and reasonable data handling capabilities. To do simple things, the user can interact at the command line. To do more complex things, the user needs to write equations in the MATLAB language, store the equations in user-defined subroutines, and call user-defined subroutines or built-in subroutines where needed. MATLAB can do linear ODE's.

MATLAB is a general-purpose tool. It has no specific tools for pharmaceuticals, as an example.

To be useful for PKPD applications requires extra MATLAB toolboxes. I have used the toolboxes for Optimization, Splines, Control, and Signal Processing. I would like the toolbox for Stats, although the basic tools are present in the standard package (i.e. F-distributions)

I have found SIMULINK to be very useful for nonlinear simulation, although this is also an extra package. SIMULINK is a graphical simulator, with about 6 different integration routines (i.e. gear, rk45). SIMULINK models can be simulated from the graphical simulator window, or the command-line. I find the latter more useful, because it allows, for example, parameter estimation and Monte-Carlo simulation.

SIMULINK models are saved as MATLAB files. Thus if one needs to write a general ODE which cannot be expressed in SIMULINK, then one can (probably) write the MATLAB file directly. I think that SIMULINK files are still needed to simulate the ODE.

Some limitations of MATLAB 4.0 are: (1) User needs familiarity with matrices, and engineering/applied math concepts; (2) Previous experience with language such as C/ FORTRAN; (3) Sometimes simulator doesn't give proper results (stiff PBPK models) Needs careful attention to choice of algorithm/simulation parameters. (4) difficult to handle discrete events.

D. Russell Wada, Pharsight Corp, 299 California Ave, Suite 300, Palo Alto CA 94306

On Nov 1997 10:03:58

In my work I use MATLAB and SIMULINK to model the transport of radionuclides in the body.

A current project is to calculate the exhalation rate of Rn-220 (Thoron) following an inhalation of thorium oxide. (a later task will be to calculate the radiation doses) To do this I have implemented what I call a six stage hybrid biokinetic model. I model the kinetics of each nuclide starting with Th-232 explicitly (thus six stages), the first 5 nuclides are modeled using the biokinetic models recommended by the ICRP while the biokinetic model for thoron is a model described by Peterman for inert gases (thus a hybrid model). All totaled, the model contains about 350 compartments. The model is stiff (transfer coefficients between the compartments range over 9 orders of magnitude, the half-life of Th-232 is on the order of 10^{10} years and the half life of thoron is 55 sec.).

So far as I can tell, the MATLAB/Simulink combination is working well. MATLAB allows the user to choose which differential equation solver to use both stiff and nonstiff solvers. In my opinion, MATLAB is very powerful and is capable of doing just about anything you want it to.

For simple pharmacokinetic systems, you would not need to use Simulink but then you would need to write your own MATLAB routines that describe the differential equations and the jacobian (Simulink does that for you). The nice thing about Simulink is that it provides a nice graphical tool to build compartmental systems such as you find in pharmacokinetics. You can "build" a single compartment and then replicate the compartment and connect the compartments using a line drawing tool.

If you use MATLAB and don't want to write your own routines for optimization, probability distributions, etc. you will probably need to add various MATLAB toolboxes. So you might want to get Matlab, Simulink, the optimization tool box, the statistics toolbox, and perhaps, the splines toolbox. All of which add to the cost. The learning curve for MATLAB and Simulink is steep, and in my opinion the manuals that come with MATLAB are not as helpful as they might be.

Richard Traub

PNNL

On 1 Dec 1997 at 08:42:14

Unfortunately I have not used METLAB but I have been using a similar program called MathCad for the same purpose as you describe. I have not seen these types of programs used in pharmacokinetics and feel there is a large potential for their use. I have used MathCad to solve differential equations resulting from compartment model. Included are functions to solve stiff equation, Fourier transform, nonlinear regression analysis, convolution and deconvolution, Symbolic solver for example: Laplace transform, integration and differential equations, all of which I've applied to pharmacokinetic problems. I am really happy to see others are applying programs like METLAB and MathCad to the field of pharmacokinetics.

Barry Koplowitz

Bristol-Myers Squibb

Exponential Fitting versus Compartmental Modeling

On 9 Oct 1997 at 10:40:16

In the course of a PK discussion recently, a colleague without much formal PK background or training asked me to explain the functional/practical difference between compartmental modeling of, say, a data set exhibiting bi-exponential disposition, and simply fitting a bi-exponential function to the data. For some reason, I've had a hard time formulating a cogent response to this question. I'd appreciate any input and discussion on this issue, especially relating to the difference in the recovered "parameters" (either their numerical values or their real meaning) from both methods, and the general utility of both methods. Thanks - I look forward to your input.

Keith Ward

Investigator, DMPK, SmithKline Beecham Pharmaceuticals, UW2720; 709 Swedeland Road, King of Prussia, PA 19406

On 10 Oct 1997 at 14:51:02

Your question is a classic one, and one that has received a lot of attention from both theoreticians and experimentalists not only in PK/PD but also in the broader field of biological and physiological modeling. There is an excellent textbook treatment of the question in John Jacquez' classic, *Compartmental Analysis in Biology and Medicine*. I believe the third edition of his book has just been published.

But a short version of the answer might be given as follows. If you fit your data set to a sum of two exponentials, you will recover four parameters, the coefficients and the exponents of

$$A \bullet e^{-\alpha \bullet t} + B \bullet e^{-\beta \bullet t}$$

If the data are sufficient, all four of these parameters will be well-defined and the classical analyses of pharmacokinetics (AUC, etc.) can be performed.

For more complicated systems or when mechanistic questions are important, many investigators have found it useful to add compartmental modeling to their arsenal of analytic tools. Most compartmental analysts will, in fact, begin their analysis by fitting the data to a sum of exponentials, but their goal is to determine how many compartments will be necessary to adequately fit the data while still permitting estimation of the model's parameter values with reasonable coefficients of variation. There is a large body of published work in this sub-discipline, which has been called Identifiability.

One of the advantages gained by including compartmental analysis in a suite of tools used by pharmacokineticists, is the opportunity to assign biological or physiological meaning to the rate constants or clearances that characterize the compartmental model. To the extent that the model structure reflects the real processes taking place in the cells, the animals, or the human subjects, the corresponding model parameters will serve to characterize the activity of those processes at the time the data were collected. The reason this cannot be said of the parameters, A , a , B , and b from the exponential fit is that all four of those parameters are functions of all of the biological processes. This can be shown from first principles. Occasionally, the numerical value of one of the exponents will be dominated by a single biological process, but no R&D effort can afford to make this assumption. There are too many circumstances, especially in more complicated systems, in which you will be simply wrong.

The opportunity to determine compartmental rate constants or clearances that characterize particular physiological processes is also the opportunity to pursue studies of mechanism and even drug interactions. These are both feasible and practical using the compartmental modeling approach.

Compartmental analysis also has the potential to effectively address major questions raised in the development and approval process for any new drug. It is often the case that there is much more information in the already-collected experimental data than can be extracted using classical pharmacokinetic approaches. This, of course, is of no consequence for drugs that sail through the approval process; classical PK is all you need. But if you are faced with going back to do more experimental/clinical work in order to answer a tough go/no-go development question or a tough approval question, it seems obvious to me that you should first try to answer that question using compartmental analysis of all the avail-

able data. The savings in time and dollars and the resulting competitive advantage could be enormous.

Robert D. Phair, Ph.D.

BioInformatics Services

12114 Gatewater Drive, Rockville, MD 20854 U.S.A.

On 10 Oct 1997 at 14:52:27

My attitude to this has always been that when a multi-exponential model adequately describes a problem it is not necessary and, in a sense it is preferable to use it rather than create an artificial compartment model. The dangers of compartmental models have been stated in the past and have to do with non-identifiability and the tendency to give physiological meaning to the parameters of the compartmental model, particular the horrible micro rate constants.

However I have to qualify this position slightly. True physiological models are compartmental models and their parameters do have a valid physiological meaning. Also multi-exponential models do not lend themselves to situations of changing physiology (eg reduced renal function) or dose dependent kinetics. For a drug which shows bi-exponential disposition at low dose but has saturable elimination, I know of no other way of handling this other than with a 2-compartmental model with Michaelis-Menten elimination from one of the compartments (usually the first). One can describe a particular dose by a sum of exponentials but this will not be predictive of other doses. Maybe someone else knows of a non-compartmental (predictive) method of doing this.

Leon Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, M13 9PL, U.K.

First Dose in Man

On 6 Mar 1997 at 11:03:44

Group: What would be the best approach to select the dose for first clinicals (beyond the classical AFDO guidelines) if the drug shows higher interspecies variability in metabolic pathways (e.g., scaling not possible).

N. N. S

On 7 Mar 1997 at 10:00:28

I will start first dosing comfortably doing good pre clinical work with the drug and identify an animal model that best represent or come very close to human, then start a conservative dose escalation study with well defined pharmacodynamic variable to watch for and establish a relationship with Cmax - PD response or clinical compliance. Once this relationship is established continue classical clinical studies with heavy emphasis on Therapeutic Drug monitoring. Best I could think is the following order.

- 1) In vitro liver microsomal work to identify possible metabolites in various species including Human. Some times we have to go beyond classical three species approach (In one case we investigated beyond 6 species to test the animal model and found Baboon a good animal model close to Human)
- 2) Try to identify primary isoform responsible the metabolism of the drug.
- 3) comparative PK in three animal models that are close to human from the # 1 study.
- 4) These three studies give good idea in designing first time in Man study.

My impression is for this type of problematic (assuming all the troubles listed are true) -- Good emphasis in Phase I studies and therapeutic drug monitoring will save lot of confusion during the large clinical studies.

Prasad N.V. Tata, Ph.D.

On 8 Mar 1997 at 22:41:44

In such cases the first dose may not be as important as the rate of dose escalation. The first dose is where one starts a journey. Without the correct road map it may be impossible to find the destination.

The first dose of a new drug in humans should always be conservative and based on a good preclinical work-up. However, one also would want to discover the maximally tolerated dose (MTD) in a timely fashion. Although you do not know what the plasma concentrations will be, you may have useful information regarding the slope of concentration response relationships (therapeutic and toxic) from animal pharmacology studies. Once you have discovered where you lie on the concentration axis of that curve in humans (e.g., after the first one or two dose levels) you will be able to rationally expedite the search for MTD.

In addition, I would explore the in vitro metabolism in human liver preparations. That should at least give you 'order-of-magnitude' estimates.

Jeffrey Wald, Ph.D.

Quintiles, Incorporated, Post Office Box 13979, Research Triangle Park, North Carolina,
27709-3979

Grapefruit Juice - Drug Interaction Warnings

On 10 Sep 1997

Should drugs that have or are suspected of having possible clinically significant interaction with grapefruit juice, have warnings against it in patient's inserts and/or doctor's data sheets?

I am asking this because of the replies to my question (ANCHODD and PharmCare) regarding the existence of such warnings. As you may have seen there are warnings for terfenadine in the UK, felodipine in Australia and indinavir and saquinavir as well.

Both felodipine and terfenadine have proven interaction with grapefruit juice. On the other hand neither indinavir nor saquinavir have been shown to interact with grapefruit juice. Yet they both have the potential of such an interaction as they have low bioavailability and major CYP 3A4 metabolism.

What about cyclosporin and nisoldipine, both having documented interactions with grapefruit juice? Should cisapride have a warning as well?

Ofer Spiegelstein

Department of Pharmacy, The Hebrew University of Jerusalem, P.O.Box 12065, Jerusalem 91120, Israel

On 11 Sep 1997 at 09:48:19

What is the basis for this warning? Is it the acidity of the juice or something else? If it is the acidity, there are other juices that should be mentioned > cranberry for one example.

Vahn Lewis

On 11 Sep 1997 at 09:48:46

Should drugs that have or are suspected of having possible clinically significant interaction with grapefruit juice, have warnings against it in patient=CCs inserts and/or doctor=CCs data sheets?

Ideally, the answer would be yes. However, as I'm sure you're aware, most office based physicians are not knowledgeable about food/drug interactions. Thus, this task falls onto the pharmacist to inform the patient. It only becomes a part of the package label if the country's drug regulatory agency specifically asks for it, and that occurs, unfortunately, after something bad has happened.

Both felodipine and terfenadine have proven interaction with grapefruit juice. On the other hand neither indinavir nor saquinavir have been shown to interact with grapefruit juice. Yet they both have the potential of such an interaction as they have low bioavailability and major CYP 3A4 metabolism.

In the US, these drugs' labels do not mention grapefruit juice as a interacting agent. One could claim that the interaction with saquinavir is beneficial because the bioavailability of saquinavir is so poor.

What about cyclosporin and nisoldipine, both having documented interactions with grapefruit juice? Should cisapride have a warning as well?

In our hospital, we have a listing of food-drug interactions that pharmacists inform the nurses/prescribers of when they are seen when orders are written. It includes the above drugs, except nisoldipine only because it is not on our formulary. At least an effort is made to avoid the interaction when it is seen.

Dr. Vince Pearson

Drug Information Pharmacist, The Johns Hopkins Hospital, Baltimore, Maryland USA

On 12 Sep 1997 at 10:22:22

The interaction of several drugs with grapefruit juice is thought to be due to the presence of a bioflavonoid in the juice (most likely naringin which is metabolized to naringenin in man) and inhibition of in vivo cytochrome P₄₅₀ mediated drug oxidation, and is not related to the juices acidity. However the exact nature of the interaction has not, to my knowledge, been unequivocally demonstrated. Naringin is the major bioflavonoid in grapefruit juice (in fact this is what gives the juice its bitter taste), but is not found in many other juices such as orange juice. There are many compounds for which an interaction with grapefruit juice has been demonstrated (several 1,4 dihydropyridines including nifedipine,

felodipine, nisoldipine, and other drugs such as caffeine, coumarin, terfenadine, midazolam, cyclosporine, and 17 beta-estradiol come to mind). One important point about the nature of these interactions is the rather large inter-individual variability with respect to observed increases in drug bioavailability and also the differences observed in the magnitude of the grapefruit juice effect for different drugs. Hence, in my opinion the magnitude (and variability) of the interaction should be evaluated for each specific compound to determine if label warnings should be added to package inserts or data sheets.

John S. Grundy

On 11 Sep 1997 13:57:17

Grapefruit juice known to inhibit the metabolism of drugs that are metabolized CYP-450 3A4 isozyme. Very popular example is Terfenadine-Grapefruit interaction quoted in media as is your cough medicine (Terfenadine) and your breakfast do not see eye to eye? something like this. Grapefruit known to inhibit the metabolism of cyclosporine.

The rationale for this type of drug interaction is believed to be Syringinine a constituent of grapefruit juice? But there is no conclusive proof Syringinine alone is responsible for this interaction. Hope this clarifies.

Prasad Tata, Ph.D.

Division of Bioanalytical & Drug Metabolism, Otsuka America Pharmaceutical, Inc.,
2440 Research Blvd., Rockville. 20850

On 12 Sep 1997 09:01:56

For more details on grapefruit juice interactions see:

Ameer B, Weintraub RA. Drug interactions with grapefruit juice. *Clinical Pharmacokinetics* 1997 August; **33** (2): 103-121

The predominant mechanism for enhanced bioavailability is presumably the inhibition of oxidative drug metabolism in the small intestine. The consistent findings across studies of diverse cytochrome P450 (CYP) 3A substrates support the mechanistic hypothesis that 1 or more grapefruit juice components inhibit CYP3A enzymes in the gastrointestinal tract.

From abstract of the above article.

Jane Duffy

Publication Manager, Clinical Pharmacokinetics, Adis International, New Zealand

On 11 Sep 1997 14:28:58

From what I understand, grapefruit juice (I don't know if a specific chemical has been isolated) has been shown to inhibit the CYP1A2 enzyme system. The acidity has nothing to do with these warnings. Does anybody know the clinical significance of grapefruit juice interactions? How much grapefruit juice needs to be ingested to see this? How long does the interaction last, etc.? Any other drugs to be worried about?

Bill Murray Pharm.D.

Children's Hospital San Diego

On 12 Sep 1997 08:06:13

What is the basis for this warning? Is it the acidity of the juice or something else? If it is the acidity, there are other juices that should be mentioned > cranberry for one example.

Please see the commentary in *Clinical Pharmacology and Therapeutics* Vol 61, 4:395:400 1997. This article by David J Spence discusses in depth interactions with grapefruit juice.

It is nothing to do with the acidity of the juice. Grapefruit juice contains naringenin which is the aglycone of naringin, a bioflavonoid. Naringenin would appear to be in higher concentrations in grapefruit than other citrus species, however this does need further investigation. It is known that naringenin is a 3A4 inhibitor. It has also been suggested that there may be a chemical in grapefruit which inhibits 1A2.

The inhibiting effect of grapefruit juice is remarkable, with increases in AUC with drugs metabolised by 3A4 pathway ranging from 2 to 10 fold This is particularly important for drugs such as terfenadine (causing QT prolongation), cyclosporin, calcium channel blockers, cisapride, HMGCoA reductase inhibitors, and midazolam.

Carl Kirkpatrick

On 12 Sep 1997 11:35:33

Grapefruit juice is known to inhibit the CYP_{3A4} metabolism in small bowel enterocytes but not in the liver or colon. This inhibition is primarily due to naringen, naringenin and 6',7'-dihydroxybergamottin and possibly other constituents contained in the juice. Even one drink or one grapefruit within hours of ingestion may significantly increase the C_{max} (up to 700%) of drugs metabolized by CYP_{3A4} (e.g., terfenadine, nisoldipine, cyclosporine) and such increases may be of clinical significance. Orange juice does not appear to possess such activity.

Lown K.S. et al., *J. Clin. Invest.* **99**:2545-2553, 1997

Benton R.E. et al., *Clin. Pharmacol. Ther.* **59**:383-388, 1995

Bailey D.G. et al., *Clin. Pharmacol. Ther.* **60**:25-33, 1996

Edwards D.J. et al., *Drug Metab. Dispos.* **24**:1287-1290, 1996

Sun Dong Yoo

On 12 Sep 1997 15:13:26

What is the basis for this warning? Is it the acidity of the juice or something else? If it is the acidity, there are other juices that should be mentioned > cranberry for one example.

Grapefruit juice (the only citrus fruit juice) has an enzyme inhibitory effect. It is discussed that some of the flavonoid glycosides (naringin or the aglycon naringenin) which are partly responsible for the bitter taste of grapefruit juice, are the active compounds. There are several in vitro results, that there is an Cytochrome P₄₅₀ IIIA₄ inhibiting effect with these flavonoids, but in vivo studies with the pure flavonoid are sparse and without a clear outcome. Additionally there are some more compounds which occur in grapefruit juice and not in orange juice (which does not act as an enzyme inhibitor). These compounds (coumarins and psoralens) also showed enzyme inhibitory properties. As far as I know there is nobody, who really knows what compound it is, which inhibits the metabolism of drugs metabolized by Cyt. P₄₅₀ IIIA₄.

Ralph Quadflieg, Pharm D

Department of Pharmaceutical Technology and Biopharmacy, University of Bonn, An der Immenburg 4, D-53121 Bonn, Germany

On 15 Sep 1997 at 10:59:02

I want to add a new twist to the current knowledge on the inhibition of P₄₅₀ 3A₄ isozyme by constituents present in the grapefruit juice.

There is convincing data in the literature that grapefruit juice constituents inhibit P₄₅₀ 3A₄ metabolism in the gut but not liver. This findings provide a simple and practical method of distinguishing gut versus hepatic first-pass metabolism of highly cleared drugs. All one would have to do is to assess the degree of first-pass metabolism produced by pre-treatment with ketoconazole (potent inhibitor of 3A₄ in the liver and gut) and grapefruit juice. The difference in clearances between these two treatments could then be utilized in calculating the contribution of first-pass metabolism by gut. Optimal conditions for such a study would naturally would have to be worked out. There is no simple method currently to distinguish between gut versus hepatic first-pass metabolism without the use of intravenous administration.

I would be most grateful for any comments and suggestions on my above hypothesis.

Aziz Karim, Ph.D.

Chicago, Illinois, USA

On 15 Sep 1997 at 15:23:45

I disagree with the experimental method proposed by Dr. Karim for determination of the contribution of the gut to the bioavailability of compounds metabolized by CYP_{3A4}. Ketoconazole would also alter the systemic clearance of the compound you want to evaluate; hence, comparison of oral clearances of a compound given with grapefruit juice or ketoconazole would give inaccurate results for the contribution of the gut to the bioavailability of a compound (i.e., when comparing bioavailability, relative bioavailability calculations, one assumes that systemic clearance remains constant). However, based on somewhat similar reasoning a simpler experiment can be done. Just compare the relative oral bioavail-

ability of your compound administered without and with grapefruit juice (assuming that grapefruit juice does not affect systemic clearance; this has been shown with compounds such as cyclosporine and midazolam). This is analogous to the ratio of F (without grapefruit juice) to F (with grapefruit juice) which gives F_g (i.e., $F = F_g \cdot F_h$; where F is oral bioavailability and F_g and F_h are the fractions of the dose escaping destruction in the gut and liver, respectively).

John S. Grundy, Ph.D.

On 15 Sep 1997 22:03:02

I am intrigued by Dr Karim's thoughts on grapefruit inhibiting only gut $3A$ metabolism. This is certainly a departure from current ideas. Could someone please provide a citation? I also wonder if anyone has given thought to grapefruit's contribution to p-glycoprotein (MDR1) inhibition? If indeed, as thought, PGP works in concert with $3A$ gut metabolism it makes sense to me that there may be some inhibitors that effect either both or just one of the two systems. By the same token, it also makes sense that there could well be some agents which are substrates for only one of the two systems (i.e., PGP but not $3A$).

Certain enigmatic drug interactions occur which are not predicted by current, state of the art, in vitro prediction models. As an example of this, I invite everyone to look at the drug interaction section of the label from HMR's fexofenadine HCl. I know of no data available in the literature to explain these findings, and offer no speculation. I just think that it is things like this that demonstrate weaknesses in our current mechanistic paradigm of drug interactions.

On 16 Sep 97 03:58:15

I appreciate the comments made by Dr Grundy. His comments still do not contradict the interesting possibility that grapefruit juice can be used (even without ketoconazole) for determining the extent of gut first-pass metabolism.

In my suggested design, grapefruit juice and ketoconazole would not have been given together but in a crossover fashion after a suitable washout period. This would bring the clearance of the test drug back to the control level similar to what we do in a comparative

crossover bioavailability studies. This of course assumes that the inhibitory activity of both ketoconazole and grapefruit juice are reversible (not an unreasonable assumption)

Aziz Karim, Ph.D.

On 16 Sep 1997 04:17:36

Dr. Karim:

There are several well described experimental approaches to studying the oral bioavailability of drugs. To accurately assess the contribution of individual components such as the fraction of absorbed dose, gut and liver extraction is no simple task. There is a series of excellent articles published recently by Seattle group (Thummel) on midazolam and Benet's work with cyclosporin. In my opinion, these articles are particularly valuable since the assessments were conducted in humans. If more physiological and direct approach is desired, animal models are the only alternative. The group at the University of Alberta (led by Y.K. Tam) has published a series of papers, describing instrumented conscious dog model that provides a very powerful tool to evaluate the first-pass effects in a great detail. I hope this helps and provides some guidance for your experimental design.

Andrej Skerjanec, Ph.D.

Lilly Laboratories for Clinical Research

On 19 Sep 1997 at 10:42:04

There are 6 examples of grapefruit juice interaction noted in the current PDR:

PLENDIL (felodipine) The bioavailability of PLENDIL is not influenced by the presence of food in the gastrointestinal tract. In a study of six patients, the bioavailability of felodipine was increased more than two-fold when taken with doubly concentrated grapefruit juice, compared to when taken with water or orange juice. A similar finding has been seen with some other dihydropyridine calcium antagonists, but to a lesser extent than that seen with felodipine.

NEROAL Capsules (cyclosporine) Patients should be given careful dosage instructions.
Neoral(R) Oral Solution (cyclosporine) oral solution for micro-emulsion) should be di-

luted, preferably with orange or apple juice that is at room temperature. Grapefruit and grapefruit juice affect metabolism of cyclosporine and should be avoided.

SULAR (nisoldipine) Nisoldipine should not be administered with grapefruit juice as this has been shown, in a study of 12 subjects, to interfere with nisoldipine metabolism, resulting in a mean increase in C_{max} of about 3-fold (ranging up to about 7-fold) and AUC of almost 2-fold (ranging up to about 5-fold). A similar phenomenon has been seen with several other dihydropyridine calcium channel blockers.

CRIXIVAN Capsules (indinavir) Administration of a single 400-mg dose of indinavir with 8 oz. of grapefruit juice resulted in a DECREASE in indinavir AUC (26% +/- 18%). Administration of a single 400-mg dose of indinavir with 200 mg of quinidine sulfate resulted in a 10% +/- 26% increase in indinavir AUC.

XANAX (alprazolam) Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice.

LEXXEL (felodipine) As with other dihydropyridine calcium channel blockers, the bioavailability of felodipine was increased when taken with grapefruit juice, compared to when taken with water or orange juice.

Norman Schmuff

On 23 Sep 1997 at 10:48:56

In reference to the above subject. I would like to add

Drug Interactions with Grapefruit Juice Barbara Ameer and Randy A. Weintraub *Clin. Pharmacokinet.* 1997 **33**, 103-121.

This seems to be a useful review. Another article I stumbled was

The fate of Naringinin in humans: a key to grapefruit juice-drug interactions Fuhr U and Kummert, A. *Clin Pharmacol. Ther.* 1995, **58**: 365-73.

Prasad Tata

Help with Unusual PK Problem

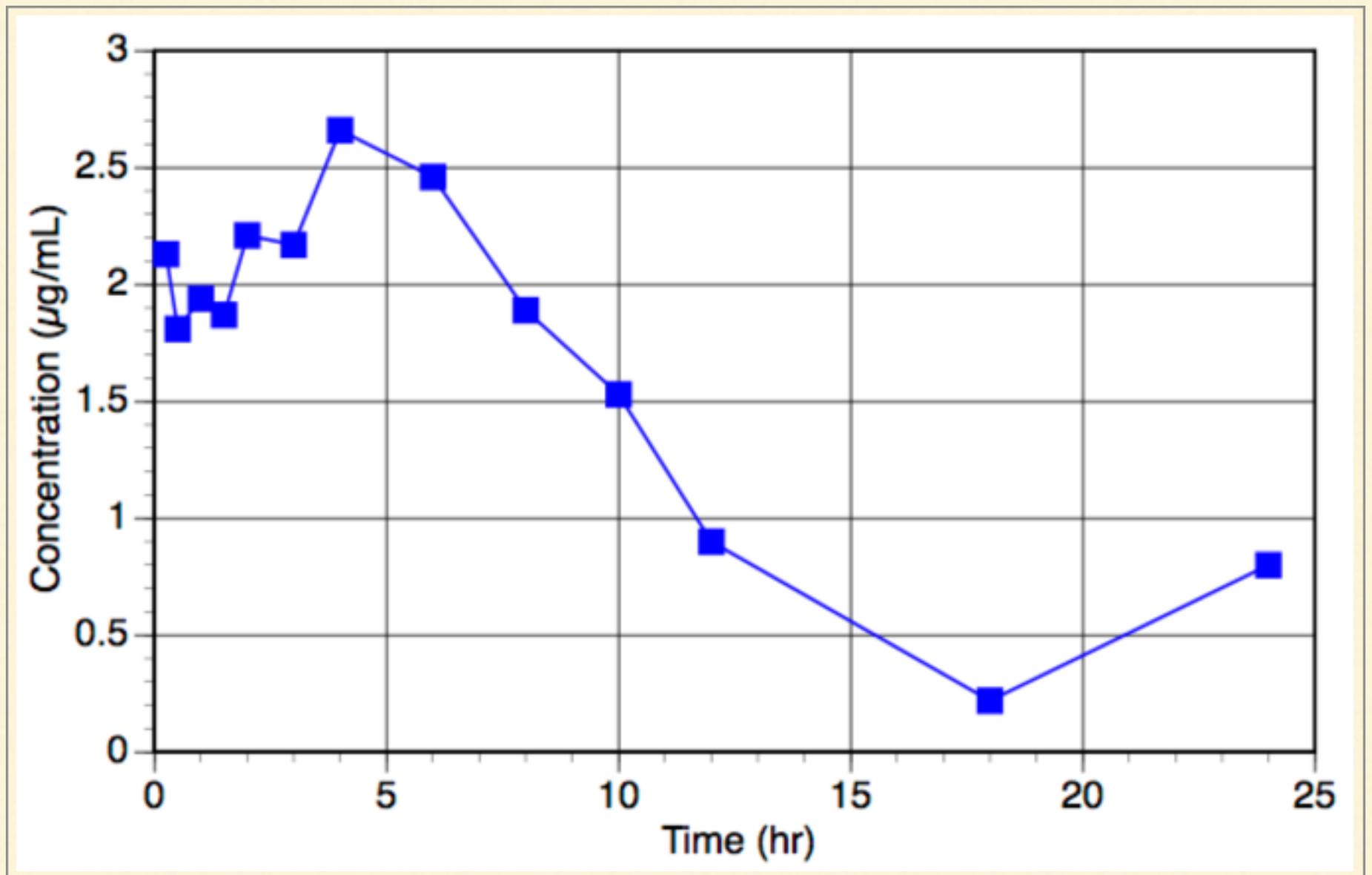
On 20 Oct 1997 at 12:34:01

I have the following drug pk problem to analyze:

Procedure: Drug administration: single IV bolus injection to dog, Drug dose: 1 mg/kg

Results

Time (hr)	Conc ($\mu\text{g/mL}$)
0.25	2.13
0.5	1.81
1	1.94
1.5	1.87
2	2.21
3	2.17
4	2.66
6	2.46
8	1.89
10	1.53
12	0.9
18	0.22
24	0.8



Questions:

1. How can the data be analyzed? Can this data be modeled on WinNonlin? What model should I use?
2. What does this data mean? The blood concentration of the drug remains the same or slightly rises over the first 4 hours following IV bolus injection to the dogs, then falls rapidly. We have dosed two other dogs with the same results. This seems unusual to me. Is there another example of a drug that behaves in this manner?

Tom Wallace

[Without looking at the graph - could it be enterohepatic recycling - any meals/food provided - what is the assay variability - db]

On 20 Oct 1997 14:43:17

I would pursue enterohepatic recirculation. You may want to perform the initial study in rats before choosing to attempt the same more time consuming and expensive procedure in dogs. Cannulated rats can be purchased from several sources.

Steven J. Weber

On 20 Oct 1997 13:57:24

I realize this doesn't respond directly to your question, but what are the SD's of your serum level data, so that each level can be given its proper credibility in whatever fitting process is done? It also looks as though you will have to evaluate several different compartmental models before you get an idea which model is best.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA 90033

http://www.usc.edu/hsc/lab_apk/

On 20 Oct 1997 18:27:19

Tom Wallace posted a PK data set with somewhat unusual characteristics and asked for possible interpretations. Among metabolic systems there are several that display kinetics such as Tom describes. One with which I have a lot of personal experience is the plasma lipoprotein delipidation cascade. This consists of a series of metabolic conversions (catalyzed by a pair of plasma lipases) that converts very low density lipoprotein (VLDL) to IDL and then to the notorious LDL, which finally is cleared from the circulation by the famous apoB receptor. In the early days of this field, VLDL and IDL were isolated together and their combined kinetics looked a lot like Tom's drug concentration time course. (a small peak or even a frank plateau followed by an apparently exponential decline.

In Tom's case, a lot depends on whether you believe the point at 18 hours or the point at 24 hours. If both are correct the system is even more complex and David's suggestion of enterohepatic recycling could be invoked. But I'd be inclined to believe the 18 hour point

and to use a model consisting of a series of compartments with elimination from the last of them. You would fit the data against the sum of all the compartments, and the injection would be into the first compartment. I have no doubt that the data set Tom supplied could be fitted to such a model.

Then the question becomes what is the physiological significance of this cascade? Without knowing more about the compound Tom administered, it's hard to say for sure, but a good initial hypothesis would be that the drug is processed intravascularly and only after several steps does it become a substrate for its clearance mechanism. To evaluate this you'd first want to know for sure that your assay measures only the parent compound and not its metabolic successors. A second hypothesis perhaps worth testing, is that the compound has a high affinity for VLDL and is adsorbed onto the surface or even dissolved in the core lipid of this lipoprotein. This would result in kinetics that are determined by lipoprotein processing, and in effect the drug becomes a tracer for lipoprotein metabolism. Under some circumstances, this could be a gold mine.

The bottom line is that a likely model for the data set Tom posted is a series cascade with the data fitted to the sum of all the compartments and elimination from the last. Models like this are easy to build and fit to data using compartmental analysis packages like SAAM 3I, SAAM II and ACSL BioMed to name just the ones I'm at least a little familiar with. There are many others, for example ScoP, and it may even be that WinNonlin will do this problem. The software is not the key. The key is recognizing the nature of the problem, and my best shot at doing that is the cascade mechanism described above.

Tom, there are definitely solutions to this class of problems. Let me know if I can be of further help.

Robert D. Phair, Ph.D.

BioInformatics Services, 12114 Gatewater Drive, Rockville, MD 20854 U.S.A.

<http://www.bioinformaticsservices.com>

On 20 Oct 1997 20:14:44

Sorry, cannot comment on equations, but, could this be an example of redistribution from another compartment? Another example might be diazepam diffusion from blood to CNS

and then diffusion back from CNS to blood. (Reason why lorazepam is recommended over diazepam for treatment of seizures.

Greg Soon

Pharmacist - ICU/Surgery, Peterborough Civic Hospital, Peterborough, ON, Canada

On 21 Oct 1997 16:29:47

We analyzed your data using the CXT software package. Since we did not know the weight of the dog, we estimated it as 15 kg, so we used the total dose of 15000 micrograms. Below please find the model function describing behavior of your system:

$$C(t) = 15000 * 2.51E-3 * \{0.0459 * \exp(-0.0572 * t) + 0.0859 * \exp(-0.5708 * t) + \\ -0.0558 * \exp(-167.6102 * t) + \\ \exp(-0.1551 * t) * [-0.0738 * \cos(0.3372 * t) + 0.052 * \sin(0.3372 * t)] + \\ \exp(-0.0102 * t) * [-2.1112E-3 * \cos(0.5939 * t) + 2.0337E-3 * \sin(0.5939 * t)]\}$$

You can plot this model function and compare it with the data measured. The value of the Akaike criterion is: 10.4. On the basis of this preliminary model, it is possible to estimate pharmacokinetic parameters e.g.:

$$\text{Clearance} = (1/2.51E-3) = 398.4 \text{ mL/h}$$

$$\text{AUC} = 37.65 \text{ microgram} * \text{h/mL},$$

$$\text{MRT} = 14.9 \text{ h}$$

$$\text{AUC}_{\text{residual}} = 28\%.$$

This model function is a solution of the seventh-order differential equation, indicating a time delay in your pharmacokinetic system. It follows then that, your system cannot be described by a multi-exponential model. We would recommend you to add the following sampling points: 5, 10 min., 15, 21, 27, and 30 h.

Maria Durisova and Ladislav Dedik

On 21 Oct 97 16:39:59

Interesting problem...

Procedure: Drug administration: single IV bolus injection to dog Drug dose: 1 mg/kg

This raises further questions:

1. What was the drug? (I seem not to be able to find it in your note.)
2. What was the salt of the drug?
3. Was it inadvertently administered SC or intradermally?
4. How was it administered IV (?via a cannula or other tubing, was the tubing flushed?)
5. How were the blood samples taken (via the same cannula?, how much blood was discarded from the sample before the remainder was kept for assay...?)
6. What condition was the dog in? (any relevant pathology?)

Steve Duffull

On 21 Oct 1997 12:46:15

What is your detection limit? The noisy data may be due to the concentration being close to or below the detection limit.

Jian-hua Liu

On 22 Oct 1997 21:39:48

Problem: sustained concentrations following iv bolus administration

You don't mention any of the drug characteristics, particularly its solubility.

When I was injecting Tribissen, a suspension of Trimethoprim and solution of sulfadiazine, into 1 day old calves we found that Trimethoprim (TMP) seemed to adhere to the walls of the vein (jugular) and give us a prolonged "distribution phase". It was not as dramatic as the data presented here but it may be the same phenomenon. Also, are you sampling from the same vein as you injected from? This can really "inflate" your plasma values.

Susan E. Shoaf

On 24 Oct 1997 at 09:39:27

About detection limits. This is an interesting issue. It relates in general to the problem of assigning the correct weight to a serum level (or any other) data point when fitting it by almost any method, and in optimal population modeling.

The really important thing is to KNOW the error with which each serum level is measured. Often people choose weighting by the reciprocal of the concentration, or its square. The best, I think, is to know the standard deviation (SD) with which each and every serum level is measured. Then one can correctly weight each level by its Fisher information, the reciprocal of its variance, in the modeling process.

Unfortunately, most labs have not done this. Once the error, usually the coefficient of variation, has been shown to be within socially acceptable limits, then the actual errors are too often ignored, and not realistically incorporated into the fitting process.

We suggest that one determine, empirically, in at least quadruplicate, the SD of representative concentrations over the working range of the assay - for example, of a blank, a low, a medium, a high, and a very high level. Now, fit the relationship of SD to concentration with a polynomial to capture this usually nonlinear, convex upward, relationship, so that you can estimate the SD from the serum concentration that is measured. Having done this, one now has a pretty good, and cost-effective way to get an estimate of the SD with which any single level is measured.

These issues are discussed in more detail in

Jelliffe R: Explicit Determination of Laboratory Assay Error Patterns - A Useful Aid in Therapeutic Drug Monitoring. The American Society of Clinical Pathologists CHECK SAMPLE continuing education program, *Drug Monitoring and Toxicology*, **10**: No. DM 89-4 (DM-56), 1990, and Jelliffe R, Schumitzky A, Van Guilder M et al: Individualizing Drug Dosage Regimens: Roles of Population Pharmacokinetic and Dynamic Models, Bayesian Fitting, and Adaptive Control. *Ther. Drug Monit.* **15**; 380-393, 1993.

The point of this is that for toxicology, one MUST have lower detectable limits, as there is no other way to make a decision as to whether the drug is present or not. However, for TDM or for PK studies, one usually knows quite well how long after each dose the sample was measured, and we also know that for most linear systems, at least, one never gets rid of the last molecule, so to speak. We therefore have the answer as to whether the drug is

actually there or not - it clearly IS. The only question remaining is what concentration, and with what error.

It has been common to think that when the levels get very low that the coefficient of variation approaches infinity. True enough, but what about the SD and the variance, and therefore, the Fisher information? All this is knowable right down through low levels, all the way down to the blank. Because of this, there is actually **NO LOWER DETECTION LIMIT** for samples measured when the time after the last dose is known, at least for drugs having linear models. Using such polynomials, from which the SD of each level can be estimated usually easily and quite well, the correct weight appropriate to its credibility can be given. For TDM at least, this whole question of lower detection limits has been a cultural problem derived from toxicology, not from TDM. Look at the articles and let me know what you guys think, and let's continue to talk about it.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA
90033

High/Low Extraction Drug

On 25 Apr 1997 at 12:12:38

Does anyone have any information on how to predict whether or not a drug is high or low extraction ?

I am trying to determine what the consequences of a decrease in hepatic perfusion (CHF) will have on a drug that is eliminated almost entirely via hepatic metabolism.

Christopher Houle

On 28 Apr 1997 at 11:20:11

I think a high partition coefficient is a hint that a drug will be a high extraction drug. e.g. Propranolol, lidocaine etc.

Steven Pomarico

On 28 Apr 1997 at 11:22:21

There are 2 papers which might help you. They show the usefulness of hepatocytes or liver microsomes (rat and human) to classify compounds into Low/Int/High hepatic extraction ratio, based on their in vitro metabolic stability :

J. B. Houston, *Biochem. Pharmacol.* **47**, 1469-1479, 1994

Th. Lave et al., *Pharm. Res.*, **14**, 152-155, 1997

Thierry Lave

High Throughput Pharmacokinetics

On 10 Sep 1997 at 10:47:38

In order to increase screening efficiency early in drug discovery, using a cocktail dosing solutions containing a certain number of drug molecules (~5) seems to be an attractive approach for PK studies. Drug interaction seems one of the major concerns. How one can minimize drug interaction and obtain reasonably useful information from cocktail design?

Are there some studies published?

What kind of criteria should be employed in selection of drugs which are going to be formulated as a cocktail dosing solution? Analog series vs. heterogeneous group of molecules

Majid Vakily Ph.D.

Principal Research Scientist, Hoffmann La Roche, Drug Metabolism and Pharmacokinetics/Discovery, Room No 1545

On 11 Sep 1997 at 09:47:20

There is only one study that I am aware of: Berman et al., *J. Medicinal Chem.*, **40**; 827-829 (1997).

Michael Mayersohn

On 11 Sep 1997 at 09:47:53

You might be interested in the following two papers:

Berman, J. et al. 1997 Simultaneous pharmacokinetic screening of a mixture of compounds in the dog using API LC/MS/MS analysis for increased throughput. *J. Med. Chem.* **40**: 827-829.

Olah, T.V. et al. 1997 The simultaneous determination of mixtures of drug candidates by liquid chromatography atmospheric pressure chemical ionization mass spectrometry as an in vivo drug screening procedure. *Rapid Commun. Mass Spectrom.* **11**:17-23.

DR P.H. Van der Graaf

Leiden/Amsterdam Center for Drug Research, Department of Pharmacology, P.O. Box 9503, 2300RA LEIDEN The Netherlands

History of Pharmacokinetics

On 3 Sep 1997 at 10:15:37

I am preparing a set of lessons about clinical PK, and I wish to introduce it by an historical perspective. However, textbooks and review papers contain few references on that topic. Would someone know about seminal works and papers on PK in the past? Who introduced first the concepts of compartment models to describe the fate of drugs in the body? When was the relevance of such descriptions recognized as clinically important? Which were the most cited papers in that field some decades ago?

Thierry BUCLIN, MD

Division of Clinical Pharmacology, University Hospital CHUV - Beaumont 633, 1011 Lausanne - SWITZERLAND

On 4 Sep 1997 at 10:20:17

This seemed to be a popular question ;-)) so I've put the replies received this morning together in one message. It seems John Wagner's paper and book are good reviews with the Rescigno and Segre book another early reference.

From Gibaldi and Perrier's first edition of **Pharmacokinetics** some early names include Dost, Kruger-Thiemer, Nelson, Teorell. The earliest reference listed was by Teorell. See the reply by Schoenwald below for the citations.

Wagner's book **Biopharmaceutics and Relevant Pharmacokinetics** provides a biography starting on page 331 (as mentioned by Schoenwald and lists as the earliest paper; Hanzlik, P.J.: The absorption of sodium iodide, *J. Pharmacol. Exptl. Therap.* **3**:387-421, 1912

David Bourne

On 3 Sep 1997 12:16:05

A paper by John Wagner History of Pharmacokinetics, *Pharm. Ther. Vol. 12*. pp 537 - 562, 1981 contains good historical information on the subject.

Don Gibson

Parke-Davis

On 3 Sep 1997 12:54:50

In the late 1960s, when I first learned about kinetics, the seminal book was by Aldo Rescigno and Giorgio Segre. Its title is **Drug and Tracer Kinetics** published by Blaisdell 1966, based on a translation of the Italian edition published in 1961. Since that time numerical solutions of the full differential equation systems have largely supplanted the Laplace transform methods of this book, but no review of the history of PK could be complete without reference to Rescigno and Segre.

Robert D. Phair, Ph.D.

BioInformatics Services

<http://www.bioinformaticsservices.com>

On 3 Sep 1997 13:13:51

In *Pharmaceutical News* there were series of articles by Dr. Gibaldi they should help you. Vol 1 of Pharmacokinetics and Biopharmaceutics presented a historical perspective.

Food thought who could have started the idea of Pharmacokinetics

My thought is Anesthesiologist.

Prasad Tata

On 3 Sep 1997 13:23:35

The best "History of Pharmacokinetics" review of which I'm aware was written by John Wagner. The reference is as follows:

Wagner JG. "History of Pharmacokinetics" in **International Encyclopedia of Pharmacology and Therapeutics**, Section 122. **Pharmacokinetics: Theory and Methodology**. Rowland M and Tucker G. (eds). Pergamon Press, NY, 1986.

Jim Coyle, Pharm.D.

College of Pharmacy, The Ohio State University, Columbus, OH

On 03 Sep 1997 18:45:02

An excellent bibliography of early pharmacokinetic work is referenced in Chapter 43 of Wagner's text titled, **Biopharmaceutics and Relevant Pharmacokinetics** 1st edition, Drug Intelligence, 1971. Page 331 of this text lists two papers by Torsten Teorell that I have always assumed to be the first publication of a solution to a two compartment open model along with the assumptions important to the modern definition of multicompartment. The reference is *Arch. Intern. Pharmacodyn.*, **57**:205-225, 1937 and *ibid*, **57**:226-240, 1937. The bibliography is excellent with regard to papers published prior to 1963.

Ron Schoenwald

Professor, Pharmaceutics Division

On 04 Sep 1997 08:09:08

I would recommend an old review by Prof. Wagner:

Wagner JG. 1981 History of pharmacokinetics. [Review] [269 refs] *Pharmacology & Therapeutics*. **12**(3):537-62

Vladimir Piotrovsky

On 4 Sep 1997 08:29:36 +0200

Dr. John Wagner wrote an excellent paper about 'History of pharmacokinetics' which appeared in *Pharmacology and Therapeutics* in the beginning of the 80's and in **International encyclopedia of Pharmacology and Therapeutics** Section 122 (Ed. m.Rowland and G. Tucker), 1986, Pergamon Press.

That paper contains many of the early references you may be looking for.

Other good references on the early work are by Rescigno and Segre, 'Drug and Tracer kinetics', 1961, 1966, Blaisdell Publishing Company or D.S. Riggs 'Mathematical Problems to physiological problems, 1963 Williams and Wilkins, or by Lassen and Perl 'Tracer Kinetics Methods in Physiology', 1979, Raven Press.

Johan Gabrielsson

On 3 Sep 1997 20:47:17

There is a PK history paper a few years ago by John Wagner of Upjohn. You might find this of value.

Xiaofeng Wang

On 5 Sep 1997 at 10:52:07

I have information probably of interest for you in the topic of history of PK:

Pharmacokinetics Bibliography. Revision of Prof. Edward Garret in the Course of Pharmacokinetics (Gainesville, Florida). I have the edition of 1981. This revision is an expanded from:

A Bibliography of Selected Pharmacokinetic Topics by David H. Cocchetto and William A. Wargin, *Drug Intelligence and Clinical Pharmacy*, **14**, 769 (1980).

Spanish publications of this topic:

a) Evolucion historica de la Biofarmacia y farmacocinetica, una nueva disciplina farmaceutica. I.G. Alonso, J.M. Lanao, A. Dominguez-Gil. *Industria Farmaceutica*: **2**: 151-156. 1990.

b) Biofarmacia y farmacocinetica: aproximacion historica. I. Origenes y ecuador de la farmacocinetica. Lopez Guzman, J., Vidal Casero, M.C., Pla Delfina, JM.. *Ciencia Farmaceutica*. **2** (5): 349-357. 1992.

c) Biofarmacia y farmacocinetica: aproximacion historica. II. La expansion de la farmacocinetica. Lopez Guzman, J., Vidal Casero M, Pla Delfina, JM. *Ciencia Farmaceutica*. **2**(6): 419-432. 1992.

c) Biofarmacia y farmacocinetica: aproximacion historica. III. *Biofarmacia: estudios de biodisponibilidad*. **3**(1): 41-54. 1993.

d) Biofarmacia y famacocinetica: aproximacion historica. IV. *Biofarmacia: modulacion de la biodisponibilidad*. **3**(2): 97-116. 1993.

e) Farmacia Clinica, farmacocinetica y adminstracion de medicamentos. Marino, E.L., Modamio, P., Montejo, O., Lastra, C.F. *Rev. O.F.I.L.* **6** (4): 258-270. 1996.

- The exactly information about the book of Rescigno and Segre, is:

DRUG AND TRACER KINETICS, ALDO RESCIGNO. University of New South Wales, Australian National University., GIORGIO SEGRE. University of Camerino, Italy., BLAISDELL PUBLISHING COMPANY. A Division of Ginn and Company. 1966. Walthman. Massachusetts. Toronto. London.

Translated from the italian: **LA CINETICA DEI FARMACI E DEI TRACCIANTI RADIOATTIVI** (1961), by PIERO ARIOTI.

In all case, I think that no review of the history of PK coul be complete without reference to Prof. Edward Garret.

Prof. Eduardo L. Marino. Pharm. D., Ph.D.

Clinical Pharmacy and Pharmacoterapy Unit., Faculty of Pharmacy. University of Barcelona., Avda. Joan XXIII s/n. 08028-Barcelona. (Spain).

On 8 Sep 1997 at 10:19:33

In the history of pharmacokinetics, as far as I know, it begins with the work of Torsten Theorell in 1937, who described the basic differential equations for a 3 compartment linear system. Then, interestingly enough, we can go back a bit further to Dr. Harry Gold at Cornell, who was the one who invented the ides of a loading dose of digitoxin followed by a maintenance dose. About 1929, for example, ie talks about cumulation being a self-limited phenomenon, and about each patient eliminating a certain fraction of drug from his body each day. In *JAMA* **92**: 1421-1423, 1929, you see this. In later works you can see that he has not followed this through formally, and, without any assays, gets this idea confused with an-

other one, that it may require more digitalis to get a patient out of failure than to keep him out of failure after that. There are articles about 1932-33 that show this.

Then we can jump to the work of A. Augsberger in *Klinische Wochenschrift* **99**; 945-951, 1954, Quantitatives zur Therapie mit Herzglycosiden, who took the ratios of commonly accepted ratios of loading and maintenance doses of various digitalis compounds, worked out their kinetics from this, and compared these predicted amounts of digitoxin, for example, with the effect of it on ventricular rate in A fib as studied by Gold later on in 1946. He also showed examples with Cedilanid and Acetyl digoxin. To my knowledge, this was the first truly pharmacokinetically oriented work dealing with digitalis therapy in its quantitative and pharmacokinetic aspects.

Then came Ekkehard Kruger-Thiemer, who laid out the formal theory of drug dosage regimens in several good articles in *J Theoret Biol* in 1966. Our work on digitalis built on this, and was first described in *Math Biosciences* **1**: 305-3325, 1967, *Ann. Int. Med.* **69**: 703-717, 1968, and 72; 453-464, 1970, and *Math Biosciences* **14**: 17-24, 1972.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA 90033

On 19 Sep 1997 at 10:27:37

I may have missed some part of the email exchanges related to the history of pharmacokinetics. Accordingly, I may duplicate information you already have.

I believe that one important person in this context is F.H. DOST from Germany who published in 1953 (Georg Thieme, Leipzig) the book: **Der Blutspiegel: Kinetik der Konzentrationsabläufe in der Kreislaufflussigkeit**. It is said that in this book he coined the word "Pharmakokinetik". This is at least what is written in the Foreword of the second edition **Grundlagen der Pharmakokinetik** of 1968 (Georg Thieme Verlag Stuttgart).

Luc P. Balant

Department of Psychiatry, 2, Chemin du Petit-Bel-Air, CH-1225 CHENE-BOURG

How are Tumor Drug Concentrations Measured

On 28 Feb 1997 at 11:51:25

We have been trying to measure drug concentrations in tumors. The problem we run into is the blood vessels surrounding the tumor. If we grind the tumor with the blood vessels, we will be measuring some composite value of the concentration of drug in tumor and in blood. We have tried to remove the blood vessels surrounding the tumor but have not been able to do it successfully. I was wondering if anyone in this group has experience in measuring the concentration of drug in tumors with a significant amount of vasculature. Is there a way to remove the vasculature or correct for the contribution of drug in blood to calculate the concentration in tumor? Any guidance you might have on this topic will be appreciated. Please include any references that discuss this issue.

Chetan D. Lathia

Pharmacokinetics and Drug Metabolism, Parke-Davis Pharmaceutical Research

On 3 Mar 1997 at 12:15:08

was wondering if anyone in this group has experience in measuring the concentration of drug in tumors with a significant amount of vasculature. Is there a way to remove the vasculature or correct for the contribution of drug in blood to calculate the concentration in tumor?

This enquiry begs the question "Why do you want to measure drug concs in tumor?". Assuming you want to know the conc at the site of action, even if you could find a way to measure 'blood free' conc in a tumor you still do not know the conc at the site of action but just the average conc in all the (non-blood) tissues (which depending on the tumor could be quite variable).

This average conc is not the 'true' conc at the site of action but just represents binding and partition among all the tissues in the sample which would only resemble the conc at the site of action by very good luck.

It is my personal opinion that all attempts at so called tissue conc measurements based on grinding up heterogeneous tissue masses are a form of fool's gold. Unless you have some good reason to believe that there is active transport to the site of action (or active transport out of the site) then concs at the site of action will be proportional to unbound conc in blood at steady state - so you may as well measure blood concs and forget messing around with the tissue.

So please let us know why you think blood free tissue concs would be useful to you.

Note that you can get an approximate answer by injecting the animal with a marker substance that does not cross blood vessels, measures its conc in blood and the amount in the tissue and thus work out the volume of blood in the tissue. If you know the blood conc of your drug then you can figure out the amount of your drug in the blood in the tissue. Similar principles can be used to work out the amount of extra-cellular drug.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 3 Mar 1997 at 12:19:15

We use a correction factor for blood volume to account for the amount of material residing in the vasculature of that tissue. A detailed review on this can be found in the book entitled **Liposome Technology**, 2nd edition, Volume 3 (Interactions of liposomes with biological milieu) edited by G. Gregoriadis. See chapter 3, the article written by Marcel Bally, Lawrence Mayer, Micheal Hope, and Rajiv Nayar, "Pharmacodynamics of liposomal drug carriers: methodological considerations" (1993, CRC Press). Correction factors (red cell volume and blood volumes) for tumor and non-tumor bearing animals are listed here.

Trust this is of help.

Rajesh Krishna

BC Cancer Agency, Vancouver, BC

<http://members.tripod.com/~rkrishna/index.html>

On 3 Mar 1997 at 12:22:46

The issue raised here by Dr. Lathia has quite interesting implications, and is one that we have been concerned for many years. Originally, in the 1970's, we would express our biodistribution data in a variety of forms:

% ID [injected dose]/g of tissue, total

% ID/g of tissue, blood corrected

% ID/organ, total

% ID/organ, blood correct

% RD [retained dose]/ of tissue, total, etc, etc,

where the injected dose [ID] is the total amount of the drug administered to the animal, and where the retained dose [RD] is the amount of the drug remaining at time t. Each of these values may have some relevance. See for example: Synthesis and Distribution of ^{195m}Pt -cis-Dichlorodiammine Platinum (II). W. Wolf and R.C. Manaka. *J. Clin. Hematol. Oncol.*, 7, 79-85 (1977).

There are, however, many more issues to consider that an simple correction, and assuming that the tumoral blood pool is totally "external" to the tumor cell mass may not be correct.

1. Which is the specific tumor that is being studied? Not all tumors are the same. Their growths may be significantly different, their microvasculature structure may have differences, as we have begun to show. See: Pharmacokinetic Imaging of Animal Tumors can be Used to Evaluate the Pathophysiological Compartments that Regulate Drug Delivery. Alfredo R. Sancho, James A. Dowell and Walter Wolf. Abstract PPDM 8245, presented at the 1996 Meeting of the AAPS. *Pharm.Res.* 13:S-454, 1996.

More of this work, where we have shown how it is possible to measure, non-invasively, the vascular space in a given tumor mass, will be presented at the upcoming AACR meeting.

2. We have also noted that an understanding of the tumoral microvascular space may be quite relevant to our understanding of drug transport into tumors, and this can be graphically seen in two posters presented at the recent meeting on the Future of NMR

in Medicine. These posters, Magnetic Resonance Spectroscopy (MRS) allows Pharmacokinetic Imaging (PKI) Studies in Human Tumors. Walter Wolf, Victor Waluch, Cary A. Presant and Hyun K. Kim., and Magnetic Resonance Imaging in Functional Studies of Human Tumors. Hyun K. Kim, Victor Waluch, Alfredo Sancho, Cary A. Presant and Walter Wolf, both of them presented at the first Internet Conference on the Future of Magnetic Resonance in Medicine, Japan, January 27-February 3, 1997 may be viewed at our URL -

<http://www.usc.edu/hsc/pharmacy/pkimaging/posters.html>

Thus, rather than ignoring the microvascular space, we postulate that it may, together with the tumor's interstitial space and the tumor's intracellular space, be one of the important elements to consider in the rather complex picture of how drugs get delivered to tumor cells. The availability of pharmacokinetic imaging methods allows the direct measurement of such spaces in individual animals - and in humans.

Professor Walter Wolf, Ph.D.

Director, Pharmacokinetic Imaging Program, Department of Pharmaceutical Sciences, University of Southern California, 1985 Zonal Ave., Los Angeles, CA 90033

On 3 Mar 1997 at 12:25:09

Not knowing the characteristics of your tumor, I'm going out on a limb as I make the following comments.

This is a classic dilemma faced by anyone who has tried to target tumors. The tumor vasculature is going to vary from tumor to tumor, how the tumors differentiate, etc.. When I used to work on radioimmunoconjugates, we washed the tumors as best as we could with saline/PBS etc and then counted the tumors for radioactivity. To show specific tumor uptake we would use a control that was non-binding. This would give us an idea of blood pool effects. Without belaboring much on this issue, here are a few suggestions: 1. If this is a targeted agent, then the solution is easy. Use a similar molecule but without any binding specificity. I am assuming here that the targeting vector is distinct from the drug. Otherwise, try the following: 2. If it is a small molecule then determine the concentration of your drug in the tumor (before extensive washing), following washing. You might even

want to slice the tumor open, if it is a solid tumor. If you then compare the Tumor to Blood ratios, you ought to get a feel for specific tumor concentrations. Of course, this will only be an estimate at best

There is no easy solution to your problem, unfortunately.

Vinay Desai

Nycomed Inc.

On 4 Mar 1997 at 13:03:14

I don't have any experience in measuring drug concentrations in tumors. But we use microdialysis to measure drug concentrations in liver. People have used microdialysis in tumors also. You implant a microdialysis probe which consist of a dialysis membrane. The probe is perfused with a solution isotonic to the tumor medium. The small molecular weight drug will pass through the dialysis membrane and be carried away by the perfusion fluid which can be collected and assayed. The samples are protein free so you don't need any sample preparation or tissue grinding. Since you can place the probe anywhere in the tumor, vasculature is not a problem. Following are some references on tumors.

1. Microdialysis Sampling in Tumor and Muscle: Study of the Diposition of 3-Amino-1,2,4-Benzotriazine-1,4-DI-N-Oxide (SR 4233) R. K. Palsmeier and C. E. Lunte, *Life Sciences* 1994 **55**(10), 815-825
2. Pharmacokinetic and Metabolism Studies of 3-Amino-1,2,4- Benzotriaznine-1,4,Di-N-Oxide In Solid Tumors By In Vivo Microdialysis. R. K. Palsmeier and C. E. Lunte: Internat. Symp. on Microdialysis and Allied Analytical Techniques. (In: BAS' Current Separations) 1993 **12**:2, Abst# 55

Chandrani Gunaratna, Ph.D.

Senior Research Chemist, Bioanalytical Systems, 2701 Kent Avenue, West Lafayette, IN 47906

<http://www.bioanalytical.com>.

On 5 Mar 1997 at 11:39:18

Dr. Gunaratna

We had thought of using microdialysis to measure antineoplastic drug concentration in and around tumors of various sizes that had been implanted in rats. We hesitated and did not use this method, instead we used true noninvasive imaging methods.

My question is: How invasive is the probe? Does it perturb to a large extent the "normal" (as normal as a tumor can be) growth and patho-histology of the tumor? Does it cause extra leakiness?

Alfredo R. Sancho,

USC-PK Imaging Ctr.

On 5 Mar 1997 at 11:41:23

Nick

I was wondering if you might suggest something for the following scenario:

I agree with you that more traditional methods of measuring drug concentration are available and up to recently used extensively. Such methods as blood sampling, urine output, and others are considered to be the "traditional" pk drug measuring methods, from these measurements "assumptions" through mathematical analysis and "data-processing" are made to "estimate" or "approximate" drug concentrations in various tissues -including tumors- can be done.

My question is, when working with patients and with novel drugs or "cocktails" of antineoplastic drugs, which are highly toxic. How do you justify pushing the limits of such drugs MTD into a patient so to sample blood and estimate the amount of drug reaching the tumor? Would it not be better to somehow administer lower dosages -less toxic, less costly, less possibilities of negative side effects- of the same drug/s and measure non-invasively the amount of the drug in the tumor? How else can you not perturb the system -possibly freeing tumor cells into the body- yet obtain meaningful data? How else can you not find yourself making leap-of-faith assumptions from calculations?

You see, after studying tumors for several years, no two tumors are alike, even if they are of the same origin and found in the same patient and tissue. Each tumor will grow in its own radically different style and madness. Particularly their microvascular network. Being that the case would you not need to measure exactly -or as precise as possible- the %ID of your administered drug? For instance, what would happen if you make assumptions based on blood sampling and due to the odd and unique pathophysiological factors found in tumors -e.g. microvasculature- the drug never reaches the tumor in any therapeutic amount? And clinicians continue the protocol for several months. Would it not be nice to know if the drug is going to reach the tumor, this from a single dose measurement? In that manner the researcher/clinician group can select the most effective drug for that patient?

Alfredo R. Sancho,

USC PK-Imaging Ctr.

On 6 Mar 1997 at 11:06:29

We've used microdialysis to measure brain extracellular drug concentrations (Scheyer, R.D., During, M.J., Hochholzer, J.M., Spencer, D.D., Cramer, J.A. and Mattson, R.H. Phenytoin concentrations in the human brain - an in vivo microdialysis study. *Epilepsy Res.* **18**:227-232,1994., Scheyer, R.D., During, M.J., Spencer, D.D., Cramer, J.A. and Mattson, R.H. Measurement of carbamazepine and carbamazepine epoxide in the human brain using in vivo microdialysis. *Neurology* **44**:1469-1472,1994). After several hours, microdialysis concentrations reflect the extracellular space, rather than the vascular compartment, although there may be some residual "leakiness" for longer periods.

Restoration of the integrity of tumor vascularity might be different, and might vary with tumor type. Possibly of greater importance is what you wish to measure. Microdialysis is a useful probe of the extracellular space. While this is a region of interest for many drugs, it may not be of particular importance for antineoplastic compounds.

Richard Scheyer, M.D.

Dept. Neurology, Yale School of Med., P.O. Box 208018, New Haven, CT 06520-8018
USA

On 6 Mar 1997 at 17:51:28

Alfredo,

I agree with you that more traditional methods of measuring drug concentration are available and up to recently used extensively. Such methods as blood sampling, urine output, and others are considered to be the "traditional" pk drug measuring methods, from these measurements "assumptions" through mathematical analysis and "data-processing" are made to "estimate" or "approximate" drug concentrations in various tissues -including tumors- can be done.

These 'traditional' methods have been used successfully to understand how the time course of the effects of anti-tumour agents are linked to drug dose via models of drug concentration in plasma and at the site of action.

In the clinical pharmacology setting this has been helpful in identifying the predictable components of the dose-effect relationship e.g. differences in clearance from individual to individual and from occasion to occasion within the same individual.

My question is, when working with patients and with novel drugs or "cocktails" of anti-neoplastic drugs, which are highly toxic. How do you justify pushing the limits of such drugs MTD into a patient so to sample blood and estimate the amount of drug reaching the tumor? Would it not be better to somehow administer lower dosages -less toxic, less costly, less possibilities of negative side effects- of the same drug/s and measure non-invasively the amount of the drug in the tumor?

I did not advocate 'pushing the limits of drugs MTD...so to sample blood and estimate the amount of drug reaching the tumor'. The kinds of studies that I am referring to may be done during Phase I (when the MTD is determined) but have been done and have been most informative at doses which are thought to provide optimal clinical responses. My question about the use of so called tumor concentrations should be considered in the setting of giving the same dose to the same patient. In that case, what could be learned from 1) blood concentrations 2) invasive tumor concentrations (as proposed originally in this thread) 3) non-invasive imaging? Which would help understand the effects of the drug? I would think that a combination of 1) and with the others would be most informative but the specificity of the average tumor concs or the imaging pictures as markers of concs at the site of action would determine their relative contributory merits. Approaches which use 1) plus some marker of drug effect and a suitable model have been very helpful (see below).

How else can you not perturb the system -possibly freeing tumor cells into the body- yet obtain meaningful data?

A combined approach should be considered, of course.

How else can you not find yourself making leap-of-faith assumptions from calculations?

Most of the assumptions I need to make are based on strong biological and chemical a priori knowledge. I mentioned one such assumption in my original posting i.e. equal free water concs in blood and at the site of action when at steady state. What leap-of-faith assumptions are you thinking of?

You see, after studying tumors for several years, no two tumors are alike, even if they are of the same origin and found in the same patient and tissue. Each tumor will grow in its own radically different style and madness. Particularly their microvascular network. Being that the case would you not need to measure exactly -or as precise as possible- the %ID of your administered drug? For instance, what would happen if you make assumptions based on blood sampling and due to the odd and unique pathophysiological factors found in tumors -e.g. microvasculature- the drug never reaches the tumor in any therapeutic amount? And clinicians continue the protocol for several months. Would it not be nice to know if the drug is going to reach the tumor, this from a single dose measurement? In that manner the researcher/clinician group can select the most effective drug for that patient?

The issues of variability, from patient to patient (or tumor to tumor if you wish), are indeed very important. They have been the focus of substantial efforts among the clinical pharmacology PKPD community. Large fractions of variability are currently without explanation so any methods that offer insights into this are very welcome. It should be noted however that PKPD studies have been critical in understanding that the variability in drug disposition and response from one treatment occasion to another can be so large that the first treatment response only predicts a very small part of the second treatment. e.g.

Karlsson MO. Port RE. Ratain MJ. Sheiner LB. A population model for the leukopenic effect of etoposide. *Clinical Pharmacology & Therapeutics*. 57(3):325-34, 1995 Mar. reported occasion to occasion variability in EC₅₀ was so large that the same average conc should be targeted for all patients but the variation in clearance was small enough that use could be made of plasma concs from the first course to predict the dose needed for the second.

An analysis based only on tumor site sampling could only have addressed the PD part (eg very variable EC₅₀) while a combined approach of PK and PD (using leukopenia as the effect) revealed the relative important of PK as a way to optimize response.

So please understand that I am not saying tumor concs are a waste of time. But neither do they offer the gold standard for understanding how to use anti-cancer agents. I would still be interested in hearing from the originator of the thread about what was hoped for by estimating blood free concentrations in a tumor.

It is also important to appreciate that different approaches are needed at different stages of understanding the pharmacology of a drug. During drug discovery tumor concs may be a very helpful screening tool for certain compounds while in phase III clinical trials blood concs may be critical in understanding what the optimal dose might be.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

On 7 Mar 1997 at 09:58:19

Nick:

I am glad that the vagueness is cleared. Moreover I agree with you that a multidisciplinary method or approach is needed to truly and fully understand what happens in and around the tumor site.

Let me throw this question in the pile:

1) If clearance is a way of calculating the amount of drug left in the blood compartment, hence how much is left in the tumor... what model are you using to compare the tumor compartment? There is no tissue in the body that has the same infrastructure as that of tumors. We could not even compare it to the tissue in which the tumor is in. Therefore, either assumptions are made or invasive measurements are needed.

Now if we agree that there is great patient inter-variability and that measurements of clearance can be used as an indicator for tumor trapping of the drug. How accurate is this? Is it not contradictory? In the clinical scenario, would a one "common" or "average" dose -statistically calculated from previous patients- and noninvasive measurements be in order? That is the first dose measured at the tumor site itself, might be a indicator -if not a predictor- of tumor response.

You see I put myself in the patients position... do I want to go through an entire protocol of chemotherapy without know if it is effective or not. Based solely on "statistical analysis" of previous patient tumor response data. Or do I want to take a single dose ("average" dose) and measure its presence or lack of it in the tumor itself. This would tell the clini-

cian that the drug is not effective for that tumor, in that tissue, with those histopathological characteristics. Which in turn would save money, time and pain, leading to possibly finding the drug that does have the desired therapeutic effect.

Now that this has been said, I understand the origin of this thread as someone coming from this point. That is, how can we measure the antineoplastic in the microvasculature of the tumor. For how much reaches the tumor's microvasculature may be indicative of how effective is the drug. Without having to see a PD response from the tumor.

At least that is how I understood the origin of the thread. Maybe they should provide the discussion group their reasons for seeking such data?

Alfredo R. Sancho,
USC PK-Imaging Ctr.

On 7 Mar 1997 at 09:58:37

Would the microdialysis suffer of "clogging", at least in the case of tumors? That is, due to the rapid and chaotic growth of tumor cells. I would hate to introduce the probe into the tumor, which already is leaky in nature. But I would hate to implant the tissue or cell around the probe and have it grow around it!

Alfredo R. Sancho

On 7 Mar 1997 at 10:03:00

Richard Scheyer

Restoration of the integrity of tumor vascularity might be different, and might vary with tumor type. Possibly of greater importance is what you wish to measure. Microdialysis is a useful probe of the extracellular space. While this is a region of interest for many drugs, it may not be of particular importance for antineoplastic compounds.

The above statement is not correct. The extracellular space [interstitial fluid space, IF + microvascular space] is definitively of very major importance in drug transport into tumoral cells. We had recognized this on mechanistic grounds when we were studying the mechanism of gallium localization to tumors, where we had suggested a pH gradient in the interstitial fluid space due to lactic acidosis. See for example:

The Mechanism of Tumor Localization of Gallium-67 Citrate: Role of Transferrin Binding and Effect of Tumor pH. S.R. Vallabhajosula, J.F. Harwig and W. Wolf. *Intl. J. Nucl. Med.*, **8**, 363-370, 1981.

The importance of the IF space became apparent again when we were trying to model the tumoral pharmacokinetics of two anticancer drugs, 5-fluorouracil (5FU) and cisplatin. We had to incorporate another compartment between the vascular and the intracellular spaces to account for the trapping of 5-FU in tumors. See:

Pharmacokinetic Imaging of 5-Fluorouracil in Tumors using ^{19}F -NMR Spectroscopy. Walter Wolf, Victor Waluch, Cary A. Presant, Hyun K. Kim and Alfredo R. Sancho. *Eurospin Annual 1995-1996*, p. 99-103. and Noninvasive ^{19}F -NMRS of 5-Fluorouracil in Pharmacokinetics and Pharmacodynamic Studies. Walter Wolf, Victor Waluch and Cary A. Presant. *NMR in Biomedicine*. In Press.

Perhaps the major difference between studies in the CNS, as reported by Dr. Scheyer, and in tumors, is reflected in what had been stated previously in that message:

After **several** hours, microdialysis concentrations reflect the extracellular space, rather than the vascular compartment, although there may be some residual "leakiness" for longer periods.

The time frame in tumors is much, much shorter. 5-FU, cisplatin, and presumably many other antitumor drugs distribute by what is essentially a first passage process. That is one of the major reasons we felt that the introduction of another process whose kinetics were likely to be slow (equilibration between the interstitial fluid space and that of the microdialysis chamber) would not be conducive of measuring the fast kinetics of transfer between the 3 spaces that need to be considered when using PK to understand transport of drugs into tumor cells: the vascular space, the interstitial fluid space and the intracellular space.

This difference in the time frames (seconds or minutes, rather than hours) is one of the main reasons why we believe that the use of noninvasive methods is essential for capturing the kinetics of drugs in tumors. Another major reason is that each tumor mass is different - in structure, in vascularization, in the ratios of the various spaces - and therefore, in the transport of drugs into tumor cells.

Professor Walter Wolf, Ph.D.

Director, Pharmacokinetic Imaging Program, Department of Pharmaceutical Sciences,
University of Southern California, 1985 Zonal Ave., Los Angeles, CA 90033

On 7 Mar 1997 10:03:48

Alfredo

Microdialysis probe is totally invasive. They need to be implanted surgically. The linear probes are very small in dimensions so they cause minimal tissue damage. I do not recommend implanting them in humans at all because they can release the tumor cells. Histological studies in liver tissues done by Prof. Craig Lunte's group at University of Kansas have shown that there is some necrosis at the implantation site in implantations of longer than 12 hours.

I don't know what you mean by "leakiness"? Is it the ultrafiltration property of the dialysis membrane or leaking of tumor components? I am not very familiar with tumor physiology. Amount of ultrafiltration depends on the membrane length, flow rate etc. Ultrafiltration is not so significant in vivo.

Chandrani Gunaratna, Ph.D.

Senior Research Chemist, Bioanalytical Systems, 2701 Kent Avenue, West Lafayette, IN
47906

On 8 Mar 1997 at 22:42:46

Walter

I'm in complete agreement that the interstitial space is vital in modeling the kinetics. My point was only regarding the presumed site of action.

Richard Scheyer, M.D.

Dept. Neurology, Yale School of Med., P.O. Box 208018, New Haven, CT 06520-8018 USA

On 8 Mar 1997 at 22:47:07

Alfredo,

1) If clearance is a way of calculating the amount of drug left in the blood compartment, hence how much is left in the tumor... what model are you using to compare the tumor compartment?

I assume "compare the tumor compartment" means "predict the tumor compartment amount (or conc)".

There is no tissue in the body that has the same infrastructure as that of tumors. We could not even compare it to the tissue in which the tumor is in. Therefore, either assumptions are made or invasive measurements are needed.

I agree with you that purely PK guided methods based on plasma concs cannot predict tumor concs. Early attempts (1970s) to explain delayed drug effects (digoxin and LSD were the classical examples) nevertheless had some success in *describing* the time course of drug *effect* using 2 compartment PK models based only on plasma concs of drug.

In 1979 Lew Sheiner formulated what is known as the effect compartment model which uses the time course of drug effect and assumes a first-order process for equilibration of active drug substance at the site of drug effect. Often a parametric model for the relationship between conc and effect is also assumed but this is not required.

Another important class of models used to explain delayed drug effects are based on a physiological mechanism which is modified by the drug. Warfarin is the classic example here but these so called indirect effect models have been used in lots of places where the drug action can be understood in terms of an influence on the kinetics of a physiological substance that mediates the observed drug response.

Some assumptions are involved but especially with the indirect effect models these are usually strongly supported by the known physiology/ biochemistry.

I personally don't have an aversion to making assumptions like these. They are not leap-of-faith as you have suggested in an earlier posting (or at least they are dont seem so to me and you have not given me any examples yet of such LOF assumptions).

Now if we agree that there is great patient inter-variability and that measurements of clearance can be used as an indicator for tumor trapping of the drug. How accurate is this?

I don't think accuracy is really the issue here. It depends on what you mean.

Is is not contradictory?

I don't see any contradiction (yet).

In the clinical scenario, would a one "common" or "average" dose -statistically calculated from previous patients- and noninvasive measurements be in order?

Sure. When planning the first dose for a patient you cannot do anything else but rely on prior knowledge.

That is the first dose measured at the tumor site itself, might be a indicator -if not a predictor- of tumor response.

I quite agree. Once you have given a dose you can observe effects (and concs) and start fine tuning how to achieve your therapeutic target (see Holford NHG The target concentration approach to clinical drug development. *Clin Pharmacokin* 1995; **29**:287-291 for details of such an algorithm).

Of course, just how good a predictor the observed concs or effects are for the response to the next dose depends a lot on the drug. The etoposide example I cited in my previous posting predicted that concs used to individualize clearance would be of more value than attempting to individualize EC₅₀ based on measured effects.

You see I put myself in the patients position... do I want to go through an entire protocol of chemotherapy without know if it is effective or not. Based solely on "statistical analysis" of previous patient tumor response data. Or do I want to take a single dose ("average" dose) and measure its presence or lack of it in the tumor itself. This would tell the clinician that the drug is not effective for that tumor, in that tissue, with those histo-pathological characteristics. Which in turn would save money, time and pain, leading to possibly finding the drug that does have the desired therapeutic effect.

The example you give is rather simplistic. If there was such a drug and such a non-invasive test that could, on the basis of the a measurement made after the first dose, predict that the drug would not be effective then I am sure it would be very helpful. But I do not know of any real example of such a drug and test. Maybe a drug which exhibits multi-drug resistance (eg via P-glycoprotein transporter action) could show such an all or none penetration into a tumor. As you belong to the USC imaging group do you have any published examples of such phenomena?

It also seems unlikely that knowing the kinetics of the drug in the tumor would be all you would need. The sensitivity (or resistance if you want to think of it like that) of the tumour to the drug as a function of the tumor conc would also need to be understood. So you need a measure of drug effect as well as drug kinetics in tumor. Now, if you have the time course of the drug effect on the tumor and you have the time course of plasma concs a model connecting the two sets of observations can be built that can identify and distin-

guish the kinetic eg. CL, and dynamic eg. EC₅₀, components of the response and the next dose can be predicted on the basis of this improved understanding of what determines the response in that patient.

Now that this has been said, I understand the origin of this thread as someone coming from this point. That is, how can we measure the antineoplastic in the microvasculature of the tumor. For how much reaches the tumor's microvasculature may be indicative of how effective is the drug. Without having to see a PD response from the tumor.

Not having the tumor response only gives you part of the picture (see above).

At least that is how I understood the origin of the thread. Maybe they should provide the discussion group their reasons for seeking such data?

I agree that it would be useful if the person who started this thread (from Parke-Davis I seem to recall) would join us again to offer some justification for wanting to determine blood-free tumor drug concs. If anyone else is doing this type of thing it would be nice to hear from you too. My impression has been that we have had technical suggestions for applying methodology but no examples showing that knowing tumor concs makes any difference to drug development or patient care. I have given an example which predicts direct patient care consequences from understanding anti-tumor drug effects based on *blood* concs and *effects*. So lets hear from you tissue drug measurement guys!

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

On 13 Mar 1997 at 15:19:19

Nick:

Pharmacodynamics and related topics If anyone else is doing this type of thing it would be nice to hear from you too. My impression has been that we have had technical suggestions for applying methodology but no examples showing that knowing tumor concs makes any difference to drug development or patient care. I have given an example which predicts direct patient care consequences from understanding anti-tumour drug effects based on *blood* concs and *effects*. So lets hear from you tissue drug measurement guys!

Although I am not a "tissue drug measurement guy", these tissue-distribution studies are extremely valuable, in that they identify non-linearities in drug uptake or drug efflux from normal tissues and tumors (i.e. as may be possible with p-glycoprotein mediated efflux, as

you mention). A well-described example of non-linear tissue uptake is provided by Dedrick et al., who constructed physiologic pk models of methotrexate disposition.

I do not know of a single example of a PK/PD model utilizing tissue concentrations to predict efficacy or toxicity; however, this is not 'proof' that such models would not be valuable (or should not be pursued)!

The development of rational therapeutic optimization strategies, based on PK/PD, requires robust (if not realistic) models. Investigation of possible areas of non-linear disposition is essential for the development of robust, useful models.

Having said this, it is worthwhile to note that any approach investigating tissue v. plasma concentration relationships should attempt to make said determinations at a range of doses (or if possible, concentrations). Evaluation of tumor distribution at a single, low dose (as suggested by someone along this string) *may* provide an inaccurate assessment of tumor distribution resulting from therapeutic doses.

Joseph P. Balthasar, Ph.D.

Assistant Professor, Department of Pharmaceutics and Pharmaceutical Chemistry, 421 Wakara Way, Room 316, University of Utah, Salt Lake City, Utah 84108

On 14 Mar 1997 at 10:55:02

So lets hear from you tissue drug measurement guys!

Thank you. I note however that you are an indirect tissue measurement guy and not really a representative of the wet tissue group I was hoping would contribute at this point. However, many of your remarks have relevance to the study of PK on an organ or regional basis.

Perhaps the most cogent reasons why we believe that relying on noninvasive methods for generating data are: A) The living system is, by its very nature, a dynamic system. Precise knowledge of the kinetic parameters is probably as important - and sometimes likely to be even more important - than knowledge of the thermodynamic values.

Thermodynamic values in this context means the same as pharmacodynamics to me. My earlier example of etoposide PKPD (Karlsson et al). illustrated exactly this point. PK (clearance) was a more useful predictor of individual response than PD (EC50).

Kinetic data, however, must be generated under conditions where the system to be studied is not perturbed - e.g., that these kinetic events are not modified during the process of attempting to measure them.

The latter constraint is only a problem if your kinetic model does not include knowledge about "system perturbations". So called physiological PK models attempt to do this (at least for blood flow and organ size perturbations).

B) Noninvasiveness does, by its very nature, not perturb the system from which one is trying to generate data.

I am not familiar with your technology but assuming it is along the lines of PET scanning etc I would say that the while not very invasive (in contrast to direct brain sampling) it is quite interventional (scanner etc). Activities such as lying down e.g. to be scanned, can change systemic PK.

C) The collection of data from a single individual, and especially, measuring in that same individual changes induced by various perturbations, yields information that is often lost when analyzing pooled data. This is because such pooled data have all the interindividual variabilities superimposed on them. This topic was well documented in the PhD dissertation of R. Ricardo Brechner (1986), and published in *J. Pharm. Sci.* **53**:873-877, 1986.

The disadvantages of naive pooled data approach have been discussed at length in the PKPD literature and popln approaches to understand responses in individuals are widely used e.g. see the book **Variability in Drug Therapy** edited by Rowland, Sheiner and Steimer. Raven Press 1985 (based on a meeting in Rome in May 1984). At the second COST B1 program meeting on "Measuring and managing variability in response, concentration and dose" was held in Geneva, Feb 1997, and included a review by Karlsson on advances in the anti-cancer area.

D) Inasmuch as tumors, by their very nature, do not obey precise rules of growth, development, etc., it is critical to understand the degree of exposure of each tumor and or metastatic site to develop proper chemotherapeutic planning.

It may be that it is feasible on a tumour specific basis to plan chemotherapy using tumour localised PK data. I acknowledge your $P < 0.000001$ statement below but this is not the same as prospectively demonstrating the value of the intervention as the history of therapeutic drug monitoring has shown.

We now have a letter appearing in this month's Annals of Oncology that states that response of a tumor to 5-Fluorouracil requires that there are 3 independent conditions that have to be met simultaneously for this drug to be active. These 3 conditions are: 1) There must be trapping of 5-FU in the tumor. 2) The tumor must have adequate perfusion to make such trapping possible. 3) The tumor type must be of a responsive type to make such trapping effective.

Fine. But note that condition 1 is rather general. Its not an all or none world. The relation between extent of trapping and tumour response needs to be established (e.g. in terms of E_{max} , EC_{50}) and in particular what is the variability in response given the same trapping from one treatment occasion to the next. Unless this variability is sufficiently small there will be no benefit from attempting to individualise doses for a specific patient.

My impression has been that we have had technical suggestions for applying methodology but no examples showing that knowing tumour concs makes any difference to drug development or patient care.

We do have examples that show that drug trapping in tumors makes a significant difference on patient care. We have shown [The Lancet, 343:1184-1187, 1994] that there is a very strong association between the trapping of 5-FU in a variety of human tumors and response [$p < .000001$]. Our clinicians have been making use of whether a patient traps 5-FU to make decisions on patient treatment, as well as to assess whether a given modulator (e.g., methotrexate, interferon, etc.) is worth using in a particular patient.

Apart from the statistical correlation what can you say about the prospective benefit of making decisions about 5-FU? As noted above is this reproducible for a specific patient in settings where repeat treatments are usually employed? If single shot treatments are used then of course it is hard to understand how any individualisation based on studying the drug in that tumour can be of use (apart from the use of tracer doses which may be misleading for non-linear disposition processes).

Our studies showing that the targeting of cisplatin [studied using ^{195m}Pt - cisplatin] to brain tumors is a function of both the method of drug administration [see Cancer Research 49:1877-1881, 1989] and modifiers of osmolality [Proc. Am. Assoc. Canc. Res. 36:360(2142), 1995] are being utilized by clinicians to achieve significant success in the treatment of patients with high grade astrocytoma.

Thank you for the info.

This thread has revealed that different groups within the overall field of pharmacology are often unaware of the advances made by other disciplines. I certainly admit to such ignorance and I am delighted to have learned from the contributions to this thread.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

On 14 Mar 1997 at 10:55:33

Although I am not a "tissue drug measurement guy", these tissue-distribution studies are extremely valuable, in that they identify non-linearities in drug uptake or drug efflux from normal tissues and tumors (i.e. as may be possible with p-glycoprotein mediated efflux, as you mention). A well-described example of non-linear tissue uptake is provided by Dedrick et al., who constructed physiologic pk models of methotrexate disposition.

This point is well taken. I wonder if this is the main reason why the "tissue measurement guys" do it? What successes have they had?

I do not know of a single example of a PK/PD model utilizing tissue concentrations to predict efficacy or toxicity; however, this is not 'proof' that such models would not be valuable (or should not be pursued)!

I accept the lack of proof concept. But on the other hand people have been at this tissue PK game for decades (Dedrick was doing his stuff in the '60s and '70s). I am not aware that even the Dedrick MTX example had a clinical spinoff but I would be happy to be corrected on that. So just how has tissue sampling helped in understanding human clinical pharmacology?

Having said this, it is worthwhile to note that any approach investigating tissue v. plasma concentration relationships should attempt to make said determinations at a range of doses (or if possible, concentrations). Evaluation of tumor distribution at a single, low dose (as suggested by someone along this string) *may* provide an inaccurate assessment of tumor distribution resulting from therapeutic doses.

Agreed.

Nick Holford

Dept Pharmacology & Clinical Pharmacology

University of Auckland, Private Bag 92019, Auckland, New Zealand

Hydroxyurea Protein Binding

On 20 Oct 1997

Has anyone information regarding hydroxyurea protein binding? Determination of protein binding of hydroxyurea with Centrifrees yields a slightly, but constant, negative number. We see the same over a wide range of concentrations done in replicates of 5. Has anyone seen the same with other compounds that exhibit little to no protein binding? References?

Steven J. Weber

On 21 Oct 1997

How are you measuring the hydroxyurea? If you are using radioactivity, it is possible that the Centrifree tubes are removing a quenching substance. You may wish to verify your quench curve for ultrafiltrated and non-filtered samples. Occasionally, investigators rely too heavily on external quench correction, perhaps forgetting that the underlying efficiency relationships are matrix dependent.

If you are using HPLC, are you observing a fixed increase in assayed concentration (i.e., ultrafiltrated recovery = control recovery + some intercept) or a fractional increase in assayed concentration (e.g., ultrafiltrated recovery = 110% of control)? If you observe a fixed increase, you may be extracting an interfering substance with your ultrafiltration step. If you see a fractional change (i.e., a matrix effect), you may wish to check for increased post-filtration extraction of hydroxyurea, decreased post-filtration extraction of an internal standard, extraction of a substance which interferes with an internal standard).

Joseph P. Balthasar, PhD

Assistant Professor, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah

Ideal Body Weight Calculations

On 24 Feb 1997 at 10:41:38

I am searching the literature for alternative equations for the estimation of ideal body weight to use in the calculation of estimated Creatinine Clearance and to use with population estimates of volume of distribution for aminoglycosides, etc. Thanks in advance for any information provided...

Del Tippey R.Ph., M.S.S.M.

DCH Regional Medical Center, 801 University Blvd. E., Tuscaloosa, AL 35405

On 25 Feb 1997 at 12:34:46

I suggest you read a consensus document that was posted recently on the pulsing dosing of aminoglycosides. In an appendix at the end of this document you will find the desired equations and more. The address is: <http://www.pharmpk.com/consensus/odacd.html>

Nasr Anaizi, PhD RPh

Univ of Rochester Med Cntr

On 25 Feb 1997

The following equation can be use :

LBW (males) = 50 kg + 2.3 kg per inch over 5 ft

LBW (females) = 45.5 kg + 2.3 kg per inch over 5 ft

Please also see page 420, **Applied biopharmaceutics and pharmacokinetics** Leon Shargel and Andrew B.C. Yu for detail

Masood Bhatti

On 25 Feb 1997 at 12:36:25

The following is the equation that I always use. It has been verified in infants, children and adults.

BSA = [see correction below - db]

Haycock GB, Schwartz GJ, Wisotsky DH: Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. **Journal of Pediatrics** 1978;**93**:62-66.

Ronald A. Herman, Ph.D.

S525 College of Pharmacy, Asst. Prof., College of Pharmacy, Iowa City, IA 52246

On 26 Feb 1997 at 10:42:01

Thank you for the reply, but are you aware of equations that estimate ideal body weight for patients that fall outside this range -i.e. height < 60 inches, below knee amputees, etc. Thanks in advance...

Del Tippey R.Ph., M.S.S.M.

DCH Regional Medical Center, 801 University Blvd. E., Tuscaloosa,AL 35405

On 27 Feb 1997 at 10:34:43

Isn't there a misprint in your formula?

In Gibaldi, M., Biopharmaceutics and Clinical Pharmacokinetics. Philadelphia: Lea & Febiger, 1984, p. 211 we find almost the same formula except the coefficient:

$BSA(m^2) = WT^{0.5378} * HT^{0.3964} * 0.024265$

Vladimir Piotrovskij

On 27 Feb 1997 at 10:34:57

Thanks for the info. Also thanks for the info you sent earlier regarding Vancomycin Vd. I'm going to check out this reference. BTW, does the ** refer to exponent?

[** is exponent, also ^ - db]

Del Tippey R.Ph., M.S.S.M.

DCH Regional Medical Center, 801 University Blvd. E., Tuscaloosa, AL 35405

On 28 Feb 1997 at 11:51:10

Yes, the last term should be 0.024265.

Also, the incorrect response was sent, my full message (but inadvertently not sent) was:

Ideal body weight (18 years of age and older):

Males: 50 Kg + (2.3 Kg for each inch over 5 feet)

Females: 45.5 Kg + (2.3 Kg for each inch over 5 feet)

(Unable to find primary reference.)

Ideal body weight (Children age 1 - 18):

Under 5 feet: $IBW (Kg) = (Ht \text{ in cm})^{**2} * 0.00165$

5 feet or taller: Males: 39 Kg + (2.27 Kg for each inch over 5 feet)

Females: 42.2 Kg + (2.27 Kg for each inch over 5 feet)

Traub SL and Johnson CE: Comparison of methods of estimating creatinine clearance in children. *Am J Hosp Pharm* 1980;**37**:195-201.

Body surface area:

$BSA (m^2) = (Wt \text{ in Kg})^{**0.5378} * (Ht \text{ in cm})^{**0.3964} * 0.024265 m^2$

Haycock GB, Schwartz GJ, Wisotsky DH: Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *Journal of Pediatrics* 1978;**93**:62-66.

Ronald A. Herman, Ph.D.

S525 College of Pharmacy, Asst. Prof., College of Pharmacy, Iowa City, IA 52246

On 5 Mar 1997 at 11:36:45

I would like to examine the various BSA formulas; we are having quite a argument at work over this. Historically our hospital utilized the charts or calculators found in many texts that are based on the 1916 Annals of Internal Medicine formula of Dubors and Dubois. When pharmacy became more involved we used the numbers in our computer software package. This formula involves the square root..... I wish I had the facts here at home. Needless to say, the numbers come out different; I expect if I use the formula in this newsgroup I will get a third figure to work with. I am not a scientist, just a pharmacist, but I would like to know alot more about the different bsa formulas and their relationship, if any. Likewise, what happens to the toxicity of my chemo doses if I use one over the other. I guess I'm really looking to defend the software program and prove the non clinicians at the hospital they should stick to their areas of expertise.

For the specific area of cancer chemo you should read Reilly & Workman Normalisation of anti-cancer drug dosage using body weight and surface area: is it worthwhile? *Canc Chemoth Pharmac* 1993; **32**:411-418 They cover in depth the issues you mention above. Unfortunately they do not recognise that PK is determined by volume of distribution (as well as other things) and they only discuss scaling that would be relevant to decisions that rely on clearance i.e. steady state concs or AUC. See Holford *Clin Pharmacokin* 1996;**30**:329-332 for a small amount of discussion of volume scaling.

The bottom line is that there is almost no evidence that using BSA or any other measure of size improves dose prediction for adults. The issue becomes important when trying to scale adult doses for paediatric use.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

In Vitro to *In Vivo* Scaling for Metabolic Parameters

On 22 Sep 1997 at 10:20:00

I am developing some human PBPK models for some volatile organic compounds. I have K_m and V_{max} data based on *in vitro* human liver microsomes. When scaling to *in vivo* I need a value for mg of microsome per gram of liver. I have been using a range of 10-50mg per g. Can anyone offer a better estimate or point me in the direction of some literature? I have found a couple of papers for rat data but none for humans.

Alex MacDonald

Graduate Student, Dept of Medicine and Pharmacology, University of Sheffield UK

On 23 Sep 1997 at 10:48:32

A good article on *in vivo*-*in vitro* correlation for human liver is Prediction of *in vivo* drug metabolism in the human liver from *in vitro* metabolism data, Takafumi Iwatsubo et.al. *Pharmacol. Ther.* **73**, no. 2, 1997 147-171

Chandrani Gunaratna, Ph.D.

Senior Research Chemist, Bioanalytical Systems, 2701 Kent Avenue, West Lafayette, IN 47906

Infusion rate versus Concentration

On 7 Mar 1997 at 10:01:31

This is for a colleague of mine.

A drug is administered by rapid bolus (rate defined) at several dosages and blood collected for analysis of test article concentration at several intervals following dosing, and the blood drug concentration vs. time profile defined. Based upon this data, I would like to model the blood drug concentration vs. time profiles for the same (or lower) dosages administered at different rates (slower or faster). I'm looking for a pharmacokinetic model which will permit me to model the effects of dosage, dosage rate, and blood drug concentration vs. time.

Vinay.Desai

On 8 Mar 1997 at 22:43:23

I may be missing something in your question but any PK model for an infusion (apart from those parameterized in the antique A, alpha, B, beta style) will allow the dose (or dose rate) and duration to be defined as part of the model and it should be straightforward to estimate PK parameters from your data and subsequently simulate profiles with different doses and input rates.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

On 13 Mar 1997 at 15:18:49

You need a model that is a good description of initial bolus kinetics to do this. I addressed these issues in a recent paper:

Upton RN. A model of the first pass passage of drugs from their intravenous injection site to the heart - parameter estimates for lignocaine. *Br J Anaesth* 77: 764-772 (1996)

You also might like to look at:

Wada DR, Ward DS. The hybrid model: a new pharmacokinetic model for computer-controlled infusion pumps. *IEEE Transcripts of Biomedical Engineering* 1994; 41: 134-42.

Krejcie TC, Henthorn TK, Shanks CA, Avram MJ. A recirculatory pharmacokinetic model describing the circulatory mixing, tissue distribution and elimination of antipyrine in the dog. *Journal of Pharmacology and Experimental Therapeutics* 1994; 269: 609-616.

Dr Richard Upton

Senior Hospital Scientist/Senior Lecturer, Department of Anaesthesia and Intensive Care,
Royal Adelaide Hospital/University of Adelaide, SA 5005 Australia

Interspecies Scaling of Lung Surface Area

On 23 Jun 1997 at 12:14:08

I am about to carry out some interspecies scaling in mammals for lung concentrations following inhaled administration.

Rather than using volumes in the scaling, it was thought more appropriate to use concentration of drug per square meter. However I am finding it very difficult to find references and values of the total surface area of lung, alveoli and bronchi, in rat, pig, dog, rabbit and humans.

J. Emelogu

On 25 Jun 1997 at 10:30:52

The following table appeared in Assessing the use of pharmacokinetic models in risk assessments on inhaled toxicants. MaryJo Miller. Dissertation submitted to the State University of New York at Albany, School of Public Health Sciences Environmental Health and Toxicology (1992).

Respiratory Tract Region	Surface Area (cm ²)		
	Mouse	Rat	Human
Nasopharyngeal	0.94	11.6	117
Tracheobronchial	3.2	37.6	5036
Pulmonary	292	3424	635545
Thoracic *	295	3462	640581
Total **	296	3473	640758
* Thoracic = Tracheobronchial + Pulmonary			
** Total = Nasopharyngeal + Tracheobronchial + Pulmonary			

Adapted from US Environmental Protection Agency (US EPA). 1989. Interim methods for development of inhalation reference doses. Washington, DC: Office of Health and Environmental Assessment. EPA/600/8-88/066F and personal communication with Ms. Margaret Menache, NSI Technology Services (under contract to US EPA), on May 3, 1991.

Jack Cook

On 25 Jun 1997 at 10:31:1

The appropriate reference is the **CRC Handbook of Toxicology**, Chapter 5 (Inhalation Toxicology); Eds. Derelanko MJ and Hollinger MA, 1995.

Anup Zutshi

IV Cannulas in Rats

On 5 May 1997 at 13:23:51

We are doing PK-PD work in rats and try to use the same rats for longitudinal studies. For that we need to maintain the iv. cannulas (indwelled into the Jugular vein) for several weeks. However, we experience constant technical problems due to plagues/ clotting/ blockade of the cannula. To prevent this problem we use heparinized PVP solution. Another problem is that after a while the rat managed to reach the cannula and to pull it out of the vein. The cannula is exteriorated at the lower dorsal part of the neck, and it is secured with 3 sutures at that attach the PE 50 cannula to the vein, the muscle and the skin. Does any of you have experience with prolonging the "life" of the cannula.

Amnon Hoffman, Ph.D.

Dept. of Pharmaceutics, School of Pharmacy, The Hebrew University of Jerusalem, POB 12065, Jerusalem 91120 Israel

On 6 May 1997 at 11:53:52

Usually, increased frequency of cannula care increases the long-term cannula patency. We use heparinized(20-50 U/ml)sterile isotonic saline to flush the cannula everyday. A blunt needle (23G1) and 1 ml syringe are used to flash the cannula. The instilled solution is withdrawn. The aspirated fluid/blood should be discarded as it may contain small thrombi. The cannula is flushed with saline to clear it of blood, and refilled with fresh heparin solution. The cannula should be flushed with a volume of solution slightly larger than the volume of the cannula. Forceful injection of saline (0.2 ml) may break up a obstruction with the risk of a trapped emboli in the vasculature of the lung. Of course the cannula has to be inside the vein to get blood.

Heparinized PVP solution offered no better advantage to us than heparinized saline.

We usually exteriorize the jugular vein cannula by subcutaneous tunneling from the vascular incision site to the back of the neck (midway and dorsal to the ears). The cannula is clipped with the skin to secure the position. The exterior length of the cannula is about 2 inches and plugged with a blunt quilting pin (0.5 inch)!

Some useful information can be found in the following article: Cocchetto et al. J Pharm Sci 72(5):465-492, 1983.

M. Delwar Hussain, Ph.D.

School of Pharmacy, University of Wyoming, Laramie, WY 82071-3375

On 6 May 1997 at 11:54:41

Here are some suggestions for jugular vein catheters in rats:

1. Be sure to flush the cannulas at least once (preferably twice) daily with heparinized saline (first thing in the morning and just before leaving for the day)
2. Exteriorize the catheter further down the back so the rats can't reach behind their heads
3. Increase the conc. of heparin in the catheter
4. Redesign your catheter (to avoid as many tubing joints as possible)
5. I have used a single piece of silastic tubing (about 6" long) with a large bead of silicone placed on the tubing about 1" from the end. The catheter is pushed in up to the silicone bead which is then sutured in place subcutaneously. The tip that enters the heart is beveled slightly. The catheter is exteriorized around the back of the neck and plugged with part of a blunt needle that has been blocked with silicone. I have never had one of these catheters pulled out and I have had good results keeping them open.
6. Also, sometimes what can appear to be a blocked cannula can often be a constriction related to the animal's position. Sometimes moving the animal a little bit or gently manipulating the area transversed by the catheter can eliminate the constriction.

Paul Damian PhD, MPH

Program Coordinator, Western Region, Food Animal Residue Avoidance Databank, Dept. of Environmental Toxicology, University of California, Davis, CA 95616

<http://farad.aaa.ucdavis.edu> (FARAD)

On 12 May 1997 at 15:55:20

I have used an indwelling plastic catheter on rats up to a couple of weeks. To keep the rats from chewing on them we made a saddle like construction in leather. It has a connection at the back for a steel-coil, in which the catheter can run. This steel-coil can be connected to the top of the cage, thus enabling a constant access to venous blood. When not doing experiments the plastic catheter can be kept under the saddle. If the rats are kept with the saddles pre-op. there are no problems post-op.

Magnus Hultin, Ph.D.

Dept of Medical Biochemistry and Biophysics

Umea University, Umea, Sweden

On 19 Jun 1997 at 13:29:04

I haven't read all of the responses yet so I don't know if you've heard this response yet. I perform dozens of vascular surgeries, and usually what we use to keep the catheter patent is heparanized saline at (100U/ml. It is necessary to flush the catheters every day in order to maintain it patency over time. I also use a tether spring system to protect the catheter. if you are not familiar with this system, it is a stainless steel spring that is placed over the catheter and is stitched to the animal's back. Because it is made of steel the animal cannot get to the catheter. It is also designed to be able to accomodate a spring if neccessary. I have recently investigated a company called Access Technologies based in Virginia that have developed silastic catheters with a rounded end. They claim that the rounded end damage the vessels less upon insertion and therefore can maintain patency for a greater length of time.

Danytza Ward

On 13 May 1997 at 11:25:05

About the issue of long term cannula in rats...

We place the cannula (Clay Adams, PE-50) in the rats right jugular. Pass it subcutaneously to the mid-scapular region of the rat, where we suture it into place using silk thread. The "free" end of the cannula we first tap it shut with clay or putty, sealing it and avoiding loss of blood. Then we re-insert it sub-cutaneously into the back region of the rat. All along we would occasionally flush the cannula with heparinized normal saline.

This has proven satisfactory, for the cannula does not become obstructed nor can the rat reach into its own body to bite the cannula. We have been able to keep this setup for several days with a high rate of success.

Also, we found that "installing" odd contraptions around or on the rat to protect the cannula, alter the rats stress level. Which you all know may very well affect the kinetics of the studied drug, due mainly to the physiological changes in the rat.

Alfred R. Sancho

USC PK-Imaging Ctr., Los Angeles, CA

Jack Knife Mean

On 23 Oct 1997 at 09:38:24

Would anyone teach me how to calculate the Jack Knife Mean (for estimating the Standard deviation of Harmonic Means) or give me a reference to any book on how this calculation is done

Raul Valverde

Phoenix International Life Sciences Inc.

On 24 Oct 1997 at 09:40:05

A reference for calculating pseudo-standard deviations for harmonic mean half-lives is:

Lam FC, Hung CT, Perrier D (1985) Estimation of Variances for Harmonic Mean Half-lives *J Pharm Sci* 74:229-231

Horst Welker

F. Hoffmann-LaRoche Ltd., Clinical Pharmacology, PDC5, CH-4070 Basel, Switzerland

On 24 Oct 1997 9:39:00

The following reference describes calculation of the harmonic mean and corresponding variance:

Lam et al: Estimation of variance for harmonic mean half-lives. *J Pharm Sci* 74:229-230, 1985.

Gary A. Thompson, Ph.D.

Clinical Pharmacology, Procter and Gamble Pharm., 11450 Grooms Rd., Cincinnati, OH 45242

On 24 Oct 1997 09:43:03

I have always found Efron's paper 'A leisurely look at the bootstrap, the jackknife and cross-validation' *The American Statistician* **37**: 36-48, 1983 a worthwhile source of information. It is well written and at a level which I feel comfortable with.

Leon Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, M13 9PL, U.K.

ka/k Values for Immediate Release Formulations

On 7 Oct 1997 at 10:53:31

I need to know does anyone have a reference that clearly states what the ratios of k_a/k would be for a drug exhibiting 1-compartment first order absorption kinetics to be considered an immediate release formulation. The values for these ratios should be consistent with the half-life of absorption being less than τ (dosing interval) when the formulation is given in a multiple dosing regimen.

Andre Jackson

On 8 Oct 1997 at 11:03:12

I would say that a k_a/k ratio between 5-10 would be satisfactory. I am not clear about your question reg: consistency with half-life of absorption being $<$ than τ . In most practical cases τ can be selected to be $>$ the time needed for absorption.

Srikumaran Melethil, Ph.D.

Professor of Pharmaceutics and Medicine, School of Pharmacy (Room 203-B)

University of Missouri-Kansas City, 5005 Rockhill Road, Kansas City, MO 64110

On 10 Oct 1997 at 14:50:30

One of our papers entitled:

M.L. Kaltenbach, S.H. Curry, and H. Derendorf. Extent of drug absorption at the time of peak plasma concentration in an open one-compartment body model with first order absorption. *J. Pharm. Sci.* **79** (5) (1990) 462.

may help you in determining the k_a/k ratio needed for a drug exhibiting 1-compartment first order absorption kinetics to be considered an immediate release formulation.

I can also remember that Dr. Macheras published an extension to this work for drugs exhibiting 2 compartments characteristics in the same journal a few years later.

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Matthieu L. Kaltenbach, PharmD, PhD

Laboratoire de Pharmacocinetique, UFR de Pharmacie, Universite de Reims Champagne Ardenne, 51 rue Cognacq-Jay, F-51100 Reims, FRANCE

Ketamine Pharmacokinetics

On 8 Jul 1997 at 09:36:57

I am writing a modeling program for the Psion computer. I have been unable to find complete 3 compartment data on the following drugs - does anyone have the data or know where to find it?

Ketamine

Alfentanil

Fentanyl

Obviously I need the compartment volumes, v_1 , v_2 , v_3 , and the coefficients k_{10} , k_{12} , k_{21} , k_{31} , k_{13} . Failing that Clearances and volumes should be enough to calculate the coefficients.

Dr Simon Ashworth

Dept Anaesthetics, Hammersmith Hospitals NHS Trust, LONDON

On 9 Jul 1997 at 11:33:11

Fentanyl

Olkkola K.T. et al. in *Clinical Pharmacokinetics*. **28**: 385-404, 1995

Ketamine

White P.F. et al. in *Br. J. of Anaesth.* **57**: 197-203, 1985

A review article published for the above two drugs before these dates can help you identify and cross-reference. This article is

Ghoneim M.M. and Korttila K. in *Clinical Pharmacokinetics* **2**: 344-372, 1977

Alfentanil

Bodenham A and Park G.R. in *Clinical Pharmacokinetics* **15**: 216-226, 1988

Anup Zutshi

On 9 Jul 1997 at 11:33:45

Here are references that I got in Dr. J.F.Coetzee's Simulation + CACI Program, STEL-PUMP:

Ketamine

Bomino et al. *Clin Pharmacol Ther* 1984; **36**: 645-653

Alfentanyl

Maitre et al. *Anesthesiology* 1987; **66**: 3-12

Scott JC, Stanski DR. *J Pharm Exp Ther* 1987; **240**:159-166

Fentanyl

Shafer et al *Anesthesiology* 1988; **69**: A460

Scott et al. *J Pharm Exp Ther* 1987; **240**:159-166 (keo from article?)

Stefan Harms

On 10 Jul 1997 at 15:56:08

According to fentanyl you will find first informations on pharmacokinetic rate constants in this articles:

Shofer SL; Varvel JR, *Anesthesiology* 1991; **74**: 53-63

Lemmens HJM; et al., *Clin Pharmacol Ther* 1994; **56**: 261-71

Willi Cawello PhD

Schwarz Pharma company, D40789 Monheim am Rhein, Germany

On 10 Jul 1997 08:29:08

The following references may be useful:

1. Youngs EJ. Shafer SL. Pharmacokinetic parameters relevant to recovery from opioids
Anesthesiology. **81**(4):833-42, 1994
2. Lemmens HJ. Dyck JB. Shafer SL. Stanski DR. Pharmacokinetic-pharmacodynamic modeling in drug development: application to the investigational opioid trefentanil.
Clinical Pharmacology & Therapeutics. **56**(3):261-71, 1994

Vladimir Piotrovskij

Ki Inhibition Constant

On 23 Oct 1997 at 09:46:38

When performing inhibition studies *in vitro* with human liver microsomes, one can determine a K_i value, that is the concentration of the inhibitor that reduces the formation speed of the metabolite (for the pathway of interest) with 50 % at low substrate concentrations ($[S] < \text{dissociation constant}$, or an affinity constant, of the inhibitor-enzyme complex. This K_i value, once determined for a specific inhibitor and a specific iso-enzyme should be constant. In the literature however the K_i varies with the reaction studied.

Is this K_i value, although theoretically constant, dependent on the substrate and the reaction studied? If so, how can one explain this phenomenon? Is there an explanation on molecular level?

Alex Hemeryck, Ph.D. student

Pharmacist, Heymans Institute of Pharmacology, University of Ghent, Medical School, De Pintelaan 185, B-9000 Gent

On 24 Oct 1997 at 09:39:41

Your definition of K_i is really the definition for the IC_{50} of an inhibitor in the presence of a specific substrate. K_i can be calculated from the IC_{50} using the equation: $K_i = IC_{50} * K_m / (S + K_m)$, where S is the conc. of substrate, and K_m is the substrate conc. (in the absence of inhibitor) at which the velocity of the reaction is half-maximal. For derivation and molecular basis, see **PRINCIPLES OF DRUG ACTION**, third ed., Pratt and Taylor. The K_i of an inhibitor for inhibition of a particular substrate (fixed K_m) is constant. For a different substrate, K_m is different, and so is the K_i .

Arnab Mukherjee

Univ. of Tennessee, Memphis

On 27 Oct 1997 at 10:49:36

In reply to the answers I received, I would like to ask the following question:

Fluoxetine and paroxetine are known as potent inhibitors of CYP_{2D6} substrates. K_i value's in the range of $0.1 - 1 \text{ M}$ are found in the literature for CYP_{2D6}-substrates such as desipramine. Also in vivo interactions between these two SSRI's and CYP_{2D6} substrates have been described. In fact these interactions could be predicted from the K_i value of the SSRI, in combination with its plasma levels and plasma:liver partition coefficient. Suppose one finds a K_i value of the SSRI's for another substrate studied, which is ten times higher than for desipramine (due to the fact that the substrate studied has a much lower K_m than desipramine), what should be expected in vivo for this new substrate ?

Alex Hemeryck

Pharmacist, Heymans Institute of Pharmacology, University of Ghent, Medical School, De Pintelaan 185, B-9000 Gent

Levodopa Concentration Fluctuations

On 27 Jul 1997 at 15:01:27

I am looking for some information about clinically relevant plasma Levodopa concentrations fluctuations i.e. What percentage change in steady-state concentrations would be considered clinically relevant, given the high variability of Levodopa and the unique PK/PD relationship of Levodopa.

Malcolm Bohm

Clinical Pharmacokineticist

On 6 Aug 1997 at 11:04:15

On the face of it, I do not think there is any very meaningful answer to your question about "percentage change in steady state concentrations". Much of the clinical response to levodopa is predictable from the overall time course of plasma levodopa concentration. The pattern of the response changes over time (described as "stable" and "fluctuating" types of response). Provided levodopa concentrations remain above the EC_{50} for that patient the response is essentially independent of the fluctuation in plasma concentration because the conc-effect relationship is steep (Hill coefficient 3 or greater). Adverse effects (eg dyskinesia) are not clearly correlated with the EC_{50} for beneficial effects so finding an optimal concentration for an individual is not easy especially in the "fluctuating" patient. It is important to recognise also that there is a component to the inter-dose time course of Parkinson's disease that is not predictable from plasma concentrations of levodopa (or other large neutral amino acids) which has been called "yoyo-ing". The "on/off" phenomenon is also used to describe this effect but it is frequently confused (not surprisingly) with the rapid but predictable "end of dose" deterioration that occurs when effect site concs fall below the EC_{50} .

I suggest you take a look at the review by Nutt and Holford (1996) which attempts to link the clinical neurology and clinical pharmacology of levodopa and discusses the above issues at some length.

Nutt JG, Holford NHG. The response to levodopa in Parkinson's disease: imposing pharmacological law and order. *Ann Neurol* 1996; **39**:561-73.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

<http://www.phm.auckland.ac.nz/Staff/NHolford/nholford.html>

On 11 Aug 1997 at 13:50:38

Dr. Peter Silverman, at the U. of Texas Health Science Center in Houston has published a proposed animal model for the "on-off" effect seen with levodopa.

You might find his work interesting.

P. Silverman, *Eur. J. Pharmacology*, vol **242**, 31-36, 1993. On-Off effect of dopamine receptor agonists in the hemiparkinsonian rat.

Vahn Lewis

Log Trapezoidal Rule

On 12 May 1997 at 15:57:45

I have some question on log-trapezoidal rule. Is there another name(formal name) of "modified log-trapezoidal rule"(in up phase, linear trapezoidal; in terminal phase, log trapezoidal)?

And I have read one protocol that use log-trapezoidal rule to calculate AUMC. I don't understand it's meaning.

Is it possible to use log-trapezoidal rule to calculate AUMC?

I think in calculating MRT or V_{dss} , in spite of using AUC calculated by log-trapezoidal, AUMC must be calculated by linear trapezoidal rule.

Young-Joo Lee

Researcher, Pharmaceutic Lab., College of Pharmacy, Seoul National University, San 56-1, Shillim-Dong, Kwanak-Gu, Seoul, 151-742, KOREA

On 13 May 1997 at 11:26:03

Since AUMC is the area under the $\text{time} \cdot C_p$ curve, and the tail of the latter behaves (irrespective to the route of administration) like a (disturbed) monoexponential function, the combined trapezoidal rule (linear in the ascending part and log-linear in the descending part of the curve) is applicable in general. Of course, the accuracy of this approximation is significantly less than in case of AUC. Moreover, the random noise in C_p will disturb the estimates of AUMC obtained by the trapezoidal rule in much more extent as compared to AUC. Therefore, to get reliable estimates of MRT and V_{ss} you need much more precise data and more data points than to estimate CL.

Vladimir Piotrovsky, Ph.D.

Janssen Research Foundation, Clinical Pharmacokinetics, B-2340 Beerse, Belgium

On 14 May 1997 at 15:59:10

There is no difference in the way AUC and AUMC should be calculated; both are areas of a continuous function, which can be calculated mathematically if the functions are known. If only data points are known, the areas can be estimated by various methods; in general, the linear and log trapezoidal rules are the preferred methods because of their robustness (more sophisticated methods may be more sensitive to outliers, et cetera). The choice between the linear and log trapezoidal rule depends ONLY on the expected profile BETWEEN the data points. If the profile is expected to be almost linear, or if the profile is expected to be higher than the linear interpolation, then the linear rule is preferred. If the profile is expected to follow a curve below the linear interpolation, the log rule should be used. The latter is obviously the case during exponential decline. The simple rule of using the linear rule during the inclining parts, and the log rule during the declining parts of the curve, can be used in most cases. A better criterion for choosing between the linear and log rule can be found in my paper in *J.Pharm.Sci.* 1985; 74:793-794.

Please note the problems of extrapolation if the last sampling point is not very low. The extrapolation errors for AUMC are much more pronounced than for AUC. As a result, the calculated MRT may be inaccurate.

Johannes H. Proost

Dept. of Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, Groningen, The Netherlands

Median and Mean

On 20 Oct 1997 at 12:36:14

Would anyone teach me which parameter, mean or median, is usually used in evaluating the typical plasma profile and PK population parameters for the data has the large inter-individual variability.

Yasuo Koyama

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On 20 Oct 1997 16:06:57

Whether to choose the median or mean depends on the distribution of the data. Typically, pk parameters are log-normally distributed, in which case the most appropriate parameter is the median. Unfortunately, most scientists mis-represent data by reporting it as though the data came from a normal distribution. Perhaps the simplest way to determine whether a distribution is normal or log-normal is to transform the data using the natural log and then use a goodness of fit test for the normal distribution. A useful reference in this regards is R.B. D'Agostino and M.A. Stephens: **Goodness of Fit Techniques**. Marcel Dekker, New York, 1986. Another good reference is LF Lacey et al: *J Biopharmaceutical Statistics* 7, 171-178, 1997.

Peter L. Bonate, Ph.D.

Hoechst Marion Roussel, Clinical Pharmacokinetics, P.O. Box 9627 (F4-M3112), Kansas City, MO 64134

On 20 Oct 1997 14:07:29

Usually the median is better, as things are usually more symmetrically distributed about it. Examples are the Vd of a drug when its distribution is not Gaussian, and it hardly ever is.

You might look at Dodge et al, Population PK Models - Measures of Central Tendency, *Drug Invest* 5: 206-211, 1993.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA
90033

On 21 Oct 97 16:55:09

It seems to me that the data will determine whether you use mean, median or perhaps the mode to describe the central tendency of the distribution.

For the typical plasma profile, I think that it is often best just to show just the individual's data. Often presenting the mean, or similar, will hide interesting things in the conc-time profile such as secondary peaks which may be due to enterohepatic cycling.

For PK population parameters, you should present the information that you have for them. If you used a computer program that yielded the geometric mean (and CV%) then this is what you should present. If, however, you used a computer program that yielded the frequency histogram of the parameters then it would seem appropriate to present the entire frequency histogram. Presenting only the arithmetic mean and standard deviation implies that the distribution of the parameter is Gaussian (which would need formal testing). Presenting the median and quartiles (etc) does not describe the distribution very well. Both parametric and nonparametric descriptions will tend to hide interesting things in the distribution of the parameters, eg subpopulations of patients that have different values (eg genetic polymorphism).

Steve Duffull

Christchurch, New Zealand

On 23 Oct 1997 at 09:42:54

NONMEM, because it is an maximum likelihood method, reports the mode for the population parameters. This is one reason that the population estimates do not equate to the mean or median of the individual estimates.

Leon Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, M13 9PL, U.K.

On 18 Nov 1997 at 13:41:23

If you want a simple answer to your simple question, it is median. More detailed analysis, however, is required if the inter-individual variability is extremely large, as in case of polymorphic metabolism. If the distribution of CL is actually bi- or poly-modal you can hardly find a unique parameter to represent a typical value.

How to do such analysis using minimal modeling assumptions? Suppose (a rather typical example) you have many individual plasma concentration-time profiles obtained at the same dosing regimen, and individual sampling times are close to each other. Calculate medians of individual measurements belonging to each sampling time cluster. Then take ratios of measurements to the corresponding medians and plot those ratios versus the individual sequential numbers. You will immediately see the 'outlying' subjects which you have to analyze separately from others. You may also pool all individual measurements adjusted for sampling time-specific medians to get idea about the form of overall concentration distribution (unimodal, poly-modal, normal, lognormal, etc.). This simple approach will help you to select an appropriate way of further summarizing your PK data.

Vladimir Piotrovsky, Ph.D.

Janssen Research Foundation, Clinical Pharmacokinetics, B-2340 Beerse Belgium

Modeling Pharmacokinetic Data

On 7 Jan 1997 at 10:59:41

Hi there, I have two questions about PK modeling

1. I am doing simultaneous curve fitting for drug concentration-time data in several tissues using compartmental models with PCNonlin. Since drug concentration magnitude is very different, say, one tissue concentration is 700 mg/g and another is 0.5 mg/g. It was suggested to transform the data into dimensionless value to get the concentrations at the same scale or even use the logarithmic transformation to decrease the data distance. My questions are (1) is there any reference about such data transformation in PK, (2) how to transform the data into the same magnitude and (3) if I transform the data by dividing them by their averages, which way I should go, transforming the data first and then doing the modeling or using the averages as weighting factors-but how to write the weighting command for the average weighting option.
2. Is there any "tricky" part about fitting infusion data from both infusion and post-infusion periods? I can use following differential equations to simultaneously fit the data of both periods. If $t > 240$, then

```
dz(1)=-kel*z(1)
else
dz(1)=D/(T*V)-kel*z(1)
endif
```

The problem is I can fit the infusion period well but the results of simultaneous fit were not satisfying, specially the post-infusion period. Is this problem model-related or drug disposition different between the infusion and post-infusion periods?

Tony Lee

On 8 Jan 1997 at 14:09:41

Your problem concerning what you call a large "data distance" is very common in physiological modeling because biological concentrations can range from 10^{-2} M down to 10^{-15} M or even less. A standard solution to this large dynamic range problem involves using relative weighting instead of absolute weighting of the data to be fitted. I'm not familiar with the way PCNonlin handles this situation, but I'm quite certain you could solve this problem easily in SAAM II.

I believe you could also reproduce your infusion-postinfusion protocol quite easily in SAAM II, and all without writing code or having to own a compiler.

Robert D Phair PhD

BioInformatics Services: <http://www.webcom.com/rphair>

Modeling versus Non-Compartmental Pharmacokinetic Analysis

On 12 Sep 1997 at 10:26:40

Would anyone in the PK group be able to briefly (or in depth, if appropriate) give some sort of guidelines as to what are the relative merits of modeling PK data or using non-compartmental PK analysis for obtaining the usual PK parameters eg F, AUC, elimination rate constant(s), accumulation, clearance etc..

A second but related question is would the answers to above query still hold if the analyses were extended to include PK/PD.

Faruq H Noormohamed

Department of Therapeutics, Chelsea and Westminster Hospital, 369 Fulham Road, LONDON SW10 9NH

On 15 Sep 1997 at 15:23:06

The clearest "guideline" to me is that non-compartmental analysis is used to describe PK parameters and PK modeling is used to describe plasma (or some other matrix) concentrations. Nevertheless, the same parameters obtained via non-compartmental analysis can be obtained from PK modeling.

Take these examples:

1. Non-compartmental analysis gives you apparent clearance which allows you to compute mean steady-state concentrations. When done correctly and with appropriate assumptions, PK modeling will allow you to compute the concentration at any time point following a dose, or multiple doses of a drug.
2. Non-compartmental analysis will give you the C_{max} of a drug. PK modeling will give you C_{max} and allow you to compute how long it will take for concentrations to decline to a sub-toxic (or sub-therapeutic) threshold

Cases where non-compartmental analysis works best are when a predefined PK hypothesis (bioequivalence, drug IX, ...) is defined and answered in a well designed study. PK modeling can be used in these cases too, but its complexity is often not warranted. PK modeling is very handy when analyzing sparse data, when complicated dosing regimens are administered, or when extrapolations (new doses, regimens, etc...) are required.

When doing PK/PD modeling, one associates concentrations with effects. Therefore, PK modeling is usually used, even if only as a "smoothing" function to supply plasma concentrations to the PD model.

Jeffrey Wald, Ph.D.

Quintiles, Incorporated, Post Office Box 13979, Research Triangle Park, North Carolina
27709-3979

On 15 Sep 1997 at 15:10:55

Would anyone in the PK group be able to briefly (or in depth, if appropriate) give some sort of guidelines as to what are the relative merits of modeling PK data or using non-compartmental PK analysis for obtaining the usual PK parameters eg F, AUC, elimination rate constant(s), accumulation, clearance etc..

IMHO non-compartmental estimates are convenient ways of *describing* PK expts. They have uses for those who enjoy stamp collecting and for satisfying regulatory requirements. However, they are of limited use for *predictive* and *explanatory* purposes. For this, a physiological/ compartmental model approach is more useful.

A second but related question is would the answers to above query still hold if the analyses were extended to include PK/PD.

PKPD analyses seem to me illustrate very clearly the severe limitations of the C_{max}, T_{max}, AUC (elementary) school of pharmacokinetics. It is only by using a model capable of describing the time course of drug concentrations that any progress can be made in understanding the time course of drug effect in vivo. I prefer physiological / compartmental models to the black box models which rely on convolution or splines because the parameters of the former classes of models are often closely linked to structure and function and thus the influence of changes in say body size or blood flow on PK and PD can be predicted.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

On 16 Sep 1997 at 13:27:16

I have found it fascinating that Nick Holford and I have come to such similar positions by such different routes. I agree so strongly with Nick's response to this inquiry, that I considered not replying so as not to use up bandwidth with "me too."

But then I saw the post from Hans Bender regarding PK in transgenic animals, and I thought a combined response to the two inquiries might be useful.

I have been working with a group at the US National Heart Lung and Blood Institute's Molecular Disease Branch on a kinetic model of lipoprotein metabolism in human LCAT transgenic rabbits. The principal experimental investigators are Drs. Meg Brousseau and Jeff Hoeg and the lab is guided by Dr. Bryan Brewer. An abstract on this work will be presented at the 1997 meeting of the American Heart Association in Orlando in November.

My experience is that analysis of data from transgenic animals is tremendously more informative in the context of a physiological/compartamental model than it could be using non-compartamental methods. This is because, as Nick emphasized, the parameters of a compartmental model are explicitly associated with known or hypothesized physiological processes. This means that a powerful constraint is available to the modeler because he or she can point to a rate constant or a clearance and say with conviction that **this** process should be up-regulated in the transgenic animal because this process is mediated by the gene product of the transgene. Such constraints make it much easier to extract new and useful information from the available experimental data. There may well be additional control mechanisms that lead to secondary changes in other clearances, but it is really powerful to see if the effect of the transgene alone is sufficient to account for the data.

Because the parameters of non-compartamental analysis are combinations of many rate constants or clearances, they can be used efficiently to make predictions. But they will not permit you to impose constraints such as the one I allude to above, and they will keep you in the dark concerning the underlying physiological mechanisms. Biologists think mechanistically, and medicine, as Lewis Thomas has eloquently emphasized, is at its best when based on mechanism. To build strong working relationships with these two constituencies,

mechanistic compartmental models are highly desirable. And while Nick is entirely correct that noncompartmental parameters are all you currently need for the FDA, there are already well-placed people in the FDA who see the power of compartmental approaches and the prudent pharmacokineticist should certainly consider adding this approach to his or her professional toolbox.

Robert D. Phair

BioInformatics Services, 12114 Gatewater Drive, Rockville, MD 20854 U.S.A.

On 16 Sep 1997 at 13:28:55

I agree with Nick on the advantages and power of using physiologically based/ compartmental modeling of PK data. There is one significant reason for the development and success of Non-Compartmental modeling of kinetic data. As the name suggests, there is no mathematical modeling of the data i.e. no judgements have to be made regarding the selection of the appropriate number of physiological compartments or exponentials to fit the data. Additionally, since the mathematical 'best' fit of sum of exponential data is based on statistical parameters such as 'goodness of fit', sum of squares, selection of optimal weighting factors, etc. this interpretation can be subjective and kineticist dependent. I am sure many kineticists have experienced difficulty in modeling oral data which falls through a 3-4 log orders of magnitude--where in attempting to fit the terminal phase, the profile around C_{max} is not well fit (It is also for this reason the FDA prefers an observed C_{max} rather than a calculated C_{max}). Non-Compartmental analysis of the data allows one to estimate most of the basic kinetic parameters for characterizing the disposition of the drug. Granted that mechanistic interpretation of the kinetic data is limited.

I prefer to use Non-compartmental analysis for basic kinetic interpretations of pilot studies etc. If there is a need for further kinetic evaluation modeling is recommended. I do not see how Non-Compartmental estimates can be extended to PK-PD modeling since we have not established the time-course of drug disposition. At best we can make qualitative (non-predictive) interpretations on the kinetic and dynamic data.

Anup Zutshi

On 16 Sep 1997 16:07:35 -0400

In reply to Anup Zutshi:

I am always surprised when people assert that no judgements have to be made with non-compartmental approaches. It appears to me than many of the most common non-compartmental parameters depend critically on the kineticist's judgement as to how to extrapolate the tail of the plasma disappearance curve to infinity. If we guess wrong or miss a slow exponential because we didn't have data points for enough hours or days, our noncompartmental answers are simply wrong. Moreover, they are wrong precisely because our judgement was faulty.

We all make errors if we think that there are no assumptions and no calls for judgement in the application of non-compartmental analysis. If PK did not require judgement, but only required plugging into published formulas, then the discipline of pharmacokinetics could be reduced to an algorithm. Non-compartmental analysis has made tremendous contributions to the rational design of therapy, but it is not magic.

The bottom line is that it's impossible to hide from insufficient data. Non-compartmental advocates do the field of PK a disservice by pretending that one method of analysis requires no assumptions or judgement while the other requires both.

Robert D. Phair, Ph.D.

BioInformatics Services, 12114 Gatewater Drive, Rockville, MD 20854 U.S.A.

On 16 Sep 1997 13:10:43

I would like to second Dr. Holford's description of the strengths and weaknesses on non-compartmental vs physiological / compartmental models. The latter give structure to the analysis, and result in a controllable system for which one can plan dosage regimens not just to achieve a desired goal in a steady state situation, but which can grab a patient (if you will) in an unsteady state and achieve a desired goal then and thereafter, until the steady state is reached. As far as I know, non-compartmental models are good for writing papers, but not so good for taking care of real people in unstable and changing clinical situations. Models having structure are better suited for developing individualized regimens to achieve, and then to maintain, chosen target goals.

Roger W. Jelliffe, M.D.

USC Lab of Applied Pharmacokinetics, CSC 134-B, 2250 Alcazar St, Los Angeles CA
90033

On 17 Sep 1997 01:28:21

Regarding Faruq Noormohamed's query and the flourish of excellent comments that followed:

In the course of planning our pharmacokinetics analysis software, "PK Solutions", we took a look at what parameters researchers are publishing and what methods they favor. A survey of all the articles dealing with pharmacokinetics appearing during the last 5 years in the *Drug Metabolism and Disposition* and in the *Journal of Pharmaceutical Sciences* revealed a >96% use of non-compartmental methods. Most papers included results derived from both graphic (AUC, etc.) and summed exponential calculations.

Observation: you are in good company with non-compartmental methods.

Dr. David S. Farrier

Summit Research Services, 1374 Hillcrest Drive, Ashland, OH 44805 USA

On 17 Sep 1997 08:59:37

Our article:

Durisova, M., Dedik, L., Balan, M.: Building a structured model of a complex pharmacokinetic system with time delays, *Bull. Math. Biol.*, **57**, 1995, 787-808,

devoted to non-compartmental modeling, describes in a tutorial manner a procedure for building a structured model of a complex pharmacokinetic system on using its transfer function. The example employed is that of the pharmacokinetic system based on gentamicin plasma concentrations after intravenous and intra-tracheal administration to guinea pigs, describing the pathway of the drug into the systemic circulation after the extravascular injection mentioned. The structured model selected consisted of a sub-model of a proportional linear subsystem, two sub-models of simple linear dynamic subsystems with time constants of 0.135 ± 0.065 hr (95 % I.C.) and 0.052 ± 0.049

hr, and two sub-models of parallel subsystems with time delays of 0.254 ± 0.046 hr and 1.135 ± 0.288 hr, connected in serial. The serio-parallel structure of the model selected allowed to estimate mean residence times for four fractions of gentamicin. From the methodological point of view, our paper demonstrates the efficiency of combination of modeling in the frequency and in the time domain, designed to facilitate studies of complex pharmacokinetic systems.

Diploma Engineer Maria Durisova CSc.,

Scientific Secretary, Institute of Experimental Pharmacology, Slovak Academy of Sciences,
Dubravská cesta 9, 842 16 Bratislava, Slovak Republic

On 17 Sep 1997 22:33:45

Anup,

Thanks for your comments and I think we basically agree but in case there are still some die hard anti-modeling types left out there...

There is one significant reason for the development and success of Non-Compartmental modeling of kinetic data. As the name suggests, there is no mathematical modeling of the data i.e. no judgements have to be made regarding the selection of the appropriate number of physiological compartments or exponentials to fit the data. Additionally, since the mathematical 'best' fit of sum of exponential data is based on statistical parameters such as 'goodness of fit', sum of squares, selection of optimal weighting factors, etc. this interpretation can be subjective and kineticist dependent.

The very fact that there is some subjectivity and kineticist dependency is one of the reasons why modeling is valuable. Having to THINK about what you are doing instead of blindly cranking out T_{max} , C_{max} , AUC is the way to understand what the data is trying to say. When the model does not fit an opportunity presents itself to ask why. Indeed models that fit the data are less interesting in the spirit of scientific enquiry than those that don't.

> I am sure many kineticists have experienced difficulty in modeling oral data which falls through a 3-4 log orders of magnitude--where in attempting to fit the terminal phase, the profile around C_{max} is not well fit

Sure. I recognize the problem. And it has made me more aware of the need to think more carefully about the processes that govern drug input. The difference between the necessarily simple prediction of the model and the observed reality is the only way to learn more about the PK of absorption. T_{max} and C_{max} are even more naive than the elementary

one compartment first-order input, first-order elimination model and will teach you next to nothing about a drug's absorption rate.

Nick Holford

Dept Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand

On 18 Sep 1997 at 10:17:06

Further comments on compartmental *versus* non-compartmental PK

I have used non-compartmental approach in PK analysis for considerable time and feel compelled to express my opinion. I certainly agree with the merits of compartmental PK/PD analysis in understanding mechanism of drug kinetics and dynamics. However, let's not discard and ridicule non-compartmental approach entirely. One can do very sophisticated PK analysis (with effects of covariance included) using non-compartmental approach. One can even do simulation of concentration time curves using superposition method.

The greatest advantage of non-compartmental approach is in drug development where one needs an accurate measure of drug exposure across different species. One of the most powerful non-compartmental PK parameter is AUC(τ) at steady state which allows us to determine CL_{ss}/F as well as drug exposure. This approach requires minimum assumptions

In my opinion inaccuracies in the error and structural model in the compartmental PK approach especially with sparse sampling is grossly underestimated and there are times where I get the feeling that compartmental PK is being reduced to number crunching.

Both compartmental and non-compartmental analysis have their place in pharmacokinetics and serve as useful tools in understanding drug kinetics.

Aziz Karim, PhD

On 19 Sep 1997 at 10:26:47

As far as I have seen, the replies on this topic did not deal with the parameters Mean Residence Time (MRT) and V_{ss} in non-compartmental PK analysis. Therefore I would like to add two notes:

1. Calculation of MRT and V_{ss} in non-compartmental PK analysis (using AUC and AUMC) implies the assumption that the rate of elimination from the body is proportional to the (plasma) concentration (equivalent to: elimination from the central compartment in compartmental analysis). If this is not the case (for many drugs, e.g. atracurium which breaks down spontaneously in any body fluid), the values obtained for MRT and V_{ss} are meaningless. Of course, the same is true in compartmental analysis, but in that case one is 'forced' to choose a model, including the route of elimination (do we all realize this every time we use an open two- or three-compartment model?).
2. Calculation of MRT and V_{ss} in non-compartmental PK analysis implies calculation of AUMC (area under the first moment curve). Calculation of AUMC without a curve-fitting procedure is prone to large extrapolation errors (much more than AUC!).

In conclusion, be very careful in calculating MRT and V_{ss} by non-compartmental PK analysis!

Johannes H. Proost

Dept. of Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, Groningen, The Netherlands

On 24 Sep 1997 at 11:01:25

Dear Faruq hi!

Only some observations for your first question:

1. It's important remember that non-compartmental methods (NCM) ASSUME LINEAR PHARMACOKINETICS for observed drug.
2. NCM are useful to estimate some PK parameters, useful for clinical practice (bioavailability, clearance, apparent volume of distribution, fraction of a dose converted to a

metabolite, rates of absorption), but they do not describe the time course of drug in the blood (different half-lives, k-rates, etc)

NCM do not require the assumption of a specific compartmental model for drug and are based essentially on the theory of statistical methods, and concentration-time course after single administration can be considered a statistical distribution curve. The results are also independent enough on changes of metabolism/distribution/elimination during the time.

Compartmental methods required for PK of a drug, depends in part on the experimental design and you can have problems of accuracy when the frequency and timing of samples are not correct (too sparse, interrupted too early, etc).

In addition calculation of PK parameters and of distribution rates are dependent on the model selected, but "many" models sometimes are structurally identifiable and give you "acceptable" solution. You should therefore perform a robust error-analysis on your data.

Elena Strocchi

Laboratorio di Farmacocinetica ANT, Dipartimento di Chimica Organica, Universita' di Bologna, Viale Risorgimento, 4, 40136 Bologna - Italy

Nephrotoxicity of Antimicrobials

On 24 Apr 1997 at 11:10:33

I need to know what are the most important parameters of nephrotoxicity to be studied for a given antimicrobial drug (aminoglycosides, Polymyxin B etc) in animal models (rats). For how long that drug will be administered (chronic and acute)? and what dosage? etc.

I need this information for toxicological studies.

Abdel Omri

On 28 Apr 1997 at 11:22:05

My lab is presently investigating exacerbation of NSAID-induced renal toxicity by gentamicin and other such peri-operative minefields. We use a rat preparation with several indices of renal toxicity .

1. Plasma clearances of iothalamate to approximate GFR and paraaminohippurate to approximate renal plasma flow
2. Plasma and urinary electrolytes and osmolality
3. Histopathology of kidney

No one index is enough. Gentamicin alone can trigger all three indices. Hope that this helps provide a basis for your further consideration.

Laurie Mather

Professor of Anaesthesia and Analgesia (Research), University of Sydney at Royal North Shore Hospital, St Leonards NSW 2065 Australia

On 5 May 1997 at 14:28:33

I would like to study the nephrotoxicity of an antibiotic but I don't know which are the most important parameters of nephrotoxicity (creatinine, histopathology of the kidney etc)

Abdel Omri

On 12 May 1997 at 15:57:15

This is an interesting question. It would appear, that there are a number of proposed methods for measuring the nephrotoxicity of antibiotics. These include NAG, renal proteins, creatinine, phospholipids and true antibiotic clearance. I have some experience using various markers in an animal model.

Creatinine is an insensitive and slow changing marker. Changes in creatinine change 48 to 72 hours after the renal damage has occurred.

NAG and renal proteins are a bit more sensitive, however can also be disturbed by other pathology.

Changes in aminoglycoside clearance would appear to be more sensitive than all the above indices in my animal model. I need to complete the remainder of my experiments to sort this out. However, anecdotal evidence in humans would also appear to support this.

It would appear that the most sensitive and earliest marker of renal damage is the measurement of phospholipiduria. I have some experience in the measurement of this index of aminoglycoside induced nephrotoxicity using an animal model.

Carl Kirkpatrick

Department of Clinical Pharmacology, Christchurch Hospital, New Zealand



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AAPS

American Association of Pharmaceutical Scientists

<http://www.aaps.org/>

Related Glossary Terms

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Chapter 1 - 1994

ABW

Actual Body Weight

Related Glossary Terms

IBW

AR

Accumulation Ratio

Related Glossary Terms

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AUC

Area under the curve, especially under the plasma concentration *versus* time curve

Related Glossary Terms

Drag related terms here

BID

Twice daily dosing

Related Glossary Terms

QD

CR

control release

Related Glossary Terms

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CVVH

Continuous Venovenus Hemofiltration

Related Glossary Terms

CVVHD

CVVHD

Continuous Veno-venous Hemodialysis

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CVVH

DVT

Deep vein thrombosis

http://en.wikipedia.org/wiki/Deep_vein_thrombosis

Related Glossary Terms

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EC₅₀

Effective concentration 50%. The concentration which produces a response equal to half (50%) of the maximum response

Related Glossary Terms

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HPLC

high pressure (performance) liquid chromatography

Related Glossary Terms

Drag related terms here

IBW

Ideal body weight

Related Glossary Terms

ABW

IS

Internal standard

Related Glossary Terms

Drag related terms here

LBM

Lean body mass

Hallynck T, Soep HH, Thomis J, Boelaert J, Daneels R, Fillastre JP, D
Rubinstein E, Hatala M, Spousta J and Dettli L, 1981 Prediction of creatinine
clearance from serum creatinine concentration based on lean body mass
Journal of Clinical Pharmacology and Therapeutics, **30**(3), p 414-21.

Related Glossary Terms

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LMWH

Low molecular weight heparin

http://en.wikipedia.org/wiki/Low_molecular_weight_heparin

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LOD

Limit of detection

Related Glossary Terms

LOQ

LOQ

Limit of quantitation

Related Glossary Terms

LOD

LR

Loo-Reigelman method analysis

Related Glossary Terms

WN

PD

Pharmacodynamics

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PK

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QD

Daily dosing

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BID

SR

Sustained release

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SS

Steady state

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USP

United States Pharmacopeial Convention

<http://www.usp.org/>

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WN

Wagner-Nelson method of analysis

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LR