

DR. MINER: I'd like to take the privilege of introducing Dr. Koritz. Gary Koritz is presently involved in teaching and research at the University of Illinois, specifically in the pharmacokinetics area. He graduated from the University of Illinois in 1968 with his D.V.M. degree, was involved in private practice, and since then has returned to the University of Illinois where he received his Ph.D. degree in pharmacology.

DR. KORITZ: I would first like to state that pharmacokinetics dates back to 1937 -- veterinary pharmacokinetics probably back to the early 1960's -- and there are many people in this room today that contributed to that effort so that we have had about 20 years of experience with this science in the veterinary profession. Give us another 20 years and we may be able to answer a lot of the questions that we can't handle yet. The concept, once again, with the therapeutic window is with multiple dosage to get ourselves within that window for a desired period of time that will suppress the bacterial population to the point where the host's defense mechanisms can eliminate the infection. We generally derive the needed information from single dose studies. Then, we must verify that information by looking at it in a clinical situation with multiple doses; this tests the model and helps to improve it. Another thing is, if we know nothing about an antibiotic, we should at least try to stay above what is thought to be an MIC; subsequently, we may find because of the post-antibiotic effect and so forth, that we can allow these concentrations to fall below the MIC. Presently we don't know enough about the combination of bacterial kinetics, pharmacokinetics, and host interactions to make those types of predictions -- it is a clinical judgment.

THE VALUE AND LIMITATION OF PHARMACOKINETICS IN
PREDICTING DOSAGE REGIMENS
Gary D. Koritz, DVM, PhD

Whether an antimicrobial dosage regimen is determined empirically or pharmacokinetically, the objective is to administer the drug at an appropriate dose and frequency to sufficiently suppress a bacterial population at a site of infection in order to assist the host's defense mechanisms in the final elimination of the pathogen. An upper limit to the dose and frequency of administration is established by the need to avoid toxic side-effects of the drug to the host. Whereas the empirical approach to dosage regimen determination is guided primarily by the end results, the pharmacokinetic approach requires additional information. Depending upon the quality and inherent variability of this information, it should be possible to determine a dosage regimen for a given antimicrobial with greater speed, less expense, and better understanding of the underlying mechanisms of interaction between host, drug, and pathogen than is provided by the empirical approach (19). What additional information, then, is required to predict a dosage regimen based upon pharmacokinetic principles and what are its applications and limitations?

The Therapeutic Window

The pharmacokinetic approach requires knowledge of the minimum effective concentration (MEC) in the host of the antimicrobial drug to the pathogen and the minimum toxic concentration (MTC) of the drug to the host. The MEC and MTC form the lower and upper limits of the therapeutic window and thereby govern the dose and frequency of drug administration. However, these limits are not well delineated and are imperfectly understood.

The MEC is dependent upon both the host and pathogen. If host defenses are impaired, the MEC will increase even though the minimum inhibitory concentration (MIC) of the antimicrobial for the bacterium in vitro is unchanged. However, the MIC multiplied by a poorly defined safety factor is used as an estimate of the MEC. Furthermore, the MIC varies between and within strains of bacteria. The controversy surrounding the clinical relevance of MIC determination is reviewed elsewhere (10,27). Although it is apparent that in the uncompromised host many drugs have antibacterial effects at concentrations less than the MEC (1,14) and that it may in fact be desirable to allow drug concentrations to periodically fall below the MEC (16), the initial objective of a dosage regimen should be to maintain drug concentration in excess of the MEC for the infective organism. When the duration and extent of the decline in concentrations below the MEC to achieve optimum antibacterial therapy is better defined either through clinical experience or improved understanding of the mechanisms involved, then the dosage regimen may be adjusted accordingly.

The MTC of an antimicrobial drug is determined from toxicity (Phase I) studies conducted in the target species during the drug development and approval process. This upper limit to therapeutic drug concentrations varies according to the relative sensitivity or tolerance of an individual animal to a drug's toxic effects.

Both the MEC and MTC are reported as drug concentrations in plasma. The site of infection or toxicity, however, may not be in the plasma but rather in a peripheral tissue whose drug concentrations may or may not be accurately reflected by those in plasma (4,23).

Pharmacokinetic Information

Pharmacokinetic analysis involves the study of the time-course of drug and metabolite concentrations in various tissues and excreta and the formulation of mathematical models which explain the data. Such models can sometimes be further refined to relate drug concentrations to the time-course and intensity of pharmacologic and toxicologic effects. The time-course of a drug in the body is dependent upon the rates and extents of drug absorption, distribution, metabolism, and excretion. Although this information is gathered throughout the drug development process, a simple pharmacokinetic model should be proposed as early as possible to provide for dosage regimen predictions with which to guide drug formulation and toxicity (Phase I) studies and efficacy (Phase II) studies (18,22,26). Pharmacokinetic analysis of data from these studies can in turn be used to refine the original model in order to improve its predictive ability.

The processes of drug absorption, distribution, metabolism, and excretion are variable both between and within individuals of the same animal species. This is because of the underlying physiologic variability in such factors as the pH of body fluids, gastrointestinal motility, blood flow, enzyme activity (which might be inducible or saturable), plasma protein binding, relative obesity, urine output, and so forth (6,11,24). Furthermore, the normal physiology of the animal may be altered by the bacterial infection through effects such as pyrexia, dehydration, uremia, decreased gastrointestinal motility, and others (3). Pharmacokinetic analysis of data obtained from normal and diseased animals in which these physiological changes have been monitored can lead to a pharmacokinetic model which is adaptive to changes in physiologic processes (9) such as occur in renal failure (20,25).

Pharmacokinetic models are well discussed in a number of texts (2,8,20). For the purpose of understanding the application of pharmacokinetic parameters to dosage regimen calculations, we will first examine the one-compartment open model of drug disposition.

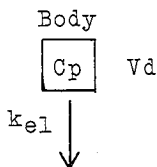


Figure 1. One compartment open model of drug disposition.

The apparent volume of distribution V_d generally lacks physiological meaning but serves as a proportionality constant to relate the amount of drug in the body to its concentration in plasma, i.e., $A_b = V_d C_p$. Drug concentrations in body tissues are assumed to be in essentially instantaneous equilibrium with plasma concentrations, but they are not necessarily equal in concentration. The overall rate constant of elimination k_{el} is assumed to be first-order, i.e., the rate of drug elimination is directly proportional to the drug concentration in plasma such that $dA_b/dt = k_{el} V_d C_p$. The product $k_{el} V_d$ equals the total body clearance Cl_B of the drug. The Cl_B is in turn comprised of the sum of the metabolic, hepatic and renal clearances for a given drug (and perhaps other minor excretory pathways). The integrated equation for C_p following intravenous injection is monoexponential, i.e., $C_p = (\text{Dose})_0 e^{-k_{el} t}$ and $\ln C_p$ plotted versus time is linear.

Generally a two-compartment open model and occasionally a three-compartment open model are required to adequately describe the data. Only the two-compartment model will be discussed to illustrate the relationship of multicompartmental models to the one-compartment model.

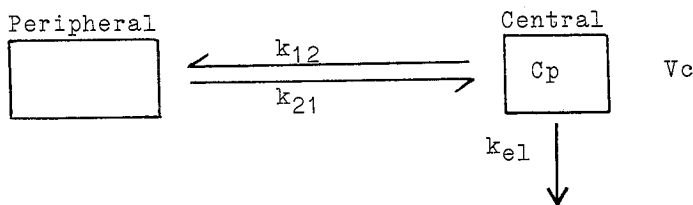


Figure 2. Two compartment open model of drug disposition.

In this model, drug concentrations in the central and peripheral compartments do not rapidly equilibrate. Thus, the proportionality between drug concentrations in a tissue of the peripheral compartment and plasma concentrations will vary with time. The amount of drug in the central compartment may be found from the product of the volume V_c and the plasma concentration. This added to the amount of drug in the peripheral compartment equals the total amount of drug in the body. The model can calculate the amount of drug in the peripheral compartment but not the concentration. Thus, if the site of

infection or toxicity is in the peripheral compartment, drug concentrations at this site must be determined by tissue analysis rather than by simple proportionality to the plasma concentration. Once the simultaneous time-course of tissue and plasma concentrations has been determined, the model can be further refined to predict tissue concentrations in future studies. The integrated equation for plasma concentrations following an intravenous injection of drug is biexponential such that $C_p = Ae^{-\alpha t} + Be^{-\beta t}$ and a plot of the $\ln C_p$ versus time is convex with a "distribution" then "elimination" phase. From this equation a proportionality constant $V_{d_{area}}$ may be calculated which relates C_p with the total amount of drug in the body during the elimination phase, i.e., $Ab = V_{d_{area}} C_p$. During the elimination phase, the rate of drug disappearance from the body is actually controlled by β which is a complex function of k_{12} , k_{21} and k_{e1} rather than only by k_{e1} as in the one-compartment model. Total body clearance of the drug is calculated as $Cl_B = \beta V_{d_{area}} = k_{e1} V_c$.

Before continuing with a discussion of the use of these concepts to estimate dosage regimens, it is appropriate to emphasize again that any change in the clearance of the drug from the animal body will interfere with the ability of these simple models to accurately predict drug concentrations in plasma. Drugs which are highly bound to plasma proteins or can induce or saturate their own metabolism, saturate renal or hepatic transport mechanisms involved in drug excretion, and so forth require more complex models.

Dosage Regimen Estimation

The objective of a dosage regimen based upon pharmacokinetic principles is to administer the drug at a dose and frequency such that the plasma concentrations during the plateau of drug accumulation will fluctuate between a predicted maximum plasma concentration $C_{p_{max}}^{\infty}$ and minimum plasma concentration $C_{p_{min}}^{\infty}$ which are within the therapeutic window defined by the host and pathogen. The time required for the drug to accumulate in the body is equal to 5 times the biological half-life $t_{1/2\beta}$ of the drug where

$$t_{1/2\beta} = .693/\beta$$

To avoid this delay, an intravenous priming dose D^* may be given to essentially instantaneously establish $C_{p_{max}}^{\infty}$ where

$$D^* = V_{d_{area}} C_{p_{max}}^{\infty}$$

Therapy may then be continued with a constant intravenous infusion or by multiple parenteral or oral administrations of the drug.

Whatever the method of administration, at plateau the drug is provided to the animal at the same rate it is cleared from its body. Thus, for a constant intravenous infusion, the rate of infusion R_0 is equal to the rate of drug clearance, i.e.,

$$R_0 = Cl_B C_{p_{max}}^{\infty} = \beta V_{d_{area}} C_{p_{max}}^{\infty}$$

If intermittent maintenance doses are to be administered intravenously, then plasma concentrations will fluctuate

between a $C_{p\max}$ and $C_{p\min}$ which are dependent upon the duration of the dosing interval τ . This value is determined from the equation

$$\tau = \frac{\ln (C_{p\max}^{\infty} / C_{p\min}^{\infty})}{\beta}$$

Once τ has been determined, the fraction of the drug which was cleared from the body during the dosing interval f_{el} may be calculated from the equation

This value times the $f_{el} = 1 - e^{-\beta\tau}$ amount of drug in the body at $C_{p\max}$ equals the amount of drug lost during the dosing interval. This then is the amount of drug which must be supplied by the maintenance dose D to maintain the plasma concentrations at plateau. Accordingly,

$$D = f_{el} V_{d\text{area}} C_{p\max}^{\infty} = f_{el} D^*$$

Dosage regimen calculations for other than the intravenous administration of drugs are more complex since an absorption process is then involved for the drug to gain entrance to the plasma. However, if drug absorption is significantly faster than drug elimination, one needs only to correct the previous equations by the fraction F of drug absorbed into the plasma. Thus,

$$D^* = \frac{V_{d\text{area}} C_{p\max}^{\infty}}{F}$$

$$D = \frac{f_{el} V_{d\text{area}} C_{p\max}^{\infty}}{F} = f_{el} D^*$$

If absorption is not significantly more rapid than elimination and especially if absorption is slower than elimination, $C_{p\max}$ will be less than predicted and $C_{p\min}$ greater than predicted. However, the time averaged plasma concentration at plateau C_p^{∞} will not be affected and can be found from the useful general equation

$$\overline{C_p^{\infty}} = \frac{FD}{Cl_B \tau} = \frac{FD}{k_{el} V_c \tau} = \frac{FD}{\beta V_{d\text{area}} \tau} = \frac{1.44 FD t_{1/2}}{V_{d\text{area}} \tau}$$

This equation clearly shows the effect of dose, dosage interval, and drug bioavailability upon drug concentrations in plasma. Perhaps more importantly, it clearly shows the dependence of accurate pharmacokinetic prediction of dosage regimens upon Cl_B which is assumed to be constant but in reality is subject to physiologic and pathophysiologic variations in drug distribution and elimination.

Dosage Regimen Refinement

If the pharmacokinetics of a drug are more complex than the simple one or two compartment open models of drug disposition, then more complex models are required to improve the

accuracy of dosage regimen predictions. Dosage regimens may be first estimated by the previously discussed equations and then the resultant drug concentrations in plasma (and/or tissues) simulated by one of a number of sophisticated computer programs (8) in which the calculations are based upon the model provided regardless of its complexity. Examination of the simulated drug concentrations provides the basis for adjustments to the dosage regimen which may then again be subjected to computer simulation. Various combinations of dose and frequency of drug administration may be simulated in order to arrive at a dosage regimen which best provides for the therapeutic management of the patient.

Another approach to the refinement of a dosage regimen is to monitor the drug concentrations which result in the animal patient (7,17). The requirement for sophisticated analytical instruments generally limits this option to pharmaceutical and educational institutions. By monitoring drug concentrations, dose-related toxicosis or therapeutic failure may be confirmed or rejected, the influence of disease and drug-to-drug interactions can be determined, and animal owner compliance with the dosage regimen can be assessed. A number of mathematical approaches to dosage regimen adjustment based upon determination of drug concentrations in a patient's serum or plasma have been reported (15). Pharmacokinetic analysis of drug concentrations observed under clinical conditions may also provide for modification of the underlying model. Dosage regimens may then be refined by simulations based upon the improved model as discussed in the preceding paragraph.

Predictability of Drug Concentrations

Most of the reports in the literature which deal with the determination of the pharmacokinetics of drugs are based upon the administration of single oral and/or parenteral doses. Dosage regimens predicted from such information may or may not be accurate. Some investigators have undertaken the additional time and expense to conduct studies in which drug concentrations resulting from a given regimen are monitored (5,12,13, 21). It is my impression that a difference of 20 percent between observed and predicted plasma concentrations under these conditions is not uncommon. The clinical relevance of such differences, of course, depends upon the therapeutic window of the drug in question.

Therapeutic Guidelines

Given the variability of drug concentrations which result from a given dosage regimen of a certain antimicrobial administered to a particular animal undergoing pathophysiological changes in the presence of a bacterium of unknown or uncertain antimicrobial sensitivity, it is apparent that a dosage regimen recommendation can only be thought of as an initial guide to therapy. Dosage recommendations are of increased value when expressed as a range of doses consistent with the variability of the lower limit of the therapeutic window such as for bacteria of low, intermediate, or high sensitivity. Dosage

regimens may also be suggested for normal and abnormal drug disposition as occurs with changes in renal function. The provision of a more detailed pharmacokinetic profile of a drug can provide guidance to a clinician's projections of the effects on dosage regimen adjustments of pathophysiologic changes in drug absorption, distribution, metabolism, and excretion.

Conclusions

The pharmacokinetic prediction of dosage regimens offers a number of advantages over the empirical approach. Drug formulation, toxicity, and efficacy studies (Phase I and II studies) benefit from guidance based upon pharmacokinetic considerations, and in turn the underlying pharmacokinetic model can be refined by analysis of data from such studies. A pharmacokinetic model is indeed worth a thousand words as it is a functional condensation of the knowledge of a drug's disposition in the animal body from which predictions of drug behavior can be made although limited in accuracy by the variability of patient and pathogen. Today's veterinarian is increasingly familiar with such concepts and seeks to further tailor antimicrobial therapy to a particular animal patient based upon microbiologic, pathophysiologic, and pharmacologic considerations.

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