AN INTRODUCTION TO CLINICAL PHARMACOKINETICS: MODELS AND SOFTWARE

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SUMMARY

The appropriate administration of pharmacological agents to animals requires a detailed understanding of pharmacokinetics and pharmacodynamics (Figure 1). This is because the clinical dosage regimen depends on how the body acts on the drug and its dosage formulation (pharmacokinetics) as well as the safety and efficacy of the drug (pharmacodynamics). Dosage regimens are designed to achieve therapeutic concentrations and maintain a therapeutic response, while minimizing adverse side effects, expense, and promotion of antimicrobial resistance.

This brief review has 2 main objectives: 1) to present an overview of the basic processes of drug absorption, distribution and elimination and how these processes are quantified using different pharmacokinetic approaches; and 2) to identify computer software programs and web sites that are useful resources for veterinarians interested in clinical pharmacology and pharmacokinetics .
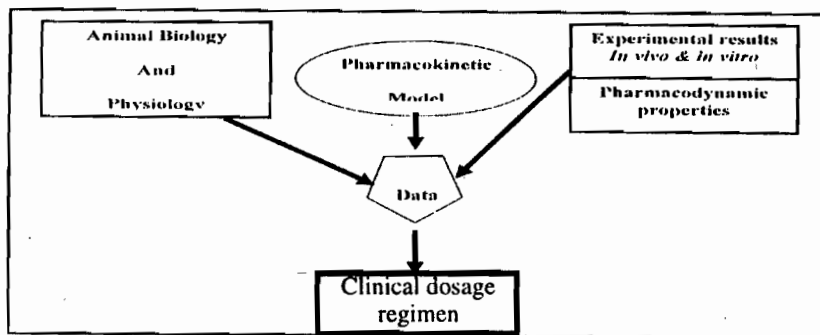

Figure 1: Conceptual framework of how a pharmacokinetic model links experimental data & pharmacodynamic properties to the underlying biology and physiology to result in a clinical dosage regimen (adapted from Riviere, 1999)

DOSAGE REGIMEN

Dosage regimen is the manner in which the drug is taken; the duration of treatment depends on whether the therapeutic objective is cure, mitigation or prevention of disease. Animals suffering from chronic diseases may have to administered drugs every day for the rest of their lives, while animals with acute inflammation or pain may take a single dose of a drug for short term relief. The duration of drug therapy is usually between these two extremes.

While it is well known that all drugs cause undesirable side effects, successful therapy is achieved by optimizing the balance between desirable and undesirable effects.

To achieve optimal therapy the appropriate "drug choice" must be made. This requires an accurate diagnosis, knowledge of the clinical state of the diseased animal, and understanding of the pharmacotherapeutic management of the disease. Veterinarians must select an appropriate drug dose based on maximizing therapeutic efficacy while minimizing cost and the likelihood and drug-induced toxicity or microbial resistance. The withdrawal time must be determined to insure that the drug residue does not persist in edible tissue or by-products such as meat, milk or eggs. The withdrawal time is a pure pharmacokinetic parameter since it can be calculated using legal tissue tolerances and clearance half time in different tissues.

Four questions should be asked and answered when treating animals:

How much? The magnitude of the therapeutic and toxic response is a function of the given dose.

What route? This determines the drug formulation and is selected based on practical application and treatment duration.

How often? Inter dose intervals are important in that the magnitude of the effect eventually declines following a single dose of the drug.

How long? Recognize the cost (side effects, toxicity and economics).

Accurate answers to these 4 questions require treating and monitoring a large number of animals in order to establish reasonable dosage regimens.

The magnitude and duration of the response depends on attaining and maintaining an effective drug concentration at the site(s) of action. The drug must move from the site of administration to the site of action. The drug is also distributed to different body organs (e.g. liver, kidneys) from which the drug will be eliminated. In order to use a drug optimally veterinarians must understand the mechanisms of drug absorption, distribution, and clearance (i.e. pharmacokinetics) as well as pharmacodynamics.

Drug absorption

Absorption is the movement of a drug from the site of extravascular administration into the intravascular compartment (blood). Absorption affects bioavailability, as well as how quickly and how

much of a drug reaches its intended site of action. Factors that affect absorption (and therefore bioavailability) include the way a drug product is designed, formulated and manufactured, its physical and chemical properties, as well as the physiologic state and the disease condition of the animal administered the drug. Drug absorption is also affected by the site of administration, degree of vascularity, barriers, plasma protein binding, and tissue binding affinity. Drug products that contain the same drug (active ingredient) may have different inactive ingredients that may change drug absorption. Thus, a drug's effects, even at the same dose, may vary from one drug product to another. Drug products that not only contain the same active ingredient but also produce essentially the same plasma concentrations over time are considered bioequivalent. Bioequivalence ensures therapeutic equivalence (that is, production of the same medicinal effect) and bioequivalent products are interchangeable (Merck manual online 2006).

Drug distribution

This refers to the movement of drug to and from the intravascular compartment (blood) and various tissues of the body (for example, fat, muscle, and brain tissue) and the relative proportions of drug in the tissues. Once absorbed, most drugs do not spread evenly throughout the body. Drugs penetrate different tissues at different rates, depending on blood flow distribution, the extent of plasma protein binding, and the ability of the

drug to cross cell membranes. Non-ionized lipid-soluble compounds can penetrate the cell wall lipid barriers. For example, the anesthetic thiopental, a highly fat-soluble uncharged drug, rapidly enters the brain, and. macrolide antibiotics concentrate in the lung, eye, testicle, mammary gland, and synovial fluid (ie. spiramycin in lung tissue {Aziza, 1987}, tylosin in camels {Aziza, 1998}). In comparison, highly water-soluble ionized drugs such as penicillins and sulphonamides do not readily cross cell membranes and remain concentrated in the extracellular compartment.

The proportion of a drug that is protein-bound is generally inactive. Some drugs, such as ceftiofur, leave the blood stream very slowly because they are highly bound to plasma proteins. Other drugs, such as macrolides, quickly leave the blood stream and enter other tissues because they are poorly bound to plasma proteins. As unbound drug is distributed to tissues and its concentration in the intravascular compartment decreases, plasma proteins gradually release bound drug. Therefore, bound drug in the intravascular compartment may act as a reservoir for the drug.

Drugs can accumulate in certain tissues, such as macrolides in respiratory, mammary, genital system, aminoglycosides in kidneys, and fluoroquinolones in lung. These sites of accumulation also act as reservoirs of drug. These tissues slowly release the drug into the blood stream, keeping plasma concentrations of the drug from decreasing rapidly and thereby prolonging the systemic

effect of the drug.

Volumes of distribution (V_d)

Volumes of distribution (V_d) are proportionality constants between the total amount of drug in the body and plasma concentrations. The volume of distribution concept can be confusing for the veterinarian because there are 3 volumes of distribution; this is because drug distribution differs according to drug affinity to tissues other than blood. V_d is the parameter used to assess the amount of drug in the body from the measurement of a plasma concentration data. The main clinical application of V_d is to compute a loading (e.g. the first dose of multiple dosage regimen) in order to immediately reach the target therapeutic plasma concentration.

The 3 volumes of distribution are: 1) the volume of the central compartment (Vc); 2) the volume of distribution calculated using the area method (V_{area}); and 3) the steady-state volume of distribution (V_{ss}). V_{area} is the appropriate V_d to consider during the terminal phase of a pseudo-equilibrium, whereas V_{ss} is the appropriate V_d to consider under steady-state conditions. All three

calculated V_d values correspond to the ratio of an amount (A) of drug in the body at a given time (A_t) and plasma concentration at that time (Toutain and Bousquet-Melou, 2004) a whereby:

$$V_d = \text{Amount of drug in the body at time t } (A_t/$$
$$C_{plasma} \text{ at time}$$

Because drug plasma concentrations can be measured in different situations (such as immediately after an intravenous (IV) drug administration, during the phase of drug distribution, during the terminal phase of drug disposition or at equilibrium),the 3 different volumes of distribution V_d are needed because the proportionality ratio between the amount of drug in the body and the plasma concentration will have different values according to the state of drug disposition Figure 2 gives four possibilities, with V_c h. . . .
ume of distribution, V_{ss} the appropriate volume of distribution when plasma concentrations are measured in steady-state conditions, and V_{area} or V_z (formerly termed $V_{d\beta}$), the appropriate volume of distribution when plasma concentration is measured in pseudo-equilibrium conditions. Measurement conditions for the C_p (plasma concentration) and selection of the most appropriate volume of distribution is summarized in Figure 2.
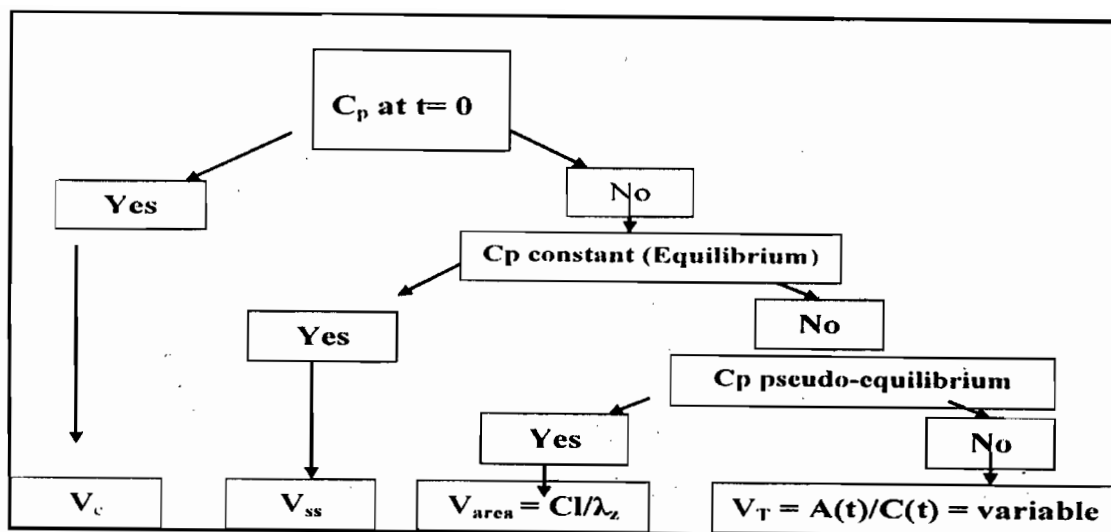
Figure 2: The different values of V_d (adapted from Toutain and Bousquet- Melou, 2004)"

1. Volume of the central compartment (V_c):

Immediately after intravenous drug administration the plasma concentration (C_0) is the maximum before any drug distribution and elimination. Because the amount of drug in the body equals the dose administered, the initial volume of distribution (volume of central compartment) can be calculated as follows:

$$V_c = Dose / C_0$$

According to compartmental analysis, the initial volume of distribution is termed the volume of the central compartment (V_c) and is calculated as follows:

$$V_c = Dose / \sum_{i=1}^{n} Y_i$$

Where Y_i are the intercepts of the different phases of the kinetic disposition obtained by fitting the plasma drug concentration vs time profile. V_c can be viewed as the apparent volume from which drug elimination occurs because the kidneys and liver, the two main organs of drug clear-ance, belong to the central compartment (Toutain and Bousquet- Melou, 2004)a.

Immediately after intravenous administration the drug begins to be distributed and eliminated. If distribution is equal to all sites in the animal, the body is reduced to a homogeneous pool (compartment) and Vc reflects the volume of distribution. If the drug is not equally distributed in animal body and the decrease in drug plasma concentration occurs at a faster rate than the proportional total amount of drug in the body, due to the distribution of drug to organs and not due to the drug elimination, the volume of distribution is a time dependent variable. Under these circumstances, V_c is not an accurate index of the true volume of distribution, and 2 other volumes of distribution need to be calculated, V_{area}, or V_{ss}.

2. Volume of distribution calculated using the area method (V_{area}):

At pseudo-equilibrium (Fig. 3), the net exchange (balance) between plasma

(central compartment) and the tissue (peripheral compartments) is zero, so that the rate of decrease in plasma concentration is equivalent to the rate of drug elimination:

Rate of drug elimination = Cl_{tot} x C_{plasma}

The amount of drug in the body at a given time t during the elimination phase is equal to the amount of drug which remains to be eliminated, and can be calculated as follows (Toutain and Bousquet- Melou, 2004)[a]:
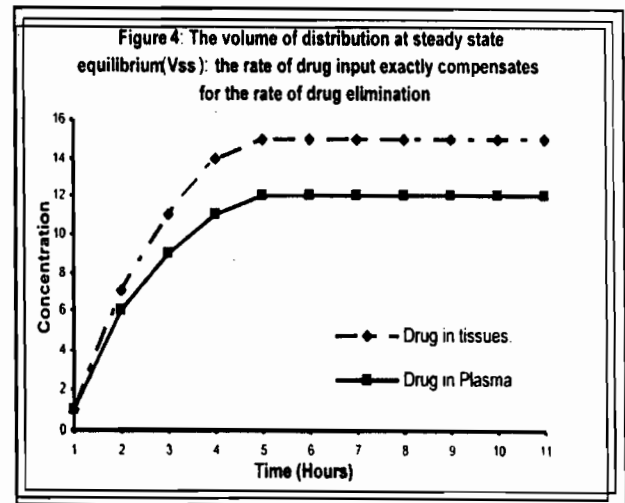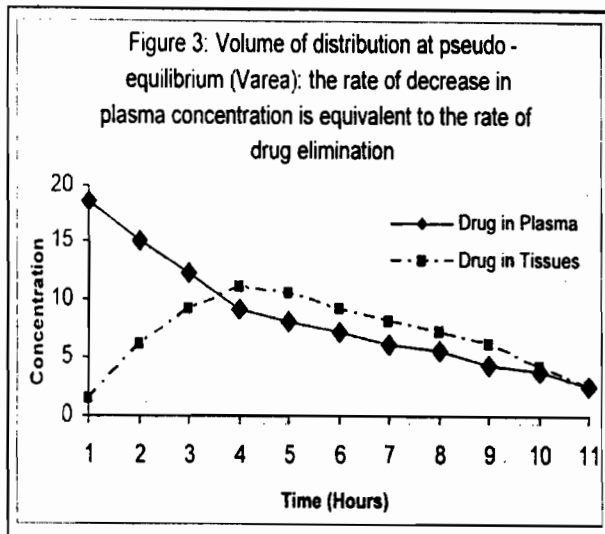
Amount of drug in the body at a time t =

$$Cl x [AUC_{(t-\alpha)}].$$

The $AUC_{(t-\alpha)}$ can be easily computed by interating equation from t/ to infinity, whereby:

$$AUC_{(t-\alpha)} = C (t_i)/\lambda_Z$$

$$V_{(area)} Cl/\lambda_Z = Dose /AUC_{(t-\alpha)} x 1/\lambda_Z$$

The computation of V requires two major assuimptions: 1) an accurate knowledge of the dose that gains access to the circulation; and 2) the terminal phase during which V_{area} is computed should be a pure elimination phase (Figure 3; modified after Toutain and Bousquet- Melou, 2004)[a]:

Figure 3: Volume of distribution at pseudo - equilibrium (Varea): the rate of decrease in plasma concentration is equivalent to the rate of drug elimination

Figure 4: The volume of distribution at steady state equilibrium(Vss): the rate of drug input exactly compensates for the rate of drug elimination

3. Steady state volume of distribution (V_{ss}) :

At steady state condition, (Fig. 4) the condition at which the rate of drug input exactly compensates for the rate of drug elimination, the system behaves equivalently to a closed system (no input and no output) with zero clearance . The appropriate volume of distribution (V_d) under steady-state equilibrium is the V_{ss}.

V_{ss} = Amount of drug in the body in equilibrium conditions/Steady-state plasma concentration (C_{ss})

V_{ss} is a clearance independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions. V_{ss} can be derived using different approaches such as compartmental statistical moments (Benet and

Galeazzi, 1979) that assume that the system is linear and that the drug elimination takes place from the drug sampling site. This method does not require curve fitting to a model and is calculated using the trapezoidal method:

$$V_{ss} = dose_{iv} \times AUCMC / (AUC)^2 = Cl \times MRT$$

In multiple dosing the moment V_{ss} can be calculated as follows: (Bauer & Gibaldi, 1983; Smith and Schentag, 1984).

V_{ss} (computed at steady-state condition) = Dose

$$[(AUMC/(AUC)^2 = Cl \times MRT$$

In multiple dosing the moment V_{ss} can be calculated as follows: (Bauer & Gibaldi, 1983; smith and Schentag, 1984).

V_{ss} (computed at steady-state condition) = Dose

$$[(AUMC_{ss})^t_0 + t(AUC_{ss})^\infty_t [(AUC_{ss})^t_0]^2]$$

What is the difference between V_{area} and V_{ss} ?

A difference between V_{area} and V_{ss} can exist if a large fraction of the drug is eliminated before reaching pseudo-equilibrium. The difference is due to difference between pseudo-equilibrium conditions. In pseudo-equilibrium conditions plasma drug concentration decreases because the drug is continually removed from plasma at a rate proportional to plasma clearance. In contrast, in equilibrium conditions plasma concentration is constant because the rate of drug elimination is compensated by the rate of drug input in the body (clearance is apparently null). Plasma concentration is lower in pseudo equilibrium than in equilibrium conditions (Toutain and Bousquet-Melou, 2004)[a].

Clinical application of the 3 different volumes of distribution (V_c - V_{ss} - V_{area}):
The main clinical value of the volume of distribution is to compute the amount of drug required for a loading dose. Vc is seldom used clinically, but it can be useful to: 1) predict the initial maximum concentration for intravenous bolus administration (e.g. in anesthesiology); 2) to anticipate possible side effects when the loading dose is rapidly administered with possible initial high peak plasma concentration; and 3) estimate the plasma volume when using a compound which is restricted to plasma such as Evans blue dye (Wamberg et al., 2002).

V_{area} is used to clinically estimate: 1) the residual amount of drug in the body when the drug decreases according to it is elimination phase, 2) how much drug remains to be excreted, and 3) the overall amount of drug residue in the body.

V_{ss} is the most clinically useful volume of distribution because it allows computation of loading dose from the steady-state clearance value and bioavailability (F), whereby:

$$Loading\ dose = - V_{ss} \times C_{ss}/F$$

Plasma protein binding and pharmacokinetics
Drugs can bind to many components in blood including erythrocytes and plasma proteins (Rowland and Tozer 1995). The drug concentration in blood (C_b) and plasma (C_p) and unbound drug concentration in plasma (C_u) can differ greatly.

Unbound drug can pass through cell membranes whereas bound drug cannot. In general, unbound drug is more easily measured (although this is dependent on the assay), and unbound drug is the pharmacologically active form. Unbound drug is best defined as unbound volume of distribution, V_u, whereby:

V_u = amount in body at equilibrium / unbound

plasma concentration = A/C_u

where the amount of drug in the body is related to the unbound drug concentration. Some times the whole blood concentration (V_b) is measured instead of the plasma concentration, in which case:

V_b = amount in body at equilibrium/ whole

blood concentration = A/C_b

where V_b is the apparent volume of distribution based on concentration in whole blood.

The amount in the body can be calculated as follows:

$$V \times C = V_u \times C_u = V_b \times C_b$$

Plasma protein binding: The binding of drugs to plasma proteins is mainly due to binding to plasma albumin. Binding is a function of affinity of the protein for the drug and the molar concentrations of both drug and proteins. Plasma protein binding of drugs can be high (ie, cloxacillin 95% and lincomycin 90%), moderate (ie, tetracycline, 50%; carbenicillin 47%), and low (ie, streptomycin 30%; amoxicillin 18%, ampicillin 25%, and gentamycin 25%) (Brander et al., 1991).

Because pharmacologic activity usually depends on the unbound drug concentration, the degree of plasma protein binding is of clinical interest. The total plasma concentration (C) depends on both the extent of protein binding (f_u) and the unbound concentration (C_u), That is,

$$C = C_u / f_u$$

Ratio of bound = concentration / total concentration

This ratio ranges in value from 0 to 1.0. Drugs with values greater than 0.9 are highly protein bound, and those with values less than 0.2 exhibit little or no protein binding.

Tissue binding: The fraction of drug in the body located in plasma depends on a drug's binding to both plasma and tissue components (Figure 5).
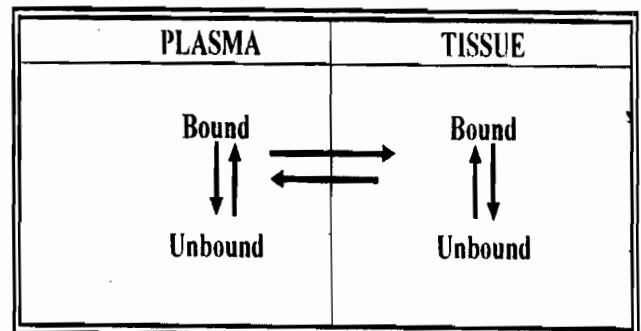
Figure 5: At equilibrium, the distribution of drug within the body depends upon binding to both plasma proteins and tissue components. In this model only unbound drug is capable of entering and leaving the plasma and tissue compartments.

Tissue binding is important in drug distribution. For drugs that have higher affinity for tissue than plasma, the drug is located primarily in tissues (e.g. macrolide antibiotics have a high affinity for lung and gentamycin has a high affinity for kidney) and tissue binding cannot be measured directly. In such cases the apparent volume of distribution expressed by the following equation (Toutain and Bousquet, 2004):
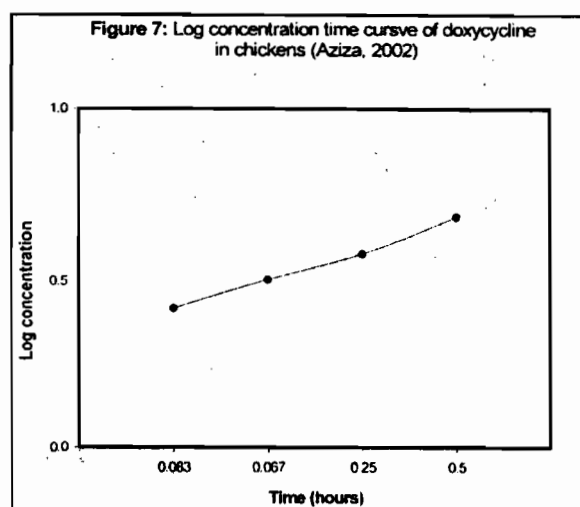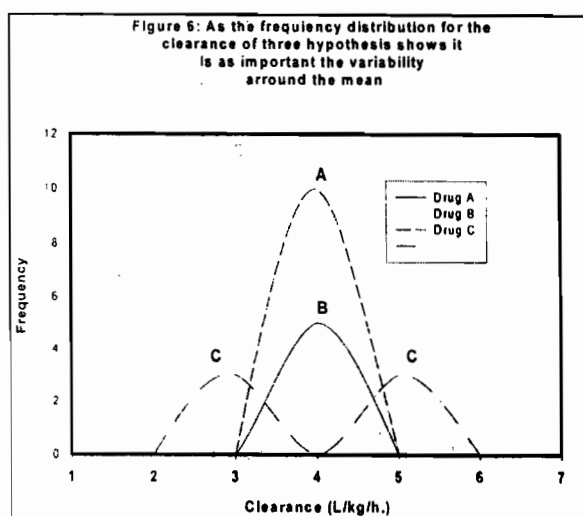
$$V = V_p + V_T \times f_{u \cdot p} / f_{u \cdot T}$$

where V_p is the plasma volume, V_T is the volume outside the plasma into which the drug distributes, $f_{u.p}$ is the fraction unbound in plasma, and $f_{u.T}$ is the fraction unbound outside plasma, the distribution ratio is determined by relative binding of drug to plasma and tissue constituents. V_T can be approximated by total body weight (Jusko & Chiang, 1982); with the exception of bone and fat, most tissues are >75% water, so that V_T is >0.75.

When the drug is restricted to the plasma volume. the volumes of distribution, apparent and real, are equivalent to the plasma volume which approximates 5 % of the body weight. For drugs that are not bound to plasma proteins or tissue the volume of distribution varies between the extracellular fluid volume (approximately 30 % of the body weight) and the total body water (approximately 60% of the body weight) or a much higher value, depending on the extent to which the drug concentrates in tissues. For many pathogens of veterinary interest, the most appropriate antimicrobial is the one for which the highest percentage of drug amount in the body is located at the site of infection as free drug (Toutain and Bousquet-Melou, 2004).

Variability

Knowing how a particular parameter varies within the patient population is important in therapy. The frequency of distributions in clearance of three hypothetical drugs as shown in Figure 6.

Figure 6: As the frequiency distribution for the clearance of three hypothesis shows it is as important the variability arround the mean

Figure 7: Log concentration time cursve of doxycycline in chickens (Aziza, 2002)

The mean or central tendency, for all three drugs is the same, but the variability about the mean is very different. For drugs A and B, the distribution is unimodal and normal; here the mean represents the typical value of clearance expected in the population (Riviere, 1999). For drug C, the distribution in clearance is bimodal, signifying that there are two major groups within the population: those with a high clearance and those with low clearance. Obviously, in this case, the mean is one of the most unlikely values to be found in this population (Rowland and Tozer 1995).

A symmetrical distribution is often obtained with the logarithm of the parameter; such distribution are said to be log-normal. A common method of examining for log-normal distribution is to plot the cumulative frequency, or percentile, on a probit scale against the logarithm of the variable. The distribution is log-normal if all the points lie on a straight line (Fig. 7). In such cases the median value differs from the mean.

Interindividual and intraindividual variations in pharmacokinetics and pharmacodynamics is reflected for many by the variety of dose strengths available, the intraindividual variability is generally much smaller than interindividual variability, and once well-established, there is often little need to subsequently readjust an individualís dosage regimen. Clearly if intraindividual variability were large and unpredictable, trying to titrate dosage for an individual would be an almost impossible task (Rowland and Tozer 1995).

Table 1: *Some factors that contribute to variability in response (Rowland and Tozer 1995).*

Factor	Observations and remarks
Noncompliance	A major problem in clinical practice; solution lies in owner education
Pharmaceutical formulation	Formulation and manufacturing process can affect both rate and extent of drug absorption
Route of administration	Patient response can vary on changing the route of administration. Both the pharmacokinetics and metabolite concentrations can change
Age	Pharmacokinetics and pharmacodynamics of many drugs vary with age
Drug	Pharmacokinetics and pharmacodynamics of many drugs vary with concurrent drug therapy
Food	Rate and occasionally the extent of absorption are affected by eating. Effects depend on the composition of food
Pollutants	Hypothesized
Time or day season	Diurnal variations are seen in pharmacokinetics and in drug response These effects have been sufficiently important to lead to the development of a new subject, chronopharmacology
Location	Dose requirement of some drugs differ between animals living in different environments
Gender	Intramuscular absorption of some drugs is slower in females than in males; this observation is explained by differences in blood flow.
Pharmacogenetics	Genetic N-acetyltransferase enzyme involved in the drug metabolism. Some drugs have genetically and breed dependent response. Ivermectin showed toxic effects in Collie dogs. The breeds of dogs most commonly affected are collies and collie-crosses. (ABVT, 2006)*** Paul et al., (1987)

Plasma clearance

Plasma clearance is the plasma volume that is totally cleared of drug per unit time. Plasma clearance provides a global index of the animal ability to eliminate a drug. Plasma clearance is one of the 2 most important pharmacokinetic parameters because it is a determinant of dosage rate (Fig. 6) (Toutain and Bousquet-Melou, 2004).[b]

Clearance = Rate of drug elimination / Driving concentration

or

Plasma clearance = Total (body) clearance / Plasma concentration

Scaling of the total rate of drug body elimination by the corresponding plasma concentration expresses the ability of the body to eliminate a drug by a constant parameter (rather than by an excretion rate which is a concentration-dependent variable for a drug following first-order elimination process (Figure 8). If drug clearance does not obey a first-order elimination process the clearance is a concentration-dependent variable

Rate of drug elimination at time t x plasma concentration at time t

For free (unbound) plasma concentration:

Rate of drug clearance = Cl_{blood} x C_{blood} = Cl plasma x C_{plasma} = Cl_{free} x C_{free}

Figure 8: Time concentration curve of lincomycin after IV injection in Broiler chickens. (Aziza, 2005)
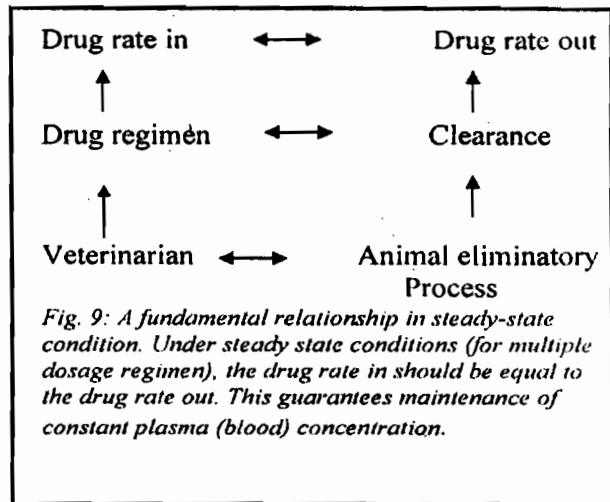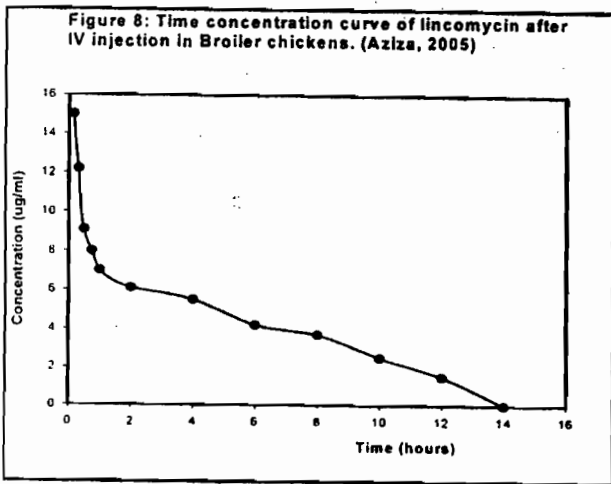

Fig. 9: A fundamental relationship in steady-state condition. Under steady state conditions (for multiple dosage regimen), the drug rate in should be equal to the drug rate out. This guarantees maintenance of constant plasma (blood) concentration.

The relationship between a dosing rate, the plasma clearance, the therapeutic plasma concentration in steady-state conditions and systemic bioavailability can be expressed as follows (Toutain and Bousquet-Melou 2004)[b]:

Dosing rate = Plasma clearance x therapeutic plasma concentration / Bioavailability

This equation indicates that dose is a pharmacokinetic/pharmacodynamic variable because it is influenced by a pharmacokinetic parameter (plasma clearance), a pharmacokinetic variable (bioavailability), and a pharmacodynamic parameter (target therapeutic concentration) (Toutain, 2002).

Evaluation of plasma clearance

Plasma clearance can be determined after intra-vascular or extravascular administration. After intravascular administration, the plasma concentration is sequentially measured until the drug concentration in plasma is less than the limit of quantification (Figure 9). The total clearance is derived as follows:
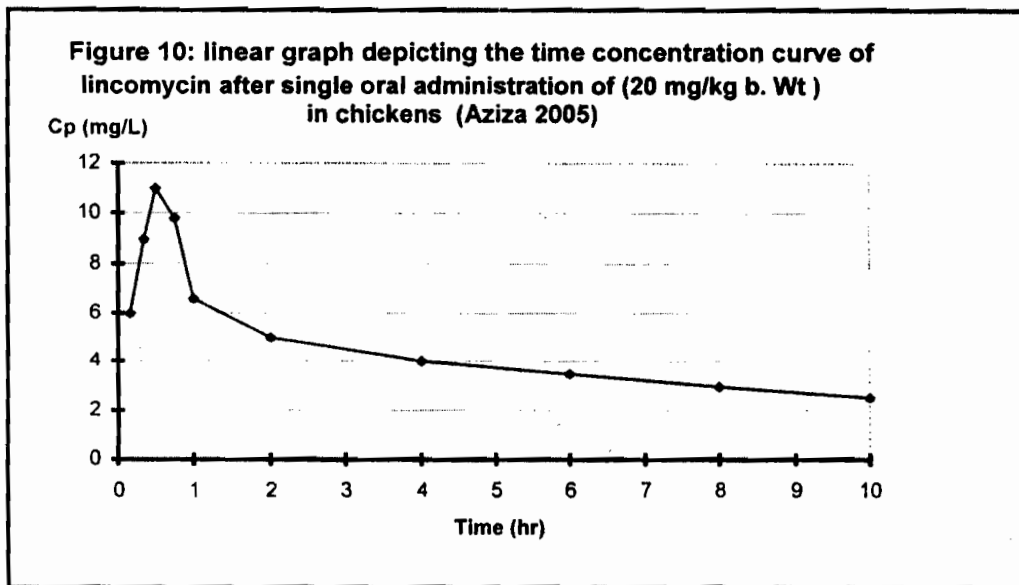
$$Cl_{tot} = Dose / AUC$$

After extravascular administration, the plasma concentration is sequentially measured in a similar manner (Figure 10), with total clearance being calculated as follows:

$$Cl_{tot} = Cl_{renal} + Cl_{Liver} \text{ and } Cl_{other}$$

When the liver and other clearance can be neglected the clearance is:

$$Cl_{tot} = Cl_{renal} = \text{total amount of drug eliminated in urine/AUC}$$

Figure 10: linear graph depicting the time concentration curve of lincomycin after single oral administration of (20 mg/kg b. Wt) in chickens (Aziza 2005)

Veterinary papers rarely attempt to interpret differences in clearance, even though clearance is one of the 2 most important determinants of dosage regimen. Wide species and drug variations exist in clearance, as indicated by the following plasma clearance values for goats and chickens: tyrosine in lactating goats, 0.3(ml/kg/min (Aziza, 1996); apramycin in lactating goats, 1.7 ml/kg/min (El-Gendi et al, 1996); lincomycin in chickens, 14.2 ml/kg/min (Aziza et al, 2005); doxycicline in chickens 2.0 (ml/kg)/min (Aziza, 2002).

Application of plasma clearance for computation of a dose

There are many practical uses for plasma clearance, the most common one is calculating a dose. The target therapeutic concentration for the average plasma concentration must be defined; this is based on the literature, pharmacokinetic/pharmacodynamic trials, and extrapolation from in vitro assay results (Toutain et al., 1994). For antimicrobials, drug potency is often assessed experimentally by measuring the in vitro minimum inhibitory concentration (MIC) for a given pathogen. In addition surrogate indices to predict antibiotic efficacy have been proposed such as the area under the inhibitory curve (AUIC) for fluoroquinolones (Lees and Shojaee Aliabadi, 2002; Toutain et al., 2002):

$$\text{Dose (per day)} = \text{AUIC} \times \text{MIC} \times Cl_{plasma} / f_u \times F$$

where AUIC (or AUC/MIC) is the end point in

hours (e.g. 24 hours), MIC in µg/ml is for the target pathogen, Cl_{plasma} is the total clearance per unit time, f_u the free fraction of drug in plasma (range in value of 0 to 1), and F is the bioavailability which ranges from 0 to 1 (Hyatt et al., 1995; Toutain et al., 2002 and Toutain 2003).

Plasma clearance values are also very useful when extrapolating drug dose from one species to another. When the drug dose is known in one species; the dosage can be calculated for a different species assuming that the same overall body exposure (AUC) will produce the same effect in both species (ie. drug potency is species independent) . The following relationships therefore hold:

$$AUC_{species1} = AUC_{species2} = Dose_{species1}/$$
$$Cl_{species1} = Dose_{species2}/Cl_{species2}$$
$$Dose_{species2} = Dose_{species1} \times Cl_{species2}/$$
$$Cl_{species1}$$
$$Dose_{species1} = Dose_{species1} \times f_{u1} \times Cl_{species1}$$

These equations can be used to calculate a drug dose from data from one species, such as morphine in human (Stanski et al., 1978); morphine in dogs (Branhart et al., 2000); morphine in horses (Combie et al., 1983). No correction for drug protein binding is usually required because the extent of plasma binding is usually similar for different species (Baggot & Davis, 1973).

PHARMACOKINETIC ANALYSIS

Pharmacokinetic analysis is the mathematic quan-

tification of the relationship between plasma concentration and time following drug administration. Pharmacokinetic analysis also estimates drug distribution and elimination profiles following different dosage regimens at normal, disease condition, and physiologic states. From these estimations the efficacy or toxicity of drug under these conditions can be more efficiently predicted (Gibaldi and Perrier, 1982; Rowland and Tozer, 1995).

There are 2 conceptual approaches in pharmacokinetic descriptions and calculations: the first approach called compartmental pharmacokinetics considers the body as compartments according to the site of drug administration and distribution rate to different organs. The distribution compartments are interconnected by first-order rate constants that define drug transfers and are used to describe the pharmacokinetic behavior of drugs. These compartments are mathematical entities that may have no physiological counterparts. The second approach considers the whole the body as one compartment with the drug distributed in blood, body fluids and all organs equally, in physiological relevance to animal body physiology; this is called non-compartmental pharmacokinetics (Adams 2001). A pharmacokinetic model is therefore a mathematical description of the underlying interaction of a drugís pharmacology with an animalís physiology (Figure 1). The nature of the link will determine the type of parameters calculated.

Compartmental analysis

The most widely used pharmacokinetic modeling approach in veterinary medicine is the compartmental approach. In this analysis, the body is viewed as being composed of a number of so called equilibrium compartments, each defined as representing nonspecific body regions where the rate of compound disappearance are of a similar order of magnitude (specifically, the fraction or percent of drug eliminated per unit time from such a defined compartment). These compartments are classified and grouped on the bases of similar rate of drug movement within the kinetically homogeneous but anatomically and physiologically heterogeneous group of tissues. The physiological processing of drug absorption, distribution and elimination are the primary phenomena that are quantitated using the compartmental model approach (Riviere 1999). The objectives of compartmental analysis are to: 1) provide a conceptual understanding of distributional behavior of a drug between the plasma (and blood) and the other tissues or organs in the body; 2) empirically assess the change in physiological processes such as membrane transport or metabolism without thorough mechanistic investigation; and 3) estimate various pharmacokinetic parameters such as rate constants, clearance and apparent volumes of distribution (Kwon 2001).

Compartmental analysis is usually based on one compartment (rare), two compartments (common), three compartments (common), or four or

more compartments (rare).

One compartment model

The one compartmental model (incorrectly) assumes that the dose absorbed is distributed into what is conceived to be a single compartment and eliminated from this compartment by first-order processes of metabolism and excretion (Loo and Riegelman (1968) (Figure 11). This assumption is rarely met in animal drug studies, but the one compartment model provides a useful basis for development of more biologically appropriate pharmacokinetic models (specifically 2 and 3 compartment models).
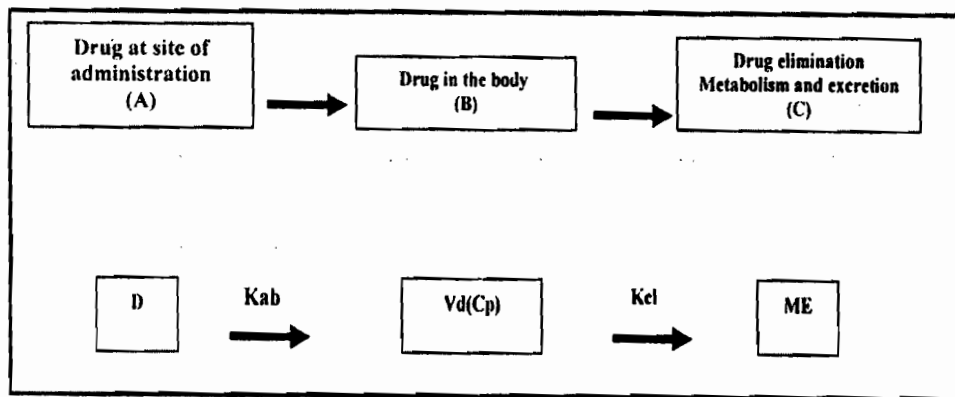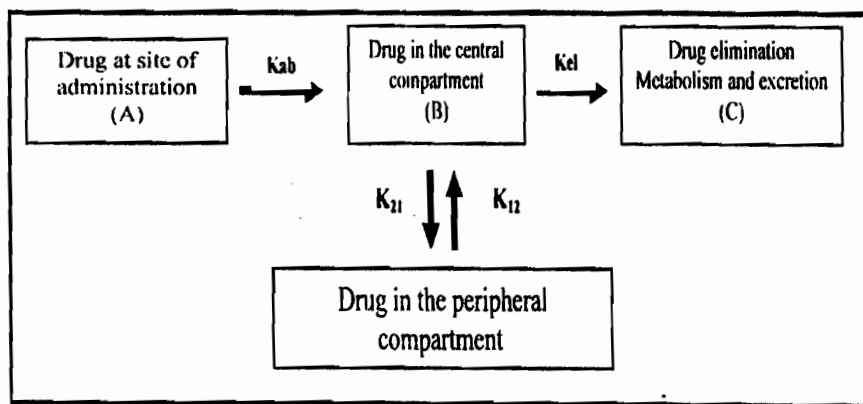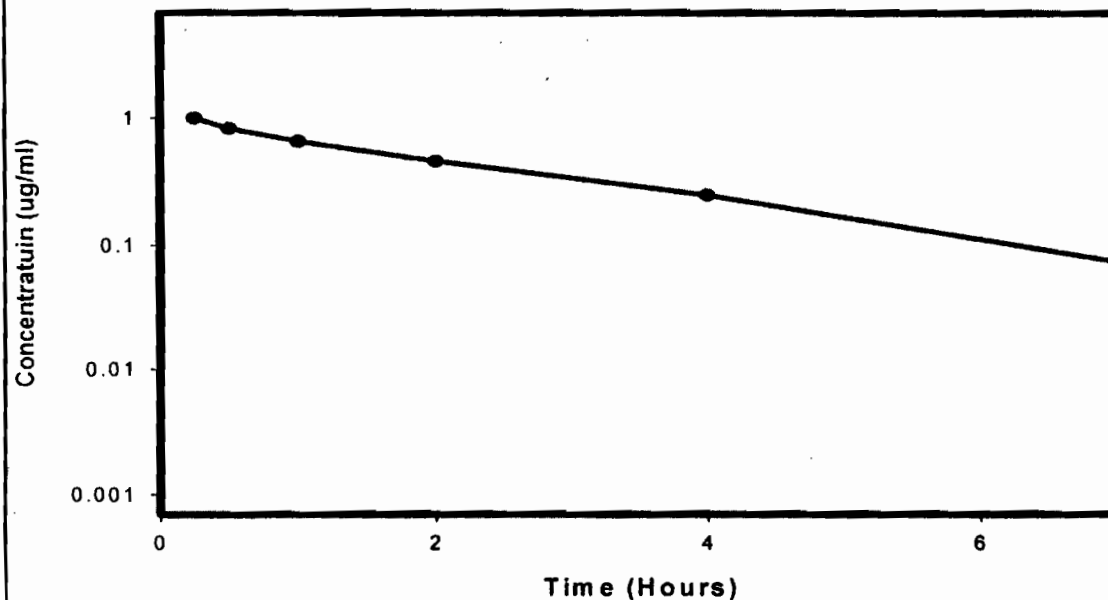

Figure 11 (adapted from Loo and Riegelman, 1968), where D is the amount of drug remaining at the absorption site, Cp is the concentration of the drug in the blood, V_d is the apparent volume of distribution based on the assumption that the body behaves as a single compartment, ME represents the combined amount of drug metabolized and excreted by simultaneous first-order processes. K_{el} is the first order rate constant for the elimination of the drug from the body and equal to the sum of the individual rates of metabolism and excretion

For some intravenously administered drugs the disposition curve can be approximately by a mono exponential equation (Figure 12, Aziza, 1985), where the plasma concentration at time t ($C_p(t)$) can be exposed in terms of time (t), a rate constant (β), and an extrapolated intercept value assuming instantaneous mixing (B):

$$C_p(t) = Bxe^{-\beta t}$$

Figure 12: Time concentration curve of oxytetracycline in chicken's serum after a single intravenous injection of 6 mg/kg BW

Figure 13 (adapted from Loo and Riegelman, 1968). where Kab is a first order rate constant for absorption; Kel is a first order rate constant for elimination; K_{12} is a distribution rate constant from the central compartment to the peripheral compartment; K_{21} is a distribution rate constant from the peripheral compartment to the central compartment

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Two-Comparttment model

Loo and Kiegelman (1968) reported a method for calculating the absorption rate constant k_{ab} in case where the drug distribution according to two-compartment model (Figiure 13).

The two compartment open model (Figure 14 A and B) adequately describes the disposition kinetics of many drugs in animals. For the two compartment model, the plasma concentration at time t ($C_p(t)$) is expressed in terms of time (t), two hybrid rate constants (α,β) and two extrapolated intercept constants assuming instantaneous mixing (A,B). The mathematical curve fit to the data is a biexponential equation, whereby:

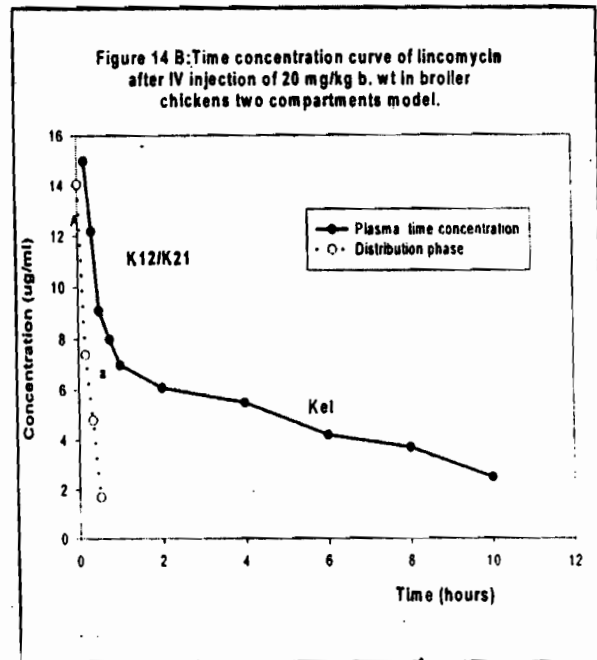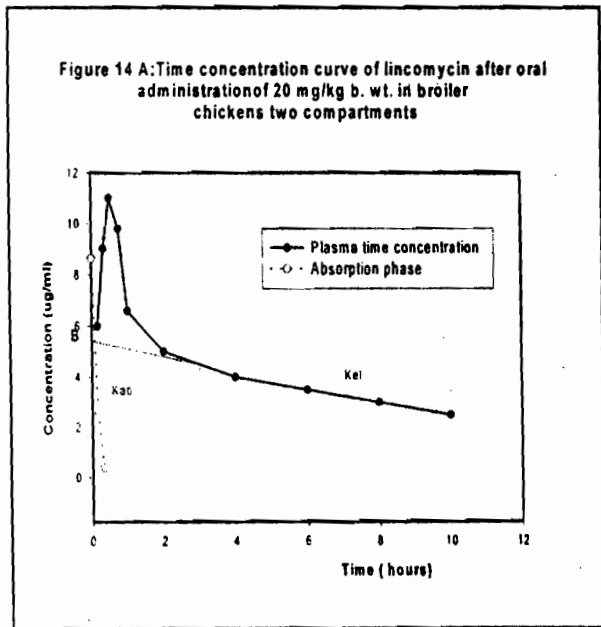$$C_p(t) = A \times e^{-\alpha t} + Bx\ e^{-\beta t}$$

The values of the actual pharmacokinetic rate constants (K_{ab}, k_{12}, k_{21}, K_{el}) are then calculated from the derived hybrid constants (A,B,α,β) by means of appropriate equations (Riegelman et al., 1968 and Baggot 1977, Baggot et al., 1977)., whereby:

$$K_{21} = (A\beta + B\alpha/\ A + B,\ K_{el} = \alpha\beta/K_{21}\ \text{and}$$
$$k_{12} = \alpha + \beta - K_{21} - K_{el}$$

The log linear terminal portion of the disposition curve is the elimination phase (Fig.14 A & B) and from its slope- ($-\beta/2.303$) the half-life can be calculated, as well as the zero time intercept (B). The second log linear segment is called the distribution phase, which has slope ($-\alpha/2.303$) and zero time intercept (A) (Rowland and Tozer, 1995).

Figure 14 A:Time concentration curve of lincomycin after oral administrationof 20 mg/kg b. wt. in broiler chickens two compartments

Figure 14 B:Time concentration curve of lincomycin after IV injection of 20 mg/kg b. wt in broiler chickens two compartments model.
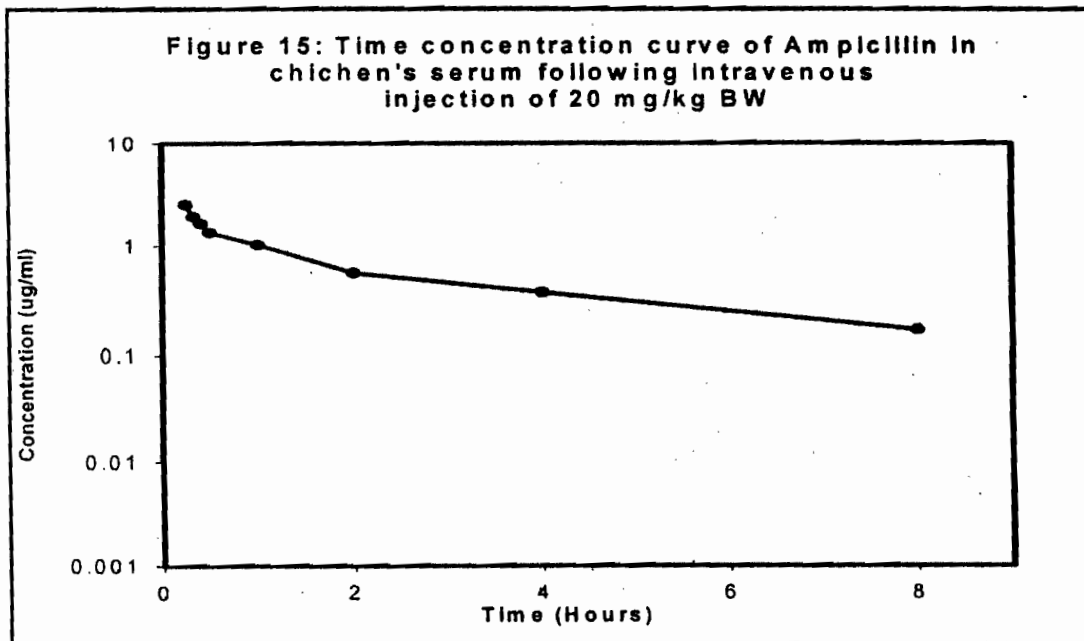
Three-Compartment model

The pharmacokinetic behavior of a drug that has a high affinity for a particular tissue (through selective binding) or undergoes redistribution is usually described more accurately by a 3 compartment model instead of a 2 compartment model. The three compartment open model may be necessary to completely characterize the pharmacokinetic profile of oxytetracycline in dogs (Baggot et al. 1977); sulfadoxine in horses (Rasmussen et al. 1979); sulphdimethoxine in cattle (Boxenbaum et al. 1977), gentamycin in various species (Brown and Riviere, 1991), and ampicillins in chickens (Aziza, 1985).

The following mathematic exprestion describes the fri-exponential disposition curve

$$C_p(t) = A \times e^{-\alpha t} + B \times e^{-\beta t} + C \times e^{-\gamma t}$$

The hybrid constants $(A, B, C, \alpha, \beta, \gamma)$ can be calculated by interactive least-squares linear regression in conjugation with examination of the residuals for determining distribution and redistribution phases (termed curve stripping). However, the best method for determining the constants is to model the plasma concentration-time data using nonlinear least-squares regression analysis (Glantz and Slinker, 1990) or available computer software programs (Figure 15, Aziza, 1985). Under these circumstances, the actual values for elimination constants can be calculated, but such calculations requires sophisticated mathematical techniques which have been largely supplanted by computer software programs.


Figure 15: Time concentration curve of Ampicillin in chichen's serum following intravenous injection of 20 mg/kg BW

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Four compartment and other multi-compartmental models

Pharmacokinetic models with four compartments, namely two body compartments, one compartment for the stomach, and one compartment for the site of rapid absorption in the small intestine have been developed (Figure 16) (Clements, et al. 1978).
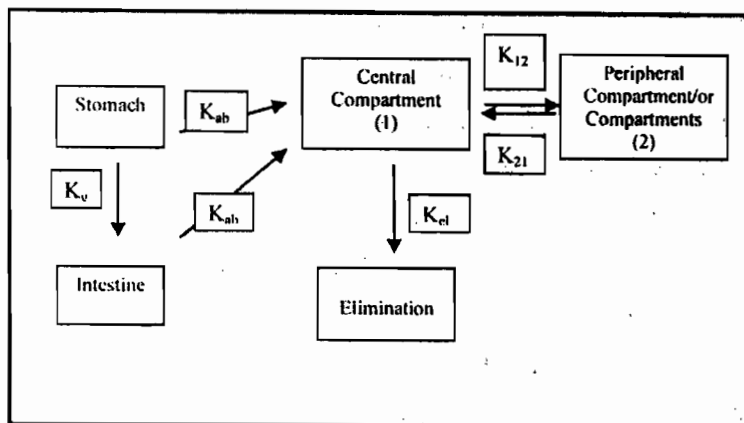
Figure 16: Representing 4 compartments oral absorption of the drugs considering stomach absorption as one compartment, intestinal absorption as another compartment, the blood and highly vascularized organs is the central compartment and other organs and tissues as the peripheral compartment (Clements, et al. 1978).
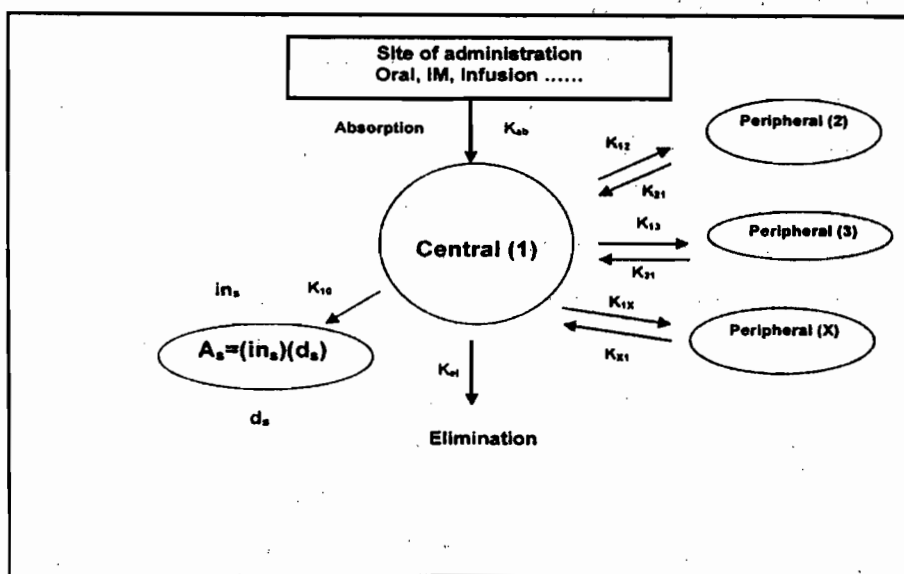
Figure 17: A general model with elimination allowed from every compartment. The disposition function d_s describe the model necessary to describe accurately drug body concentration after the drug has distributed into blood circulation. Input functions in_s describes the process or processes necessary to get the drug into the blood stream. The products of the input and disposition functions yield the Laplace Transform* for the equation describing the time course of the amount of the drug in compartment (a_s) Described after Benet (1972).

Non-compartmental analysis

Non compartmental analysis reduces the assumptions that must be made in modeling plasma concentration versus time data. The main advantage of non compartmental analysis is that it requires fewer assumptions than that needed for compartmental analysis. The approach also avoids some of the common problems seen with compartmental analysis, in that the plasma concentration-time profile of individuals in a treatment group may be best described by different compartment models (such as one, two or three compartments). This problem can be are largely avoided with non-compartmental analysis. When using non-compartmental analysis, the concentration-time data is calculated according to the mean time concept which does not require an explicit compartmental pharmacokinetic model for the pathway of drug molecules through the body. However, when it comes to the interpretation of the results, a clear idea of the molecule's pathway through the body is necessary, i.e. the sequence of events and thus a sum of components must be stated and validated (Brockmeier, 1999).

The total transit time of an individual molecule through a system is the sum of its time up to absorption into the central circulation $z_{i.abs}$ and the time the molecule spends in any part of the volume the molecule can reach $z_{i.vss}$. Therefore, the total mean time of all drug molecules available is the sum of the mean absorption time MT_{abs} and the mean time in the steady state volume of distribution $MTvss$. It is obvious that we can estimate the two components of the total mean time, i.e. MT_{abs} and MT_{vss}, by an appropriate experimental setting giving the drug once intravenously and determining MT_{vss} and once giving the drug as an oral solution and deducing $MT_{abs} = MT_{total}$ MT_{vss}. Because of this very useful property of the statistical analysis of concentration-time data by moments, the non-compartmental analysis approach has been called component analysis (von Hattingberg et al., 1984). One can compute formally the total mean time from plasma concentration-time data (Fig. 18). The computed characteristic is a mean value for the individual total transit times of drug molecules if the drug pharmacokinetics are linear and if elimination takes place from the compartment monitored.

Statistical moment theory

The basic assumption of statistical moment theory (which is a component of a more general stochastic approach) is that we can observe a molecule from the time it is administered into the body $(t = 0)$ until it is could be completely eliminated $(t = t_{el})$. The actual value for t_{el} is not predictable for an individual molecule, but when viewed as a collective, the behavior of molecules appears much more regular. The collective or mean time of residence of all molecules in the administered dose is called the mean residence time (MRT).

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For intravenous administered substances the MRT can be considered as the statistical moment analog to the half-life ($T_{1/2}$), in that $T_{1/2} = 0.693/$ MRT.

The primary task of non-compartmental model is the direct estimation of moments from data. This essentially is determining the relevant AUCs and moments from the concentration and time profile. The statistical moment analysis is described as SHAM (slope, heights, area, and moments) analysis to stress that these are the only data requirements for solution of these model.

The AUC can be calculated using exponential-based formulae or trapezoidal analysis.
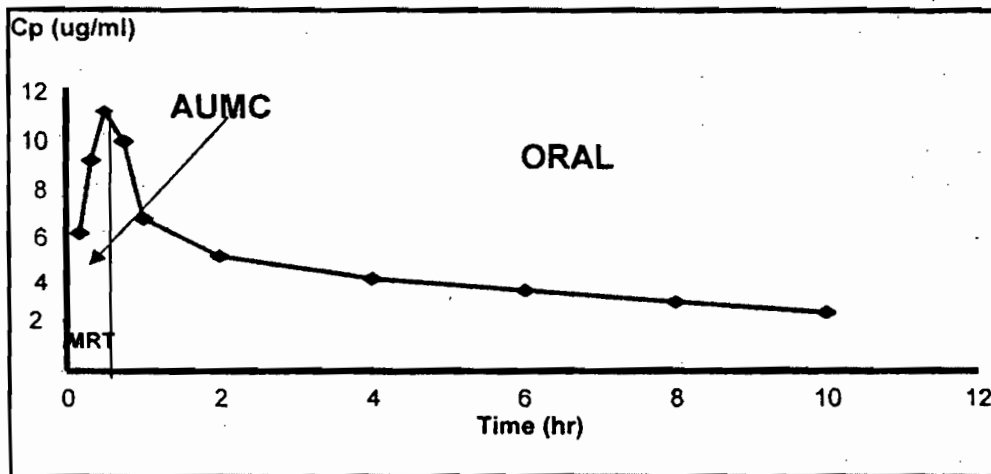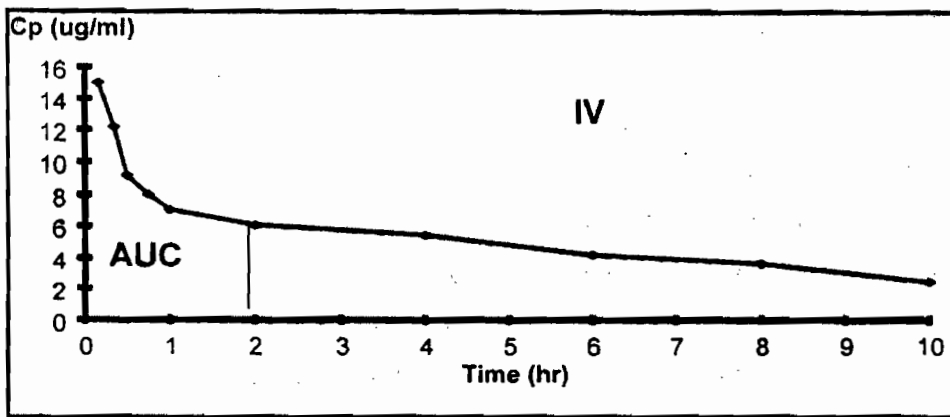
Figure 18: *Plasma concentration versus time plots demonstrating AUC, AUCM and MRT*

Drug Metabolites

It seems worthwhile to note that the mean time of a metabolite upon intravenous injection of the parent drug encompasses the mean time of the parent drug. The total mean time of the metabolite $MT_{total.met}$ is the sum of the mean time of the unchanged drug with respect to its steady state volume of distribution $MT_{vss.par}$ and the mean time of the metabolite with respect to its own steady state volume of distribution $MT_{vss.met}$ Brockmeier and Ostrowski (1985):

$$MT_{total.met} = MT_{vss.par} + MT_{vss.met}$$

The 'mean residence time' of the metabolite, i.e. the mean time of the metabolite with respect to its own steady state volume of distribution $MT_{vss.met}$ can be determined by the difference of the total mean time $MT_{total.met}$ and the 'mean residence time' of the parent drug $MT_{vss.par}$. In doing so, we assume that any molecule of parent drug which disappears due to metabolism almost immediately appears as metabolized molecule in the volume monitored. Otherwise we must account for a mean conversion time (Riegelmann and Collier, 1980).

Oral Dosage Solution form

Upon administration of an oral solution, the total mean time encompasses the absorption (MT_{abs}), distribution and elimination (MT_{vss}) Yamaoka et al. (1978), Cutler (1978):, von Hattingberg et al. (1980).

$$MT_{total.sol} = MT_{abs} + MT_{vss}$$

If the drug must be transported to the site of absorption prior to being absorbed, the total mean time also includes the mean transport time MT_{LT}:

$$MT_{total.sol} = MT_{LT} + MT_{abs} + MT_{vss.}$$

If the transport of drug to the site of absorption is considered as a simple lag-time, the mean MTLT is just the lag-time itself. One must decide carefully whether the mean transport time should be included in the further considerations and/or calculation.

Solid Oral Dosage Forms

Regularly, one is interested in the in vivo dissolution process of a solid oral dosage form. After administration of this formulation, the mean in vivo dissolution time $MT_{diss.vivo}$ is included in the total mean time computed from plasma/serum or excretion data (von Hattingberg and Brockmeier (1978) von Hattingberg et al., (1980), Tanigawara et al., (1982):

$$MT_{total.vivo} = MT_{diss.vivo} + MT_{LT} + MT_{abs} + MT_{vss}$$

The transport of the formulation may precede the dissolving of drug molecules, e.g. in the case of enteric coated tablets or pellets, or they may be dissolved first and then transported to the site of absorption. Here again the mean in vivo dissolution time can be obtained by the difference of the total mean time for a readily available oral dosage form and the total mean time for the solid oral dosage form.

$$MT_{diss.vivo} = MT_{total.vivo} - MT_{total.sol}$$

This requires the solution and the solid dosage form being administered separately to the same individuals.

If the solid dosage form is compared with an intravenous administration, the difference of the total mean times is not the mean in vivo dissolution time but encompasses the mean transport time and mean absorption time:

$$MT_{total.vivo} - MT_{total.iv} = MT_{diss.vivo} + MT_{LT} + MT_{abs}$$

Here again the transport may precede dissolution or vice versa.

COMPUTER SOFTWARE PROGRAMS

A large number of computer software programs are now available. These have greatly simplified the computation of pharmacokinetic parameters, and permit rapid exploration of alternative compartmental and non-compartmental pharmacokinetic models. Some of these programs are available as free down loads, whereas others are commercially available. The URL's for selected software programs are listed below: These Sites have a lot of informations and some free programs)

PK Solutions 2.0 non-compartmental pharmacokinetics data analysis copyright c, Summit Research services.

PK/PD modeling (www analyticon, co.uk/PKPD page htm).

Sigmaplot (www. systat. com/products/Sigma Plot)

Excel work sheets (www.snapsurveys. com/work sheets/work sheets 003,shtml)

SAAM II (https:// depts washington.edu/saam2/ support/index. html)

Win-nonline (www.pbpk.org/modules, php? name = Forms & file).

USEFUL WEB SITES

A number of useful web sites are available. These vary in their emphasis on pharmacokinetics and pharmacodynamics. Some of the more helpful web sites are listed below:

www.boomer etc & list others you found of value
www.merck.com/mmhe/sec02/ch011/ch011c.html
www.efunda.com/mth/laplac_transform/index.cfm
www.safe2use.com/scabiesboard/ivermectin/iverm.html
www.whatislev.com/gogoole-search.html
www.pharmj.com/noticeboard/series/pharmacokinetics.html
www.hpru.com/pharma.html

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مقدمة عن المسار الحركي الأكلينيكي للأدوية : النمازج و برامج الكمبيوتر
AN INTRODUCTION TO CLINICAL PHARMACOKINETICS:
Models and Software

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يحتاج الاستخدام الأمثل للأدوية في العلاج الي فهم المسار الحركي للأدوية وكذلك التأثيرات المختلفة لها. ولأن الجرعة العلاجية تعتمد علي كيفية تأثير الجسم علي الدواء (Pharmacokinetics) وكذلك سلامة وفاعلية الدواء (Pharmacokinetics) . للوصول الي الدواء الأمثل يجب اختيار الدواء اعتمادا علي :التشخيص الدقيق ـ معرفة الحالة الأكلينيكية للحيوان المريض ـ الوعي بالدواء العلاجي وكيفية تعامله مع المرض.

هناك هدفين رئيسيين لهذه الدراسة:

1ـ القاء الضوء علي المراحل الرئيسية المسار الحركي للدواء (الأمتصاص ــ الانتشار ــ التمثيل الدوائي ــ تخلص الجسم من الدواء) والتي يمكن تحويلها الي قيم كمية باستخدام الطرق المختلفة لحساب للمسار الحركي الدوائي (Pharmacokinetics) .

2ـ تحديد برامج الكمبيوتر وكذلك المواقع الالكترونية ذات الأهمية للأطباء البيطريين و المهتميين بالأدوية التطبيقية و المسار الحركي التطبيقي للأدوية.

هناك أربعة اسئلة يجب الاجابة عليها عندما نختار الدواء لعلاج حالة معينة:

1ـ *الي اي مدي؟* تكون الاستجابة العلاجية و السمية للجرعة المستخدمة

2ـ *ما هي؟* طريقة الإعطاء المثلي للشكل الدوائي التي يعتمد عليها الاستخدام الحقلي ومدة العلاج.

3ـ *الي اي حد؟* تعتبر الفترة ما بين الجرعتين مهمة والتي تعتمد علي معدل نقص تركيز الدولء في الدم بعد اعطاء الجرعة الأولي.

4ـ *ما هي مدة العلاج؟* والتي تعتمد عليها التكلفة (الأعراض الجانبية ــ السمية ــ الاقتصادية).

للاجابة علي هذه الأسئلة يجب اجراء تجارب علي عدد كبير من الحيوانات لوضع النظام الجيد للعلاج.

تلقي هذة الدراسة الضوء علي:

ـ المسار الحركي للدواء (Pharmacokinetics) (الأمتصاص ــ الانتشار ــ التمثيل الدوائي ــ تخلص الجسم من الدواء).

ـ تحليل المسار الحركي للدواء (Pharmacokinetic analysis) وهو عبارة عن تحديد كمي ورياضي للعلاقة بين تركيز الدواء في البلازما و الوقت بعد اعطاء الدواء.

يهتم تحليل المسار الحركي الكمي للدواء بتحديد مدي:

- انتشار واخراج الدواء بعد الاعطاء بجرعات مختلفة في الحالات المختلفة للحيوان (السليمة ــ المريضة ــ الفسيولوجية)
- كفاءة وسمية الدواء

هناك وجهتي نظر للتعامل مع المسار الحركي للدواء من حيث الوصف والحساب:

أ- المسار الحركي الجزئي (Compartmental pharmacokinetics)
وفية يعتبر جسم الحيوان عبارة عن عدة اجزاء علي حسب مكان اعطاء الدواء ومعدل انتشاره في الأنسجة المختلفة : جزء واحد (نادر) ــ جزءين (شائع) ــ ثلاثة اجزاء (شائع) ـ أربعة أجزاء (نادر).

ب- المسار الحركي الغير جزئي (Non-compartmental pharmacokinetics) وفيه يعتبر الجسم كله جزء واحد , يكون فيه انتشار الدواء في الدم وسوائل الجسم والأعضاء المختلفة متساوي. ويحتاج الي عدد قليل من الافتراضات لوضع نموزج للعلاقة بين تركيز الدواء في الدم والوقت.

الخلاصة والأهمية التطبيقية: يستخلص من هذة الدراسة أن الفهم الكامل و الجيد للمسار الحركي الأكلينيكي للدواء هو حجر الزاوية للعلاج الناجح وتعتبر هذه الدراسة منهاجا للباحثين والمعالجين والمهتميين بالدواء .