# A short introduction to pharmacokinetics

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**Abstract.** – Phamacokinetics is proposed to study the absorption, the distribution, the biotransformations and the elimination of drugs in man and animals.

A single kinetic profile may be well summarized by $C_{max}$, $T_{max}$, $t_{1/2}$ and AUC and, having more than one profile, 8 parameters at least, the mean and standard deviation of these parameters, may well summarize the drug kinetics in the whole population.

A more carefull description of the data can be obtained interpolating and extrapolating the drug concentrations with some mathematical functions. These functions may be used to reduce all the data in a small set of parameters, or to verify if the hypotheses incorporated in the functions are confirmed by the observations. In the first case, we can say that the task is to get a simulation of the data, in the second to get a model.

The functions used to interpolate and reduce the pharmacokinetic data are the multiexponential functions and the reference models are the compartmental models whose solutions are just the multiexponential functions. Using models, new meaningfull pharmacokinetic parameters may be defined which can be used to find relationships between the drug kinetic profile and the physiological process which drive the drug absorption, distribution and elimination. For example, compartmental models allow to define easily the clearance which is dependent on the drug elimination process, or the volume of distribution which depends on the drug distribution in the tissues. Models provide also an easy way to get an estimate of drug absorption after extravasculare drug administration (bioavailability).

Model building is a complex multistep process where, experiment by experiment and simulation by simulation, new hypothesis are proven and disproven through a continuous interaction between the experimenter and the computer.

*Key Words:*

Pharmacokinetic models, Multiexponential functions, AUC, Half-life, Volume of distribution, Clearance, Bioavailability.

## Introduction

Pharmacokinetics is proposed to study the absorption, the distribution, the biotrasformations and the elimination of drugs in man and animals[1]. Absorption and distribution indicate the passage of the drug molecules from the administration site to the blood and the passage of drug molecules from blood to tissues respectively. Drug elimination may occur through biotrasformation and by the passage of molecules from the blood to the outside of the body through urines, bile or other routes. Figure 1 shows two graphic representations of these processes.

Measuring the amounts or the concentrations of drugs in blood, urines or other fluids or tissues at different times after the administration, much information can be obtained on drug absorption and on the passage of drug molecules between blood and tissues and finally on the drug elimination. Figure 2 shows the results of a hypothetical pharmacokinetic experiment. Notice that the scale of the plot is not homogenous, because drug in urines and in the absorption site are amounts, while the other curves represent drug concentrations.

Pharmacokinetics is important because:

**a.** The studies completed in laboratory animals may give useful indications for drug research and development. For example less powerful molecules in vitro can turn out more effective in vivo because of their favorable kinetics (greater absorption, better distribution, etc.).

**b.** Pharmacokinetics supports the studies of preclinical toxicology in animals (toxicokinetics) because the drug levels in plasma or tissues are often more predictive than the dose to extrapolate the toxicity
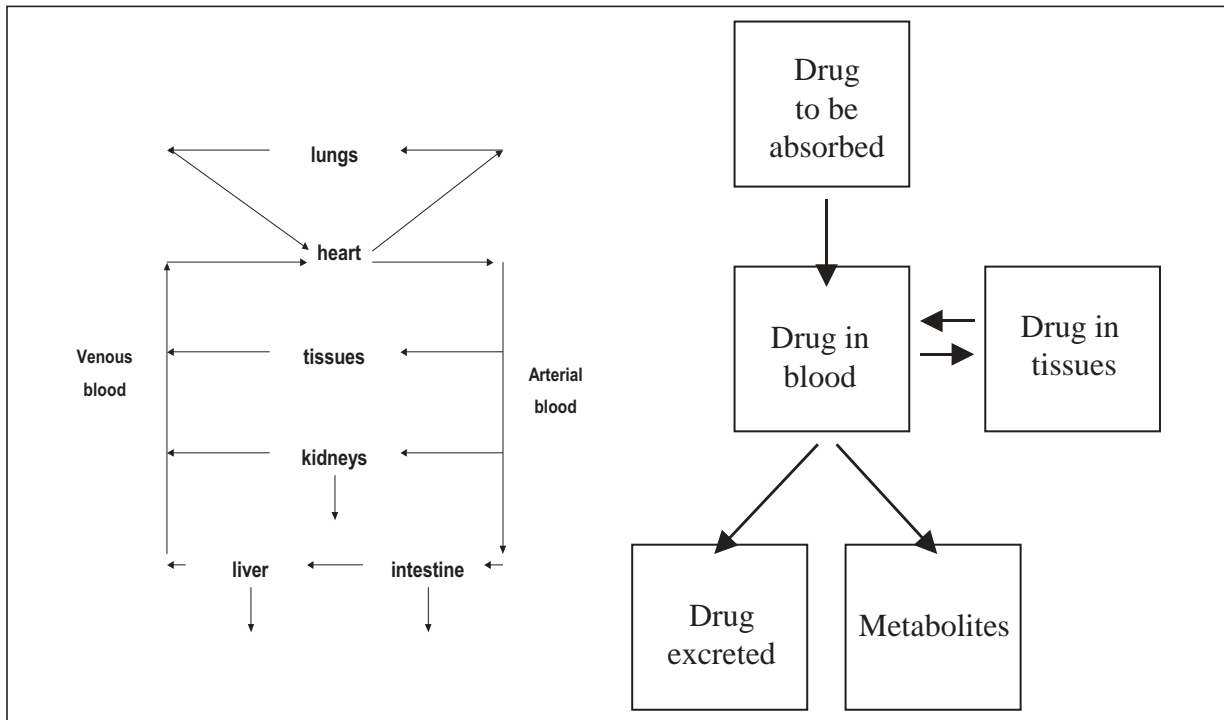
Figure 1. Drug absorption and disposition (ie distribution and elimination). **A,** Graphic representation of the blood circulation: arterial blood is pumped by the heart through all the tissues and after the passage through the organs the venous blood reaches the lungs. All the organs except the lungs are in parallel because they are perfused by a fraction of the whole blood in each passage, while the lungs are in series with the other organs because all the blood reaches the lungs in each passage. Some organs have an arrow to the outside of the body which represents the drug elimination. For example the liver may produce drug metabolites wich in turn enter into the systemic circulation. Notice that the heart is represented just for the mechanical function associated with it, and not as a perfused tissue. **B,** Blocks which represent the drug absorption, distribution and elimination.
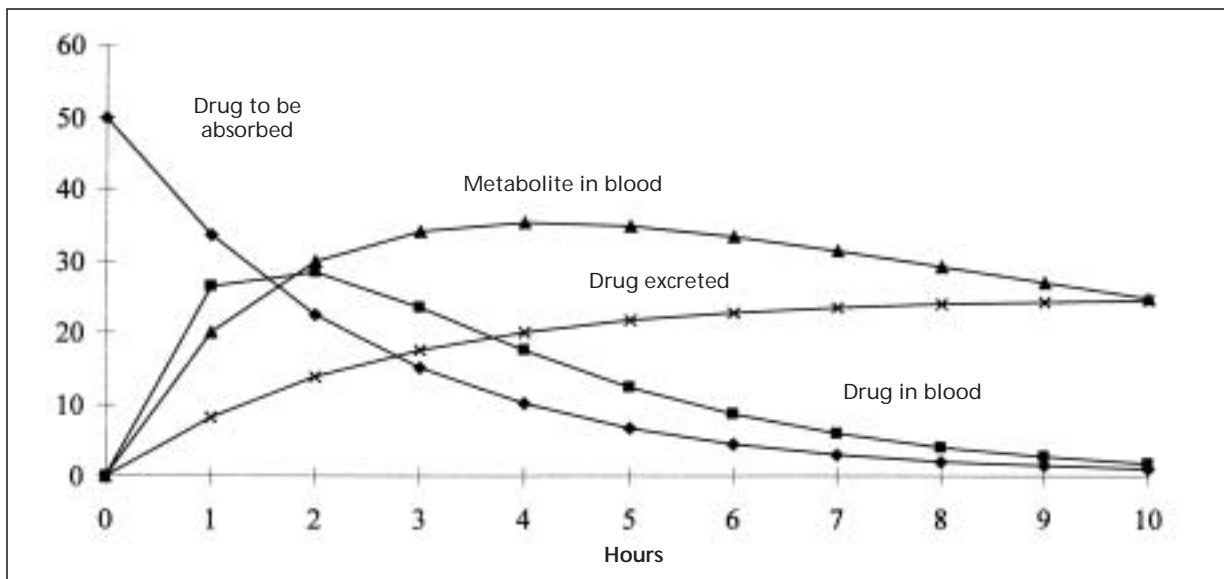


Figure 2. Observations collected during a hypothetical pharmacokinetic experiment: the unit of measure of y-axis may be not omogeneous because drug to be absorbed and drug excreted are drug amount, while metabolite and drug in blood are concentrations.

data to man. Toxicokinetics is also important to:

– verify that the animals have measurable levels of drug in plasma and that these levels are proportional to the administered dose,

– estimate the area under the curve and the maximum concentration of the drug in plasma, because these parameters can be used to represent the exposure of the body to the drug,

– evidence differences in pharmacokinetics between the various groups of treatment, the days of treatment and other factors,

– estimate the variability between animals and identify cases with abnormal levels of the drug.

**c.** Knowledge of the kinetics and of the effects (pharmacodynamics) of drugs in man is necessary for a correct use of drugs in therapy (choice of the best route of administration, choice of the best dose regimen, dose individualization).

Moreover, as the relationship between the drug levels and the effects is very often independent on the formulation, formulations which produce superimposable drug levels can be considered interchangeable and this is the basis of the concept of bioequivalence.

## Planning and Presenting the Results of a Pharmacokinetic Study

The experimental design depends closely on the purpose of the investigator. For example some studies may be planned to get accurate estimates of particular parameters (the rate or the extent of drug absorption), or to get information on the variability of the pharmacokinetic parameters in the population (population kinetics), consequently the experimental protocols may vary considerably. Anyway, in order to plan a pharmacokinetic experiment, the following conditions should be well defined: route of drug administration, dose regimen, tissues to sample, sample times, analytical method, the animal species or, in clinical settings, the inclusion and exclusion criteria of the subjects.

All these informations and the purposes of the experimenter should always be given when presenting the design or discussing a pharmacokinetic study.

Moreover, as in many protocols the sampling times are equal for all the subjects or animals under investigation, it is good practice at the beginning of the data analysis, to plot not only the observations relative to every single subject, but also the mean (and standard deviation) concentrations in the population at each time.

Plotting and listing the data may be a big job because the size of acquired data during a pharmacokinetic study is often huge. As an example, in a typical study of bioequivalence in man, there are generally not less than 12 plasma samples in at least 18 subjects treated with two formulations of the same drug. The consequence is that not less than $12 \times 18 \times 2 = 432$ set of data (time, plasma concentration) are produced. The number of data increases if also other districts have been sampled (urines for example), or if the levels of some metabolite have also been measured.

For this reason it is very helpful for evaluation and communication to sintetize all these data without loosing relevant informations, and the following few pharmacokinetic parameters can be defined:

– peak concentrations ($C_{max}$)
- peak time ($T_{max}$)
- terminal half-life ($t_{1/2}$)
- area under the curve (AUC)

When urines are also sampled, the drug amounts excreted unchanged or the percentage of the dose excreted in urines should also be computed. Notice that the drug concentrations in urines are very rarely of interest in pharmacokinetics even if this is what is measured directly, but the drug amounts allow making a mass balance getting the fraction of the excreted dose. The drug amount can be computed from the concentrations having the volumes, consequently when urines are sampled it is important to record also the volumes excrete during the experiment.

A single kinetic profile may be well summarized by $C_{max}$, $T_{max}$, $t_{1/2}$ and AUC and, having more than one profile, 8 parameters at

least, the mean and standard deviation of these parameters, may well summarize the drug kinetics in the whole population.

A short description of these parameters is presented below.

### $T_{max}$ and $C_{max}$

The peak time ($T_{max}$) and the peak concentration ($C_{max}$) may be directly obtained from the experimental observations of each subjects (see Figure 3).

After an intravenous bolus these two parameters are closely dependent on the experimental protocol because the concentrations are always decreasing after the dose. On the other hand the peak time corresponds to the time of infusion if the drug is infused i.v. at constant rate.

After oral administration Cmax and Tmax are dependent on the extent, and the rate of drug absorption and on the disposition profile of the drug, consequently they may characterize the properties of different formulations in the same subject[2].

### Half-life of monoexponential functions

The terminal half-life ($t_{1/2}$) is a parameter used to describe the decay of the drug concentration in the terminal phase, ie when the semilog plot of the observed concentrations vs time looks linear. This parameter is derived from a mathematic property of the monoexponential functions and its meaning is shown in Figure 4.

It can be seen that the monoexponential curve halves its value after a fixed time interval, independently on the starting time. Plotting the logarithms of the concentrations or using a semilogarithmic scale, a straight line can be obtained (see Figure 5). The diagrams in semilogarithmic scale are of frequent use in pharmacokinetics mainly for two reasons. First, because the log trasformation widen the scale of the concentrations so as to be able to clearly observe the full data plot even when the data range over various orders of magnitude. Second because a semilog plot helps more in the choice of the best pharmacokinetic model to fit the data.

Tracing with a ruler the straight line which interpolate better the data points, it is possible to obtain an estimate of the half-life by visual inspection of the semilog plot. All what is needed is to observe on the diagram the time at which the line halves its starting value, anyway, for a more rigorous estimation, the best line can be obtained applying the linear regression technique on log-transformed data.

### Terminal half-life of multiexponential functions

Very often in pharmacokinetics the drug profile is not monoexponential, however it has been observed that the log-concentrations of many drugs in plasma and tissues decay linearly in the terminal phase, ie after a sufficently long time from the administration
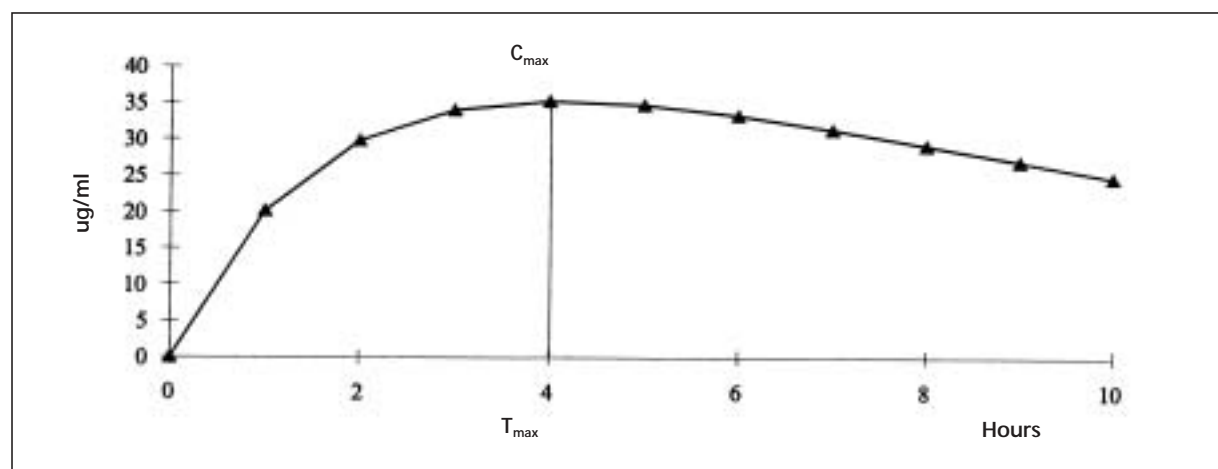


**Figure 3.** Getting the estimate of $C_{max}$ (peak concentration) and Tmax (peak time) from the observed data. ($C_{max}$ = 35 µg/ml and $T_{max}$ = 4 h).
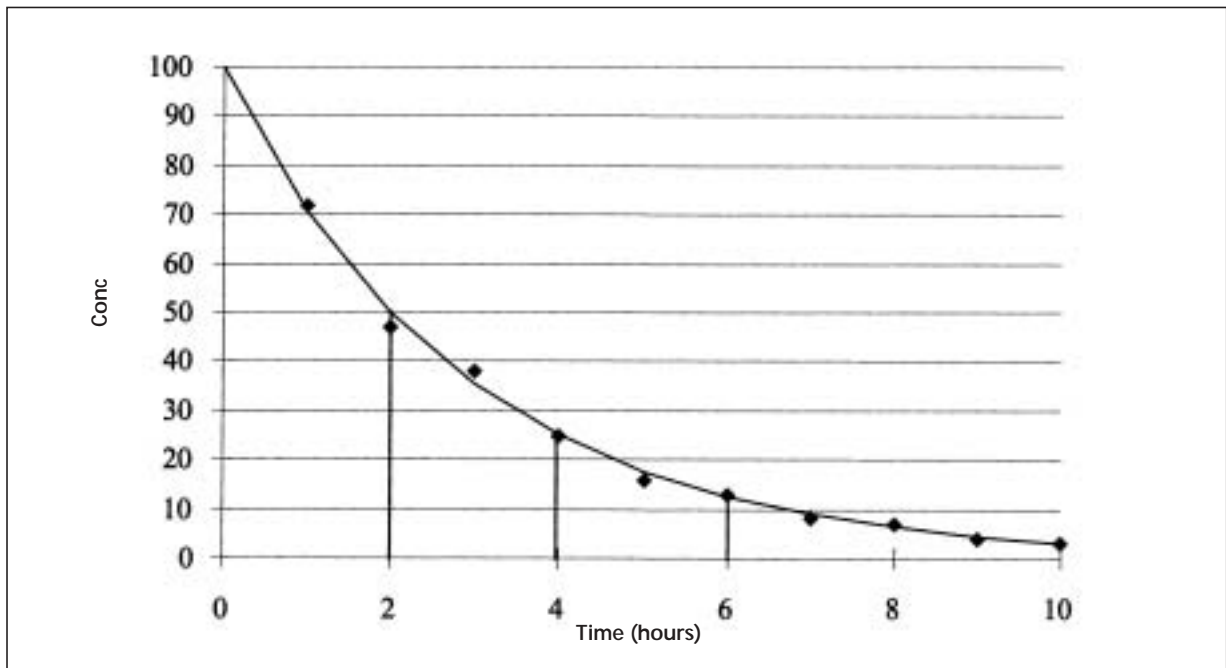
**Figure 4**. Plot of the observed drug concentrations vs time data (points) interpolated by a monoexponential function (continuous line). It can be seen that at any time the curve halves its values after 2 hours and this happens because the half-life of the curve is just 2 hours.

time. This means that the kinetic profile of many drugs is well approximated by a mono-exponential function in the terminal phase and consequently it make sense to define the half-life, or terminal half-life, in order to characterize the slope of the curve in this phase. Two examples of multiesponential curves are shown in Figure 6.

In these cases the estimation of the terminal half-life may be highly subjective because the experimenter must choose the number of points to use in the computation by visual inspection of the plot. Adding or discarding one point may have big influence on the estimate when few data are available and the experimental error is high. To avoid confusion,
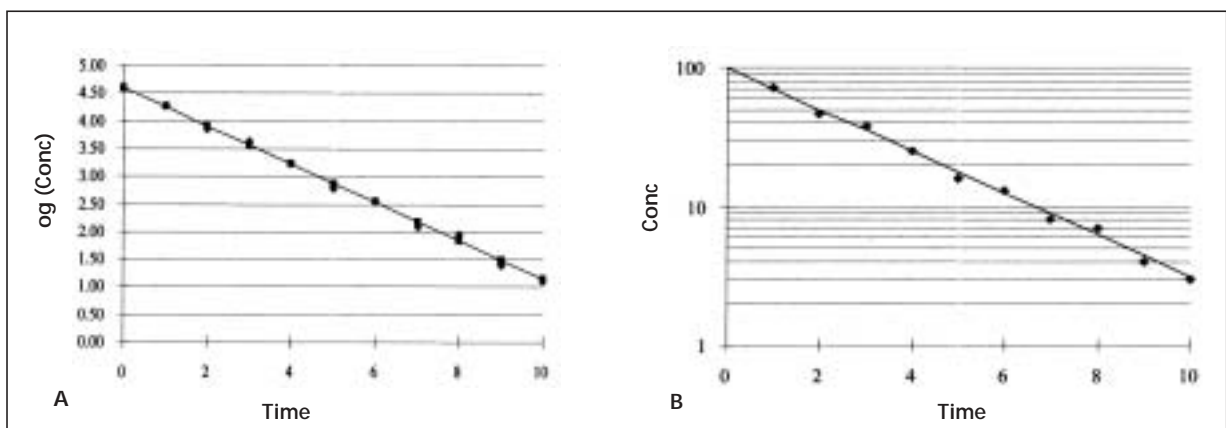


**Figure 5**. Semilog plot of the monoexponential function. *A,* Plot of the log-concentration vs time data and the interpolating monoexponential function. *B,* Plot of concentration vs time data in a semilog scale. Plot A and B are superimposable, but in plot A the log-concentration levels are reported on the y-axis while in plot B the drug levels can be read without the need of the antilog transformation.
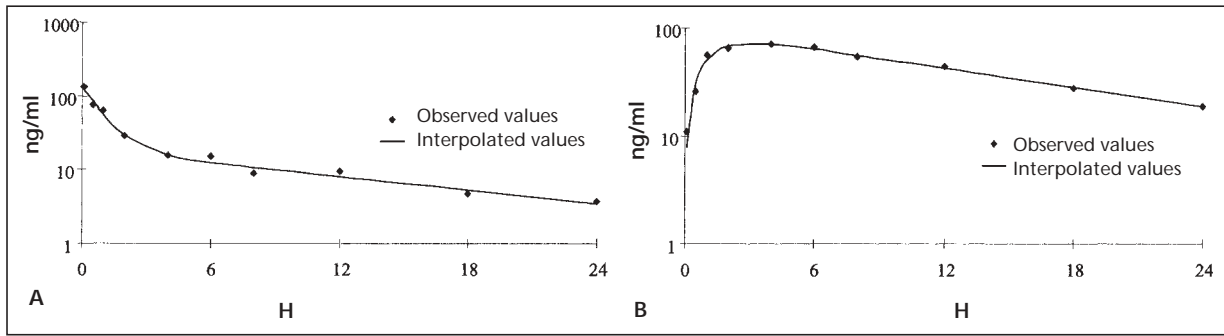
**Figure 6.** Two examples of biexponential curves. *A,* Plot of the drug levels after intravenous administration. *B,* Plot of the drug levels after oral administration. In both plots the continuous line represents the data interpolated by a bi-exponential function. Plot A and plot B show that the terminal phase of the washout curves is log-linear and consequently it can be approximated by a monoexponential function.

the points used in the estimation should always be declared when the estimate of the terminal half-life is presented.

Notice, also, that the accuracy of the estimates are very dependent on the time sampling range. Planning many sampling times over a time interval of three or more half-lives, allows to get a good estimate of the terminal half-life, while the same number of samples in shorter time intervals makes the estimate less accurate. For example, the estimate of a 24 hours half-life cannot be very ac-

curate having points up to only 12-24 hours, even when many data points have been collected.

### The area under the curve (AUC)

The under the curve (AUC) is a parameter that may be used in different ways depending on the experimental context. This parameter may be used as an index of the drug exposure of the body, when referred to the plasma drug levels, or as an index of the drug exposure of particular tissues if referred to the drug levels
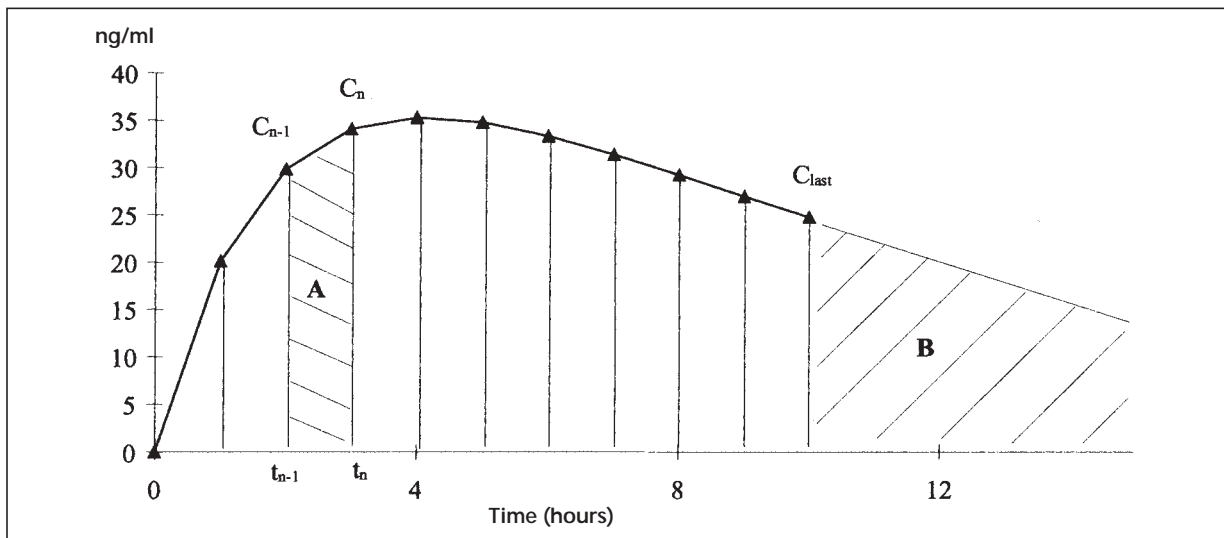


**Figure 7.** The area under the curve (AUC). The area of the trapezoid A is given by': $(C_{n-1} + C_n) \times (t_n - t_{n-1})/2$. The extrapolation to infinity (B) is computed by the terminal half-life: $C_{last} / (0.693 / t_{1/2})$. The AUC is given by the sum of all the trapezoids and of the terminal extrapolation B. The dimension of the AUC are always given by time × concentration and, in this example, we have: $AUC = ng \times h \times ml^{-1}$.

in tissues. Under very general assumptions, the area under the plasma or blood drug concentrations is a parameter that is closely dependent on the drug amount that enter into the systemic circulation and on the ability that the system has to eliminate the drug (clearance). Therefore it can be used to measure the drug amount absorbed or the efficiency of physiological processes that characterize the drug elimination.

In most cases a sufficiently accurate estimate of the AUC can be obtained applying the trapezoidal rule as illustrated in Figure 7.

It is good practice to calculate the AUC from time 0 (administration time) to infinity after single drug administration, and within the dose interval after multiple dose treatment.

In the first case the extrapolation from the last measurable concentration to infinity is computed assuming that the wash-out in the terminal phase follows a monoexponential profile, and for the calculation the terminal half-life is needed. In the second case extrapolations are not necessary provided that the beginning and the end of the dose intervals are also sampled.

## Data Interpolation and Multiexponential Functions

The estimation of $C_{max}$, $T_{max}$, $t_{1/2}$ and AUC is the first step in the analysis of the pharmacokinetic data because these parameters can well represent the data without the need of any complex mathematical model. This is the reason why $T_{max}$, $C_{max}$, AUC and the terminal half-life are often called model-independent parameters even though their definition may be well dependent on some very general pharmacokinetic assumption.

A more carefull description of the data can be obtained interpolating and extrapolating the drug concentrations with some mathematical functions. These functions should be choosen properly according to the task of the experimenter, who may want to reduce all the data in a small set of parameters, or to verify if the hypotheses incorporated in the functions are confirmed by the observations. In the first case we can say that the task is to get a simulation of the data, in the second to get a model[3].

The functions used to interpolate and reduce the pharmacokinetic data are the multi-exponential functions and the reference models are the compartmental models whose solutions are just the multiexponential functions. Below, some property of the multiexponential functions will be introduced and it will be shown how these functions may help in getting some relevant pharmacokinetic parameters.

### Monoexponential function

A monoexponential function can be written as:

$$c(t) = C_0 \cdot e^{-\lambda \cdot t} \qquad (1)$$

where $c(t)$ is the drug concentration at time t and Co and $\lambda$ are the parameters to be estimated.

This function has been used to interpolate the plasma concentration profiles of different drugs after intravenous administration, that is estimating the parameters Co and $\lambda$ by fitting the curve to the experimental data.

Co is the drug concentration at time 0 and $\lambda$ is dependent on the half-life of the curve because the following relationship holds:

$$t_{1/2} = 0.693 / \lambda \qquad (2)$$

Integrating eq. 1 between 0 and infinity, we get:

$$AUC = \frac{Co}{\lambda} \qquad (3)$$

which says that the area under the curve can also be computed easily by the ratio between Co e $\lambda$.

Co and $\lambda$ can be estimated by e non-linear regression technique or by linearizing the data using the log-trasformation, and the estimates may well be used to synthetize all the observed drug concentration of one subject in a particular pharmacokinetic study (usually no less than 10-12 set of time-concentration data). When many subject are involved, then the interest is in the population kinetics of the drug and consequently the population pharmacokinetic parameters have to be estimated. These are not only the mean vales of Co and $\lambda$, but also some measure of their

variability in the population, for example their standard deviation. Having the estimates of the parameters in each subjects, the population estimates may be obtained straightfore-ward using standard statistical formulas and this is called the two stage method. Sometimes very few data points per subject are collected, consequently the first step of this procedure is problematic, if not impossible, even when many subjects have been investigated and a lot of data are available. In this case, sophisticated statistical tecniques can be applied to get the population parameters (bayesian methods, non-linear mixed effect models). Anyway, at the end of the procedure, the mean and the standard deviations of the pharmacokinetic parameters are computed and can be used to summarize a very large number of experimental data and to represent the pharmacokinetic properties of any drug.

### Biexponential functions

In many cases a monoexponential function like equation 1 is unable to fit accurately a particular drug profile. For example, it has been shown that after oral administration the plasma drug concentrations are increasing just after the dose and decreasing after the peak time, or, even after an intravenous bolus, a clear bias may be present between the observed and the predicted data when fitted by a monoexponential function. In this case, a good interpolation of an oral or iv profile may be obtained by adding a new exponential term to this function, ie by fitting the data with the following equation:

$$c(t) = A_1 \cdot e^{-\lambda_1 \cdot t} + A_2 \cdot e^{-\lambda_2 \cdot t} \qquad (4)$$

which is called a biexponential function. This equation is frequently parametrized as:

$$c(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \qquad (5)$$

where it is assumed that $\alpha > \beta$, c(t) and t are the dependent and the independent variable respectively, and A, B, $\alpha$ and $\beta$ (or $A_1$, $A_2$, $\lambda_1$, $\lambda_2$) are the parameters to be estimated.

Notice that when $\alpha$ is much greater than $\beta$ and when t is sufficiently high, then the term $A \cdot e^{-\alpha \cdot t}$ is much smaller than the second term in eq. 5, and c(t) is well approximated by the monoexponential function $c(t) = B \cdot e^{-\beta \cdot t}$.

Consequently it may be stated that after a sufficiently long time interval the biexponential function declines to 0 with a half-life characterized by the lower exponent $\beta$ and that it make sense to extend the idea of terminal half-life even to a biexponential function.

C(t) at time 0 is given by A+B and when A+B = 0 then C(0) = 0. This means that when A is negative and equal to –B, the function c(t) is increasing at the beginning, reaches a peak level and then decreases to 0. When both A and B are positive, the curve is decreasing in all the range t > 0. In both cases the terminal half-life is given by 0.693 / $\beta$.

The parameters A, B, $\alpha$ and $\beta$ can also be used to compute the AUC, because integrating the eq. 5 from 0 to infinity, it holds:

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \quad or \quad AUC = B \cdot \left( \frac{1}{\beta} - \frac{1}{\alpha} \right)$$

Having a set of experimental data, the estimates of the parameters can be obtained by a non-linear fitting procedure or by the residual (or peeling) method which is based on a sequential log-linearization of the curve. This method gives only approximate estimates of the parameters and usually is used to get the initial estimates of the parameters needed to run the non-linear fitting procedure.

### Multiexponential functions

The majority of the drugs have approximatively a biexponential profile in plasma after an intravenous bolus, but there are exceptions expecially after oral administration, because it is common that, if n exponential terms are needed to fit the plasma concentrations after an iv bolus, then, to get a good interpolation of the data after oral or extravascular administration, one exponential term should at least be added to the equation.

In general it can be stated that the kinetics of all drugs in plasma is well described by multiexponential functions which may be written as:

$$c(t) = \sum_i A_i \cdot e^{-\lambda_i \cdot t} \qquad (6)$$

The number of the exponential terms in this equation should be choosen time to time

in order to get the best fit of the experimental data and the best accuracy in the estimated parameters. Then the initial drug level and the AUC can be computed by the parameters of the curve as:

$$Co = \sum_i A_i \quad e \quad AUC = \sum_i \frac{A_i}{\lambda_i}$$

where Co is equal to 0 after oral or extravascular administration, which means that in these cases some coefficients should be negative, and where the terminal half-life is always given by $0.693/\lambda_n$ where $\lambda_n$ is the lowest exponent.

The parameters of eq. 6 can still be estimated by a non-linear fitting procedure, but remember that in tipical pharmacokinetic settings, the exponents $\lambda_i$ should be different at least of one order of magnitude to be the estimates sufficiently accurate.

Multiexponential function are a very general tool in pharmacokinetics because they may be adapted to describe not only the profile of the drugs in plasma, but also in all other tissues or fluids after almost any kind and route of drug administration. Exceptions are very rare.

## Clearance, Volume of Distribution and Compartmental Models

We have seen in the previous paragraphs how it is possible to compute some parameters that allow to describe synthetically the results of a pharmacokinetic experiment. It has been said also that the kinetic profile of a drug depends on various biological processes which modulate the drug absorption, elimination and distribution. For practical purposes it should be usefull to correlate in some way the observed concentrations, and therefore the kinetic parameters, with these processes. The mathematical models, and in particular the compartmental models, can help to this scope and for this reason they have been extensively used in pharmacokinetics. Moreover the compartmental models allow to make predictions[4] and to describe more complex experiments where, for example, having more fluids and tissues sampled in the body at the same time, it is possible to find relevant relationships between the drug profiles.

We can start working with models by introducing two new parameters, the volume of distribution (V) and the clearance (CL) whose definitions are largely dependent on a pharmacokinetic model[5].

A tipical problem in pharmacokinetics is that on one hand the measured variables are usually the drug concentrations in tissues or, more frequently, in plasma and, on the other hand, the experimenter may be interested in knowing the amount of the drug present in the body, or the amount eliminated at time t after administration of a known dose.

V and CL have been thought to cope with this problem when the reference variable is the drug concentration in plasma, and the following very general definitions can be given:

CL = drug amount eliminated per unit of time/
    drug concentration in plasma           (7)

 V = drug amount in the body/
    drug concentration in plasma           (8)

Assuming that CL is not time dependent, it may be shown that:

$$CL = \frac{D}{AUC} \qquad (9)$$

V cannot be time independent because of drug distribution in tissues outside the plasma, but under some general assumptions it may be shown that the ratio of eq. 8 approaches a limit value given by:

$$V_{area} = \frac{D}{\lambda \cdot AUC} \qquad (10)$$

D is the drug amount that enters into the systemic circulation (after an intravenous administration, D is the dose) and $\lambda$ is the lowest exponent used to get the terminal half-life. Eq. 9 and 10 may be derived appling very general compartmental models to the drug kinetics.

$V_{area}$ has been used to characterize the drug distribution in the total body, while CL as a measure of the efficiency of the drug elimination process. The first may be shown getting

eq. 9 from a monoexponential function. In this particular case V is time independent and the following equation holds:

$$V = \frac{D}{\lambda \cdot AUC} = \frac{D}{C_0} \qquad (11)$$

After an iv bolus, D is just the drug amount present in the body at time 0 and it is given by the product between V and the concentration at time 0. This means that V may be thought as that ideal volume where the dose should dilute istantaneously at time 0 in order to get a drug concentration equal to Co. As V is not time dependent, then eq. 11 is equivalent to eq. 8, consequently the monoexponential function can be rewritten as:

$$c(t) = C_0 \cdot e^{-\lambda \cdot t} = \frac{D}{V} \cdot e^{-\lambda \cdot t}$$

The new parameters V and $\lambda$ (the dose D is known) are said to be invariant, which means that they do not change changing the dose and time, and consequently they characterize the drug kinetics in a particular subjects.

It can be noticed that the new parametrization adds new meanings to the monoexponential equation, for example now it is explicitly stated that the drug concentrations are proportional to the dose, and these meanings are a consequence of a model assumption.

Equation 11 is no more true for a multiexponential function, consequently it may be convenient to introduce two time and dose independent volumes:

$$V_c = \frac{D}{C_0} \text{ and } V_{area} = \frac{D}{\lambda_1 \cdot AUC} \; (\lambda_1 = \text{lowest } \lambda)$$

Vc is usually called the volume of the central compartment or the initial volume of distribution, while the second is said $V_{area}$ (or $V_\beta$ when derived from a biexponential function).

Vc is always equal to $V_{area}$ in a monoexponential function and always lower than $V_{area}$ in a multiexponential function, while at any time after the dose the ratio of eq. 8 is always higher or equal to Vc and lower than $V_{area}$.

$V_{area}$ can be obtained measuring the drug concentrations in plasma and as it may be highly correlated with the tissues to plasma ratio (ie the ratio between the drug levels in tissues and blood), it may be used as a measure of drug distribution: higher estimates of $V_{area}$ mean higher levels of the drug in tissues compared to plasma and vice versa.

Vc may be used to predict Co for a given iv dose or, conversely, to estimate the non toxic loading doses when the toxic levels are known.

The second aspect of our pharmacokinetic model refers to CL. Eq. 7 can be written using the following symbols[6]:

$$- da(t) / dt = CL \cdot c(t) \qquad (12)$$

where a(t) is the drug amount present in the body at time t, c(t) is the drug concentration in plasma at time t and da(t)/dt is the derivative of a(t) respect to time. Eq. 12 and eq. 7 are equivalent, because the drug amount eliminated per unit time must be equal to the absolute value of the rate of change of the drug amount in the body.

Intergrating eq. 12 from time 0 to infinity on the assumption that CL is constant, we get:

$$\begin{aligned} \text{Amount eliminated} = \\ (\text{Dose entered into the systemic circulation}) = \\ CL \times AUC \end{aligned}$$

which is equivalent to eq. 9.

CL is commonly used to characterize the efficiency of drug elimination from the body being higher values of CL associated with higher efficiency of drug elimination.

Models have also been developed to find relationships between the volumes and the reversible drug-protein binding in plasma and between CL and the blood flow through the eliminating organs (liver and kidneys) and many experimental observations support the utility of these models.

Without going into the details, it is interesting to notice that the following relationship can be derived from the previous equations:

$$V_{area} \cdot \lambda_1 = CL$$

and remembering that $\lambda_1$ depends on the half-life, we get:

$$\frac{t_{\frac{1}{2}}}{0.693} = \frac{V_{area}}{CL}$$

which means that in our models the terminal half-life is dependent on both the drug distribution and the drug elimination. For example, it may happen that the half-life increases not because the drug elimination is impaired but just because the drug distribution improves.

## Bioavailability

The extent and the rate of drug absorption play an important role in pharmacokinetics, and this parameters are usually referred as the drug bioavailability[7,8]. For example, a fraction of the dose may be metabolized during the early passage through the gastrointestinal tract or through the liver after an oral dose, or part of the dose may not reach the blood due to drug malabsorption. The consequence is an incomplete absorption of the drug into the systemic circulation and an incomplete drug availability may produce ineffectiveness of the treatment.

Absorption is a complex process which cannot be monitored experimentally in a simple way, and consequently it is not easy to get the extent of drug absorption by direct observation. Anyway pharmacokinetic models allow to estimate this parameter with a simple experimental design. Looking at the definition of clearance, it is clear that having the plasma AUC after any route of drug administration and knowing CL, it is always possible to compute the drug amount which enters into the systemic circulation in a particular subject after any route of administration. Then, an easy way to perform a bioavailability experiment is to treat a subject both, intravenously to get CL, and orally (or by any other test route) to get the AUC.

Giving the same dose and remembering that CL is equal to the ratio between the dose and the AUC after iv administration (D / AUC$_{ev}$), the following equation holds:

$$F = \frac{CL \cdot AUC_t}{CL \cdot AUC_{iv}} = \frac{AUC_t}{AUC_{iv}} \qquad (13)$$

where F is the fraction of the dose which enters into the systemic circulation and AUCt is the area under the curve estimated after the test administration. When different doses need to be administered by the different routes, eq. 13 may still be used after normalizing AUCiv and AUCt by the dose because our models say that the drug concentrations and consequently the AUC are always proportional to the dose.

Eq. 13 makes it clear why the AUC plays a key role in pharmacokinetics, especially when different drugs or different formulations of the same drug have to be compared. In the latter case, eq. 13 provides the rational to design the bioequivalence experiments in clinical settings.

## Conclusion

We have inasmuch shown as pharmacokinetics is proposed to study the absorption, the distribution and the elimination of drugs measuring the drug levels in plasma or in tissues. The mathematical models are essential tools in this task because only through the models it is possible to define a set of pharmacokinetic parameters that may give a synthetic description of the drug disposition, and, also, that may put in relationship the drug disposition with the underlying biological processes.

The area under the curve, for example, can be used to measure the exposure of all the body to the drug, but it can be used also as a parameter correlated to the clearance, and consequently as a parameter which, may give information on the drug elimination process. Clearance, on the other hand, depends on the functionality of the eliminating organs, ie the kidney or the liver, therefore possible inefficiencies of these organs can have consequences on the clearance and therefore on the AUC and on the drug levels.

It should be clear now the central position of models in pharmacokinetics, and consequently why pharmacokinetics is essentially the study of these models and of their properties.

In model building, the multiexponential functions, the linear compartmental models and what have been called the mass balance models or clearance models, constitute various passages through which, starting from a simple description of the drug profile, the ex-

perimenter may gain better and better insight into the experimental observations[9].

An important role in model building are played by the computers, as well as by a good knowledge of the biological and physiological aspects of the system and by the choise of reasonable approximations and semplifications. Compartmental models have been introduced in pharmacokinetics as tools in analyzing and describing the overall system under study, and the parameters of these models, ie the rate constants, do not represent a single physical variable, but a set of variables which may not be distinguished by the actual experimental design.

Not always such procedure arrives to good aim, in fact in model building it is necessary to have some criteria to choose between competing models and to judge the model itself[10], and it may happen that no model can be found that satisfy all the criteria in a particular experimental setting. Analyzing the asssumptions and the approximations of the model and comparing the performance of different models may be usefull in order to test hypothesis, to identify new aspects of the system and to design experiments able to give more and more information. Consequently model building is a complex multistep process where, experiment by experiment and simulation by simulation, new hypothesis are proven and disproven through a continuous interaction between the experimenter and the computer.

## References

1) Rescigno A, Segre G. Drug and Tracer Kinetics. Blaisdell, Waltham (Mass) 1966.

2) Urso R, Aarons L. Bioavailability of drugs with long elimination half-lives. Eur J Clin Pharmacol 1983; 25: 689-693.

3) Rescigno A. La farmacocinetica: evoluzione di un concetto. Atti del Convegno di Farmacocinetica Siena, 1990; 7-28.

4) Urso R, Segre G. Multiple dose pharmacokinetics. Europ Bull Drug Res 1992; 1(S2): 65-72.

5) Urso R. Clearance, un approccio sperimentale. Farmaci 1988: 10: 333-345.

6) Urso R. Modelli matematici mono e multicompartimentali – Infusioni endovenose – Dosi singole e ripetute – Calcolo del regime posologico – Modelli non compartimentali. Riassunti delle Relazioni presentate alle: Giornate di Studio in Problematiche in Farmacocinetica e Metabolismo dei Farmaci, Milano 1984; 1-5.

7) Caccia S, Urso R, Garattini S. Biodisponibilità e bioequivalenza: concetti e problemi. Metabolismo Oggi 1986; 3: 99-109.

8) Urso R. Metodi di valutazione della bioequivalenza. Riassunti delle Relazioni presentate alle: Giornate di Studio in Biofarmaceutica, Farmacocinetica e Metabolismo dei Farmaci, Milano 1988; 63-70.

9) Segre G. Relevance, experiences and trends in the use of compartmental models. Drug Metab Rev 1984; 15: 7-53.

10) Verotta D, Recchia M, Urso R. Moddis: A microcomputer program for model discrimination. Comput Meth Progr Biomed 1986; 22: 209-218.