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A short introduction to pharmacokinetics

R. URSO, P. BLARDI*, G. GIORGI

Dipartimento di Farmacologia "Giorgio Segre", University of Siena (Italy)
**Centre of Clinical Pharmacology, Department of Internal Medicine, University of Siena (Italy)*

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}, $t_{½}$ 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

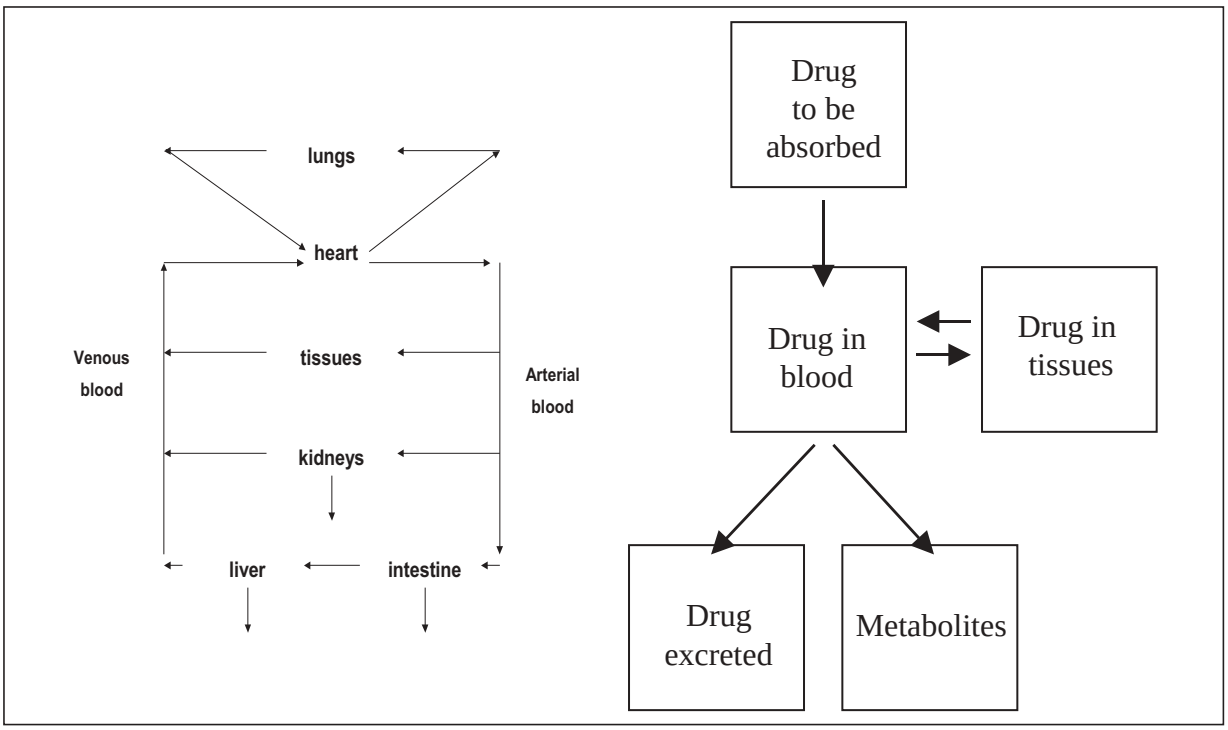

Figure 1. Drug absorption and disposition (ie distribution and elimination). ***A,*** Graphic representation of the blood circulation: arterial blood is pumped by the heart through all the tissues and after the passage through the organs the venous blood reaches the lungs. All the organs except the lungs 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.

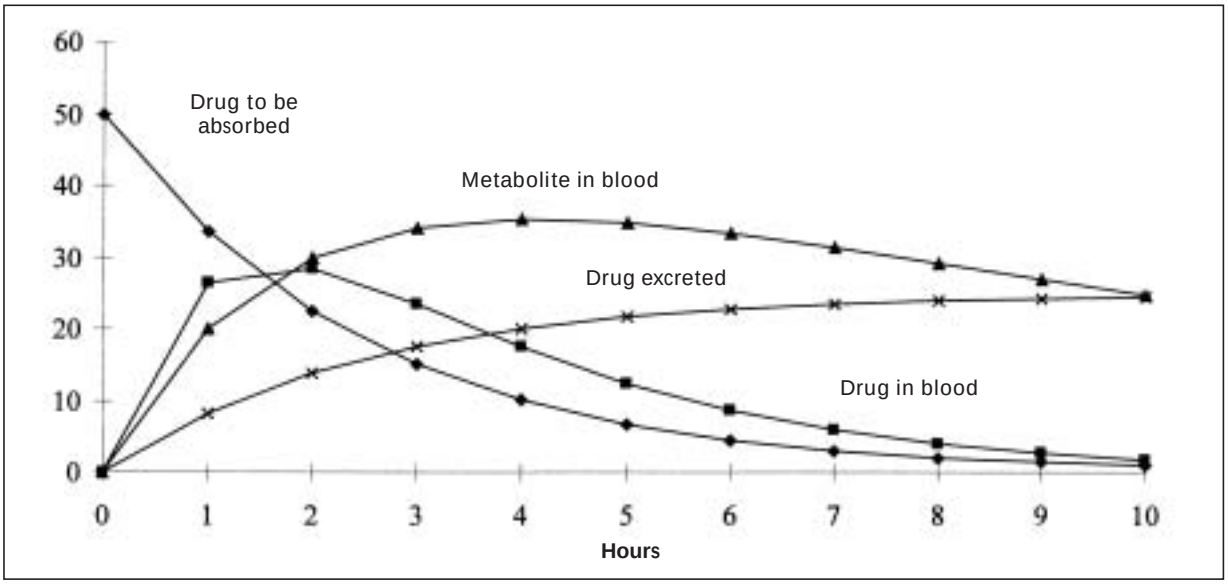

Figure 2. Observations collected during a hypothetical pharmacokinetic experiment: the unit of measure of y-axis may be not omogeneous because drug to be absorbed and drug excreted are drug amount, while metabolite and drug in blood are concentrations.

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 ($t_{½}$)
- 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.

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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 ($t_{½}$) 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

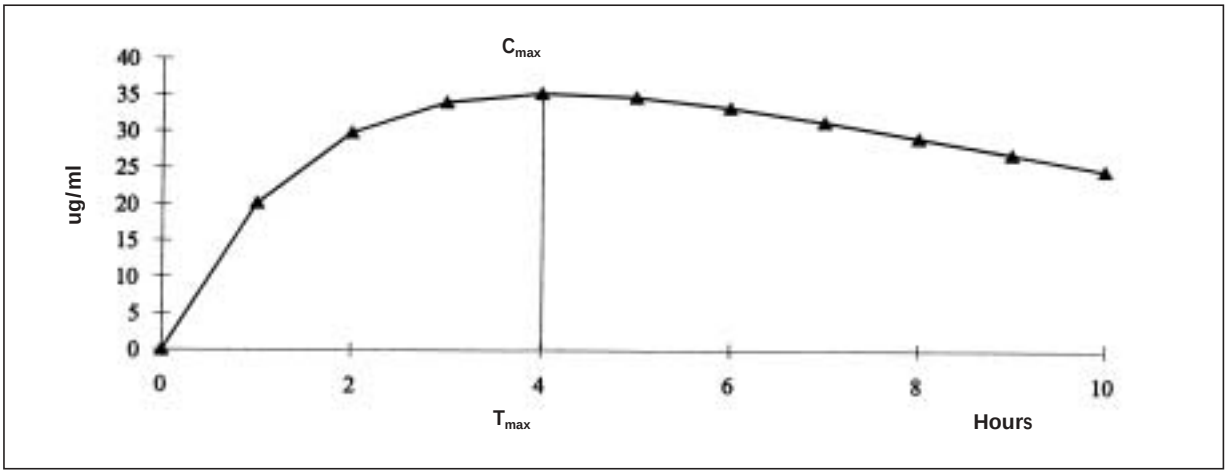

Figure 3. Getting the estimate of C_{max} (peak concentration) and Tmax (peak time) from the observed data. (C_{max} = 35 µg/ml and T_{max} = 4 h).

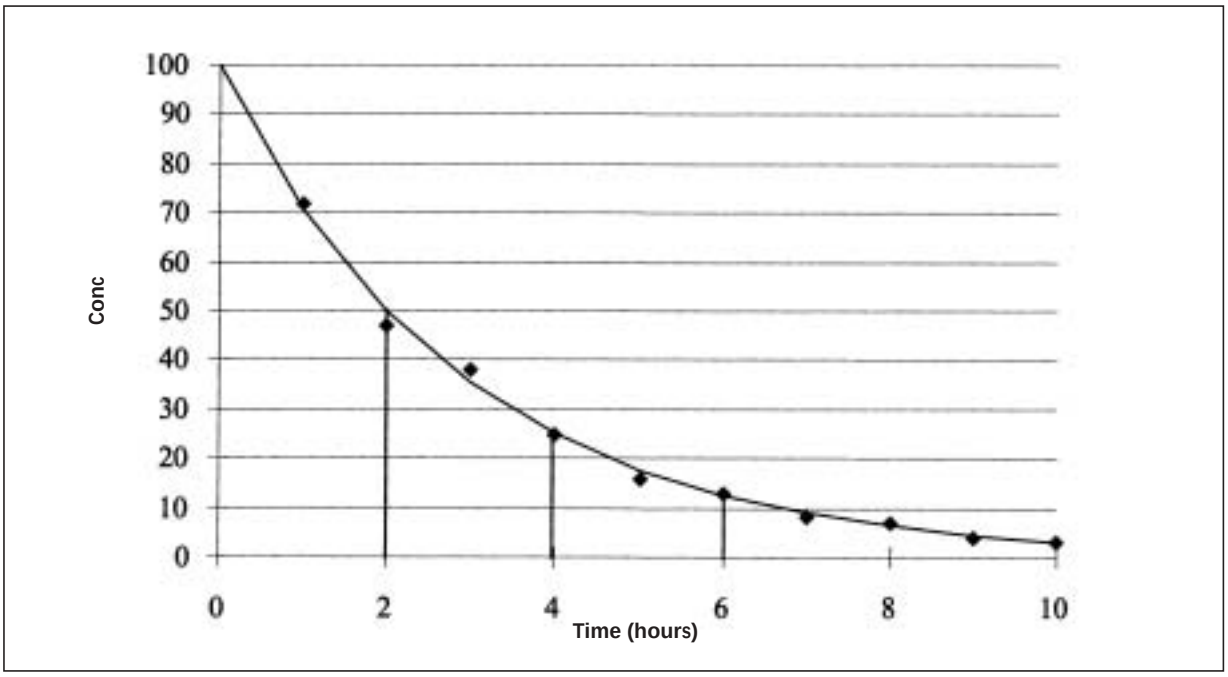

Figure 4. Plot of the observed drug concentrations vs time data (points) interpolated by a monoexponential function (continuous line). It can be seen that at any time the curve halves its values after 2 hours and this happens because the half-life of the curve is just 2 hours.

time. This means that the kinetic profile of many drugs is well approximated by a monoexponential 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,

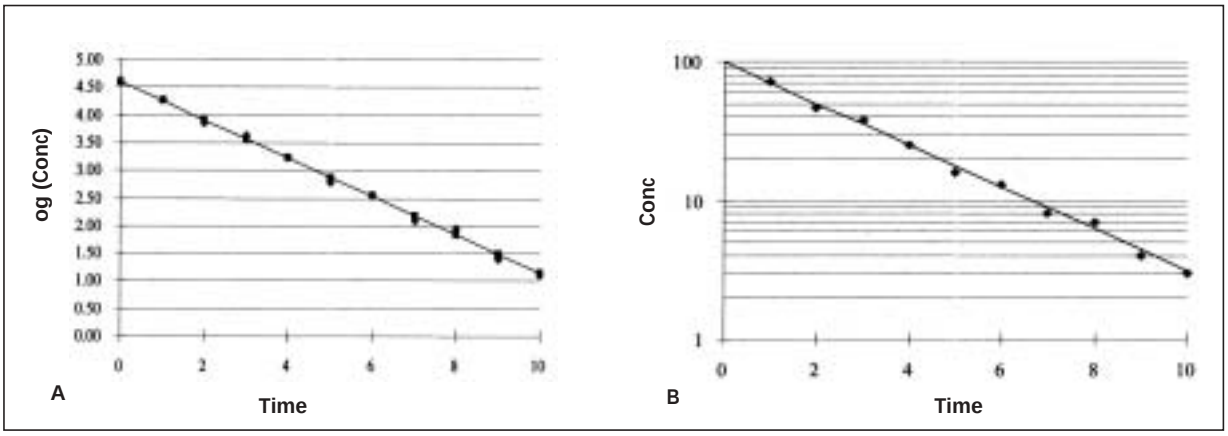

Figure 5. Semilog plot of the monoexponential function. ***A,*** Plot of the log-concentration vs time data and the interpolating monoexponential function. ***B,*** Plot of concentration vs time data in a semilog scale. Plot A and B are superimposable, but in plot A the log-concentration levels are reported on the y-axis while in plot B the drug levels can be read without the need of the antilog transformation.

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