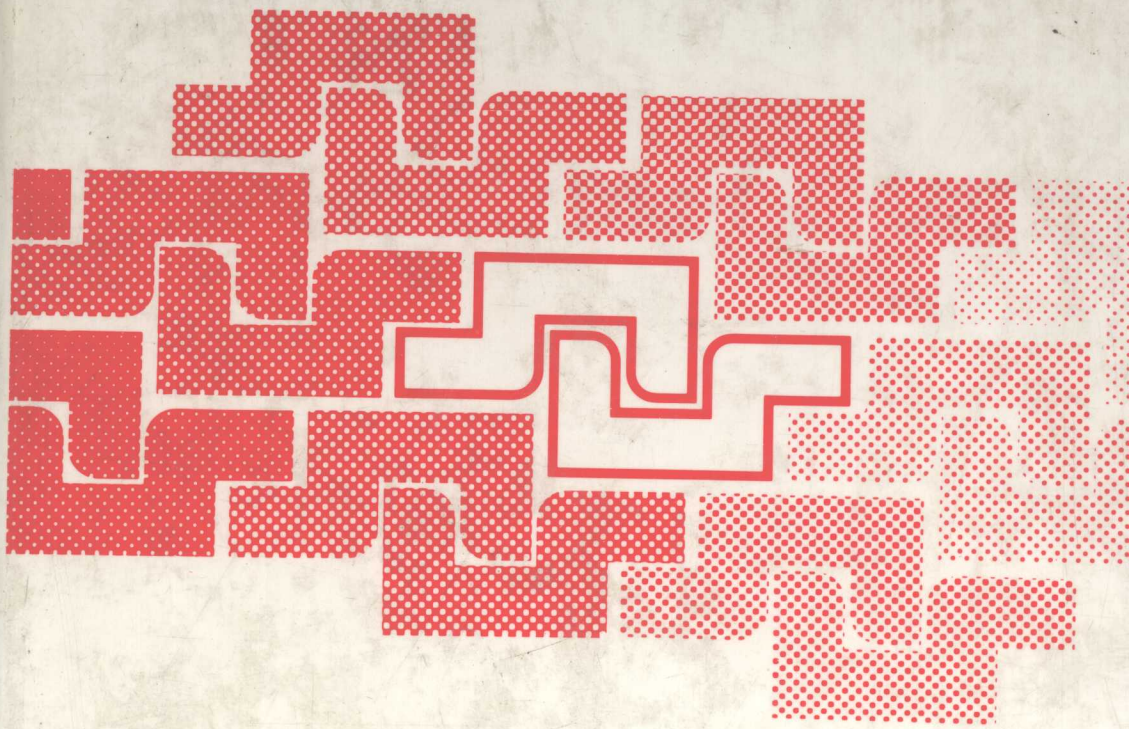

New Trends in Pharmacokinetics

Edited by
Aldo Rescigno and
Ajit K. Thakur

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New Trends in Pharmacokinetics

Edited by

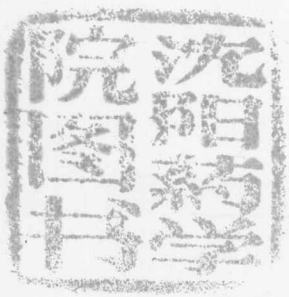
Aldo Rescigno

University of Parma
Parma, Italy

and

Ajit K. Thakur

Hazleton Washington, Inc.
Vienna, Virginia



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New Trends in Pharmacokinetics

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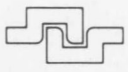

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PREFACE

The last decade or so has witnessed tremendous progress in methodology in the field of drug development in general and pharmacokinetics in particular. Clinical pharmacokinetics is using new tools for probing into the "black box" once being accessible only partly through experimental techniques and mostly through mathematical and computer means. Development of computerized scanning, positron emission tomography (PET), stereoselectivity and other techniques are now enabling investigators to have better pictures of the systems they are studying. Mathematical models through computer simulation and statistical estimation, mostly due to easy access because of inexpensive yet powerful personal computers, are enabling us to investigate ultrastructures and their functional connectivity in more detail. As a consequence, new hypotheses are being formed and tested in various related fields.

In clinical pharmacokinetics, mostly due to mathematical modeling, more accurate interspecies scaling of pharmacokinetic parameters and dosimetry can be done now-a-days. The concept of "a human is a bigger rat" does not necessarily fly as a consequence. Pharmacokinetic concepts are becoming powerful tools in meaningful carcinogenic and toxic risk extrapolation of different chemicals in humans. New dose delivery designs are being formulated using pharmacokinetic techniques for different pharmaceutical compounds. Investigations continue in the academia, research institutions, pharmaceutical, biotechnological, and agricultural industries in developmental and physiological aspects of different chemicals for the benefit of mankind.

The idea of a school on "New Trends in Pharmacokinetics", from which the present publication was made possible, took shape over almost a year. The organizing committee, consisting of Drs. Aldo Rescigno, Ajit K. Thakur, James T.Stevens, and Giuliano Mariani, spent many hours and days worth of efforts to gather experts in various fields of clinical, experimental, and computational pharmacokinetics. The idea was to have these experts from various research environments to teach in this intensive workshop in September, 1990 in Erice,Sicily. The historical background and natural serenity of this island paradise provided the exact atmosphere needed for such an international exchange of ideas under the auspices of the Ettore Majorana Centre.

Of course, none of this could have happened if no money were available for the workshop. Students, investigators, and the speakers had to be supported with funds. The organizing committee relentlessly pursued many different organizations

for funds. The ultimate success was due to the generous contributions with funds from the North Atlantic Treaty Organization, the Farmindustria (Rome, Italy), C.N.R. (Rome, Italy), Sigma Tau (Pomezia, Italy), the Italian Section of the Bragg Creek Institute (Parma, Italy), the National Science Foundation (Washington, U.S.A.), Ciba-Geigy Corporation (Basel, Switzerland), and Dr. Ronald Sawchuk of the School of Pharmacy, University of Minnesota (U.S.A.). Thanks to the above, the organizing committee did not have to sell their houses to pay for all expenses, after all!

The lectures and the materials were excellent. Many of the participants took active roles in discussing their research topics with their peers from different countries. Such an international gathering is always enriching from cultural standpoint as well. That was clearly evidenced in the course of the workshop. Several students, post-doctoral fellows, and senior investigators from various countries also presented some of their works in leisurely fashion. The present book is the result of culmination of extensive works by many individuals who, at times, must have wished that they had never seen the faces of the Editors or heard their voices on the telephone! Let the glory be all theirs.

Aldo Rescigno and Ajit K. Thakur

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PHARMACOKINETICS: UNFOLDING OF A CONCEPT

Aldo Rescigno and Bianca Maria Bocchialini

School of Pharmacy
University of Parma
Parma, Italy

INTRODUCTION

The word "Pharmacokinetics", coined from the Greek words φαρμακον, drug, and κινητικος, moving, was used for the first time in 1953 by F. H. Dost, a German pediatrician, in his book "Der Blutspiegel" [Dost, 1953], but the concept had been around for a long time before that. The object of Pharmacokinetics is the study of absorption, distribution, and elimination of drugs; but, since the existence of Pharmacology, it has been known that drugs are absorbed, distributed, and eliminated from the organism, and that the rates of absorption, distribution, and elimination are fundamental in determining the effects on the organism they are administered to. Pharmacokinetics as such can be therefore considered a new discipline only since more sophisticated methods have been introduced to study the kinetic properties of drugs. These quantitative methods have been offered by Analytical Chemistry, by Physical Chemistry, and by Applied Mathematics.

In the following few pages we shall try to show how the different concepts used in Pharmacokinetics have unfolded in recent years.

THE INVARIANT QUANTITIES

The volume of distribution

It is not easy to decide which is the earliest paper dealing with the quantitative solution of a pharmacokinetic problem. An important pioneering study is due to Widmark [1919], who in 1919 published in Sweden a paper about the elimination of ethanol and acetone from blood. Widmark observed that, in its final phase, ethanol is eliminated according to an exponential law. He introduced the concept of what we now call the *volume of distribution.*

If a drug is introduced intravenous, let's call D the dose administered and c(t) the concentration in the plasma measured at time t. If we ignore the short interval of time necessary for the drug to distribute uniformly in the plasma, then

$$\lim_{t \to 0} c(t) = D/V,$$

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i.e. the ratio D/V represents the concentration of the drug in the plasma before a fraction of it has been eliminated or has been distributed to other organs. The quantity V must be the volume of the plasma, and can be calculated from the formula above. This observation may seem obvious, but when we measure in an experiment the values of c(t) and D, and compute V using the formula above, sometimes we get values much different from the expected plasma volume. There may be several reasons for this discrepancy; for instance, the drug may be bound to some tissues before being distributed in the plasma. Nowadays we call the ratio

$$V = D/\lim_{t\to 0} c(t)$$

the *apparent volume of distribution.* This is one of the fundamental concepts in Pharmacokinetics, but, as any fundamental concept, it took a while before becoming part of our basic concepts.

Naturally if the biological condition of the subject does not change, with a different dose D the concentration c(t) will change in the same proportion; therefore, the ratio computed with the formula above will not change. The quantity V therefore is called *invariant.* Within the limits of validity of the hypotheses incorporated in the equations used for its computation, an invariant quantity does not depend on the particular experimental conditions.

The time of maximum concentration

Another invariant quantity is t_{max}, i.e. the interval of time necessary for a drug to reach its maximum concentration in the blood, when it has been injected as a bolus. This concept was introduced in 1933 by Gehlen [1933]. He showed that the t_{max} of a drug, other conditions being equal, does not change with the dose. This observation too, apparently obvious today, is a fundamental concept of Pharmacokinetics. It is important to remember, though, that all invariance properties depend on some very specific hypotheses. In the case of t_{max} in particular, the required hypothesis is the linearity of the biological system. Indeed the invariance of t_{max} is commonly used to check the linearity of the system under observation.

The eigenvalues

The second contribution, in chronological order, to the formation of fundamental pharmacokinetic concepts, is due to Biehler [1925], who in 1925 described the elimination of ethanol from blood with a bi-exponential function. But the first systematic treatment of pharmacokinetic problems with exponential functions is due to Teorell [1937a, b], generally considered the originator of Pharmacokinetics. In 1937 Teorell published the paper "Kinetics of Distribution of Substances Administered to the Body;" in that paper Teorell, starting from some general hypotheses, built the equations of what we would call today a "compartmental model". The solutions of Teorell's equations were sums of exponential functions, exactly as used today in most pharmacokinetic models. The exponents of those exponential functions are the *eigenvalues* of the matrix formed with the coefficients of the differential equations [Rescigno, Lambrecht and Duncan, 1983] describing the biological system observed, and do not depend upon the experimental initial conditions. The eigenvalues therefore are invariant quantities, independent not only of the dose, but also of the mode of administration. In other words the eigenvalues do not change if the drug is administered in a single dose or in multiple doses or by continuous infusion.

The following year, 1938, another fundamental paper appeared [Artom, Sarzana and Segré, 1938]. It was written by a physiologist, a histologist, and a

physicist who combined their expertises to do a very innovative piece of work. Using the isotope ^{32}P prepared by Ernest Lawrence at the University of California in Berkeley, they studied the synthesis and distribution of phospholipids in rats after administration of inorganic Phosphorus. Theirs is probably the first paper dealing with the use of radioactive isotopes for the solution of pharmacokinetic problems. It is worth noting that, even though they did not use the term "compartment" explicitly, they were the first authors to use this concept in a precise and consistent way.

The half-life of a drug

Finding the eigenvalues from the experimental data is not always an easy problem. Most of the times the observation errors propagate in such a way as to invalidate most of the numerical procedures towards this goal. In general, the easiest eigenvalue that can be computed is the smallest one in absolute value.

Suppose that a particular drug in a particular organism is characterized by three eigenvalues; in other words, the function representing the concentration of that drug in the plasma is a sum of three exponential functions; then

$$c(t) = A_1 e^{-\alpha_1 t} + A_2 e^{-\alpha_2 t} + A_3 e^{-\alpha_3 t}, \tag{1}$$

where $-\alpha_1, -\alpha_2, -\alpha_3$ are the three eigenvalues. Suppose also that

$$\alpha_1 > \alpha_2 > \alpha_3.$$

When t increases, the first two exponential functions decrease faster than the third, so that after a sufficiently long time

$$c(t) \cong A_3 e^{-\alpha_3 t},$$

and as a consequence,

$$\ln(c(t)) \cong -\alpha_3 \cdot t + \ln(A_3); \tag{2}$$

The plot of $\ln c(t)$ versus t is a straight line of slope $-\alpha_3$, therefore α_3 can easily be determined by plotting c(t) as a function of t on a semilogarithmic scale and extrapolating for $t \to \infty$.

The interval of time necessary for c(t) to decrease 50%, in the range of t where the approximation of equation (2) is valid, is called $t_{1/2}$ or *half-life* of that drug. Clearly

$$t_{1/2} = \ln 2/\alpha_3 = 0.693 \cdot 1/\alpha_3.$$

We mentioned earlier that this particular eigenvalue is easy to determine, but this is not always the case. There are at least two cases when this determination is difficult and inaccurate. If A_3 is very small, the approximation in equation (2) is still valid, but only for values of c(t) correspondingly small, that is for measurements of c(t) taken for large values of t, when experimental errors are more likely. This difficulty sometimes can be overcome. In fact, α_3 is invariant, but A_3 is not; if the initial conditions are modified appropriately, for instance, by using a continuous infusion, A_3 may sufficiently increase while α_3 stays constant.

Table 1

	κ=2	κ=3	κ=4
τ=2	14~41	2~9	0~2
τ=3	5~20	0~2	0~0
τ=4	2~9	0~0	0~0
τ=5	1~4	0~0	0~0
τ=6	0~2	0~0	0~0

Table 1 shows the relative errors in % committed when assuming

$$A_3e^{-\alpha_3 t} \cong A_1e^{-\alpha_1 t} + A_2e^{-\alpha_2 t} + A_3e^{-\alpha_3 t};$$

the entries of the table are $\kappa = \alpha_2/\alpha_3$ and $\tau = \alpha_3 t$; the range of values indicated for the error corresponds to the different possible values of α_1; the larger the difference $\alpha_1 - \alpha_2$, the smaller the error.

Table 2 shows the corresponding errors when the drug is given with a continuous infusion until steady state is reached, then c(t) is measured and extrapolated as above. The reduction of the errors in considerable.

Another case when the determination of α_3 is difficult is when $\alpha_2 = \alpha_3$; in this case equation (1) must be substituted by

$$c(t) = A \cdot e^{-\alpha_1 t} + (B \cdot t + C)e^{-\alpha_2 t};$$

if $\alpha_1 > \alpha_2$, for t sufficiently large, the approximations

$$c(t) \cong (B \cdot t + C)e^{-\alpha_2 t};$$

$$\ln(c(t)) \cong -\alpha_2 \cdot t + \ln(B \cdot t + C)$$

are valid, but this last one is not the equation of a straight line.

Of course the probability of two eigenvalues being exactly equal is extremely small. Suppose that

$$\alpha_1 > \alpha_2, \quad \alpha_2 - \alpha_3 = \varepsilon > 0,$$

where ε is small; the coefficients of equation (1) are given by [Rescigno and Beck, 1972]

Table 2

	κ=2	κ=3	κ=4
τ=2	7~24	1~3	0~2
τ=3	2~11	0~1	0~0
τ=4	1~5	0~0	0~0
τ=5	0~2	0~0	0~0
τ=6	0~1	0~0	0~0

$$A_1 = \frac{c(0)}{(\alpha_1 - \alpha_2)(\alpha_1 - \alpha_3)}, \quad A_2 = \frac{c(0)}{(\alpha_2 - \alpha_1)(\alpha_2 - \alpha_3)}, \quad A_3 = \frac{c(0)}{(\alpha_3 - \alpha_1)(\alpha_3 - \alpha_2)};$$

therefore

$$c(t) = \frac{c(0)}{(\alpha_1 - \alpha_2)(\alpha_1 - \alpha_3)(\alpha_2 - \alpha_3)}\left((\alpha_2 - \alpha_3)\, e^{-\alpha_1 t} - (\alpha_1 - \alpha_3)\, e^{-\alpha_2 t} + (\alpha_1 - \alpha_2)\, e^{-\alpha_3 t}\right)$$

$$c(t) = \frac{c(0)}{\varepsilon\cdot(\alpha_1 - \alpha_2)(\alpha_1 - \alpha_3)}\left(\varepsilon\cdot e^{-\alpha_1 t} - (\alpha_1 - \alpha_3)\, e^{-\alpha_2 t} + (\alpha_1 - \alpha_2)\, e^{-\alpha_3 t}\right).$$

For t very large we may use the approximation

$$c(t) \cong \frac{c(0)}{\varepsilon\cdot(\alpha_1 - \alpha_3)}\, e^{-\alpha_3 t},$$

but the error of this approximation does not decrease very rapidly with t; in the best case, i.e. when $\alpha_1 >> \alpha_2$, the relative error is given by $e^{-\varepsilon t}$. Table 3 shows some typical values for this error.

Table 3

εt	2	3	4	5
$e^{-\varepsilon t}$	13.5%	5.0%	1.8%	0.7%

The area under the curve

The area under the curve measuring the concentration of a drug in the plasma as a function of time, often abbreviated AUC, depends in a simple way upon the fraction of the drug reaching the systemic circulation and upon its clearance therefrom.

If c(t) is the concentration of a drug in the plasma and Cl the volume eliminated per unit time, then $Cl\cdot c(t)\cdot dt$ is the amount of drug eliminated during the interval of time from t to t+dt. Suppose that the drug present in the plasma will be eliminated completely in due time, then

$$F\cdot D = \int_0^\infty Cl\cdot c(t)\cdot dt, \tag{3}$$

where D is the *dose* or amount of drug administered, and F is the fraction reaching the systemic circulation.

If Cl is constant, then equation (3) can be written in the form

$$F\cdot D = Cl\cdot \int_0^\infty c(t)\cdot dt. \tag{4}$$

This equation is known as the "Stewart-Hamilton principle," often written in the form

$$AUC/D = F/Cl$$

where

$$AUC = \int_0^\infty c(t) \cdot dt.$$

Evidently the ratio AUC/D is another invariant quantity, provided our hypothesis is valid, i.e. Cl is constant.

The transfer time

Another important invariant quantity is the *transfer time* of a drug from a compartment to another compartment, as introduced in 1961 by Rescigno and Segre [1961a]. If $c_a(t)$ and $c_b(t)$ are the concentrations of a drug in compartments a and b respectively, and a is the precursor of b, the transfer time from a to b is the difference

$$T_{ab} = \frac{\int_0^\infty t \cdot c_b(t)dt}{\int_0^\infty c_b(t)dt} - \frac{\int_0^\infty t \cdot c_a(t)dt}{\int_0^\infty c_a(t)dt}. \qquad (5)$$

This quantity does not depend upon the dose or the mode of administration of the drug.

We shall say more about the transfer time in the sections about compartments and moments.

The transfer function

Consider a system where X(t) is the amount of drug present at time t in the compartment where it was first supplied, while Y(t) is the amount present at time t in another compartment. We call the first compartment the *precursor* of the second, and the second the *successor* of the first [Rescigno and Segre, 1961b]. If all the processes involved in the transfer of the drug from precursor to successor are linear and do not change in time, the relationship between X(t) and Y(t) can be described by the integral equation

$$Y(t) = \int_0^t X(\tau)\ g(t-\tau)\ d\tau. \qquad (6)$$

The integral above is called a *convolution*, and the function g(t) is called the *transfer function* [Rescigno, 1960] between X(t) and Y(t). The transfer function is not, strictly speaking, an invariant quantity, but it is a characteristic of the system and many invariant quantities can be derived from it.

The actual process of determining function g(t) is not a simple one because small experimental errors in X(t) and Y(t) propagate non-linearly in the numerical

computation of g(t) and may become very large. Nevertheless, there are a number of properties of the transfer function that are important and can be easily observed.

Consider the ratio

$$\frac{Y(t)}{t \cdot X(t)} = \frac{\int_0^t X(\tau)\, g(t-\tau)\, d\tau}{t \cdot X(t)}, \tag{7}$$

which can easily be computed for a number of values of t; for t = 0 this ratio is indeterminate, but using L'Hospital's rule one gets

$$\lim_{t\to 0} \frac{Y(t)}{t \cdot X(t)} = \lim_{t\to 0} \frac{\int_0^t X(\tau) g'(t-\tau) d\tau + X(t) g(0)}{X(t) + t \cdot X'(t)}.$$

Now, if $X(0) \neq 0$, then

$$\lim_{t\to 0} \frac{Y(t)}{t \cdot X(t)} = g(0).$$

If $X(0) = 0$, we can use L'Hospital's rule once more to get

$$\lim_{t\to 0} \frac{Y(t)}{t \cdot X(t)} = \lim_{t\to 0} \frac{\int_0^t X(\tau) g''(t-\tau) d\tau + X(t) g'(0) + X'(t) g(0)}{2X'(t) + t \cdot X''(t)}.$$

Now, if $X'(0) \neq 0$, then

$$\lim_{t\to 0} \frac{Y(t)}{t \cdot X(t)} = \frac{g(0)}{2}.$$

Proceeding in the same way we find that, if

$$X(0) = X'(0) = X''(0) = \cdots = X^{(n-1)}(0) = 0,$$

but

$$X^{(n)}(0) \neq 0,$$

then

$$\lim_{t\to 0} \frac{Y(t)}{t \cdot X(t)} = \frac{g(0)}{(n-1)!}.$$