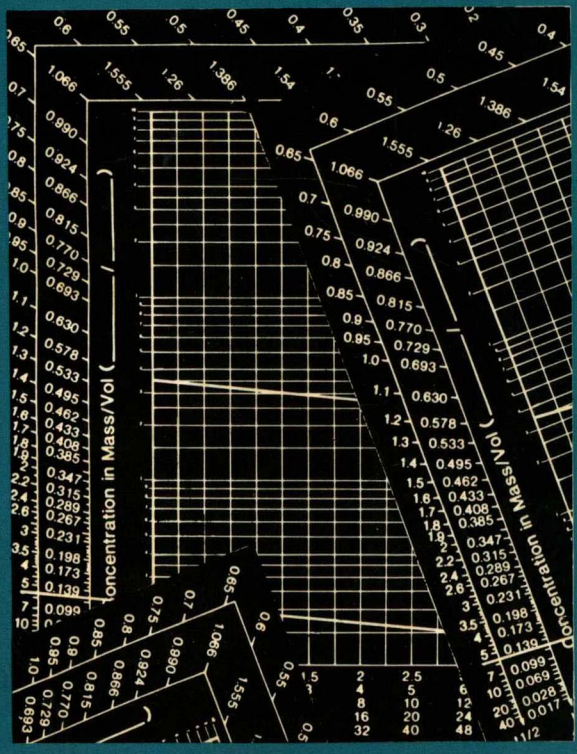
GRAPHIC APPROACH TO CLINICAL PHARMACOKINETICS

W.A. Ritschel



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Graphic Approach to Clinical Pharmacokinetics

With a Foreword by David J. Greenblatt

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To Barbara

FOREWORD

The discipline of clinical pharmacokinetics utilizes mathematical models to describe and predict the time-course of concentrations and amounts of foreign chemicals in various parts of living organisms. The theoretical framework of clinial pharmacokinetics is grounded in Newtonian calculus and strictly speaking is centuries old. Yet the specific application of these principles to understanding of the fate of foreign chemicals in the living organism did not emerge until the early part of this century, with theoretical work of Teorell and others. The pioneering contribution of these individuals for several decades remained largely theoretical, since analytical methodologies needed for experimental confirmation of the concepts developed more slowly than the concepts themselves. By the early 1960's, analytical chemistry had begun an exponential phase of technological growth, and numerous sensitive and specific techniques became available for quantitation of foreign chemicals in biological fluids. Clinical pharmacokinetics suddenly became a biologic as well as a mathematical science, and a new generation of pioneers guided the prodigious development of the discipline over the last two decades through and beyond the present.

Wolfgang A. Ritschel is among the most prominent of these pioneers. His work over the years has added immeasurably to the conceptual basis of clinical pharmacokinetics, as well as to its validation and application in experimental and human biological systems. Dr. Ritschel, furthermore, has always been committed to the idea that clinical pharmacokinetics can and must be intelligible as well as scientifically excellent. Its mathematical framework, though not highly sophisticated for applied mathematicians, often transcends the expertise (and tolerance) of biological scientists – most importantly, physicians who actually treat ill patients with drugs. The accomplishments of Dr. Ritschel are all the more remarkable in light of his determination to render pharmacokinetics understandable and usable to those who treat patients.

The present volume reflects this commitment, utilizing a highly innovative and unique approach. The technique is based on a hybridization of classical graphic methods and nomographic derivations. Data points, as we know, yield kinetic variables when analyzed graphically –elimination half-life, volume of distribution, clearance, absorption half-life, etc. Mathematical analysis of the derived variables yields predictive data –steady state concentration, peak and trough, time for achievement of steady state, etc. Dr. Ritschel's new technology allows any individual who can plot data points to simply read both the derived variables and the predictive data directly from a nomogram without time-consuming and complex intervening calculations. Simplicity is preserved with no loss of accuracy.

An innovator has developed another innovation which should bring clinical pharmacokinetics closer to patient care than it has ever been.

David J. Greenblatt, M.D.
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PREFACE

Clinical Pharmacokinetics, the application of basic pharmacokinetic principles for optimizing drug therapy in the individual patient, has become widely accepted and is practiced in all major medical centers. A simplified method of pharmacokinetic calculation is proposed in this book; it is intended to contribute significantly to broadening the base for the application of pharmacokinetics by clinicians and practitioners.

The method is based on one primary and two auxiliary nomograms designed to enable the busy practitioner to find solutions to pharmacokinetic problems often encountered in practice quickly and on the spot. Calculations using exponentials and logarithms are altogether avoided; they are an obstacle to the application of pharmacokinetics as a clinical tool since their use requires tables, calculators and formulas that only the specialist can recall from memory. All calculations requiring those functions are carried out graphically by drawing a few straight lines in the nomograms. The rest of the calculations is reduced to the four basic methods of arithmetic. Evidently, any graphic method will only yield an estimate. But an estimate is usually all that is clinically required. The proposed format, i.e. the nomograms combined with the evaluation form on its back, has the additional advantage that it may become a part of the permanent documentation in the patient's record or file.

"Graphic Approach to Clinical Pharmacokinetics" is not intended to be a textbook but a manual for clinical application. Nevertheless, it is hoped to be useful in classroom instruction to medical and pharmacy students by helping them to understand the basics of pharmacokinetics and its practical application to patient care. The large number of examples given in this text should help the practitioner or student to gain proficiency in the use of the nomogram without going into more sophisticated mathematics. The examples given will serve as guidelines for the most important and most frequently encountered tasks encountered in clinical practice.

I would like to thank two individuals who have been instrumental in the final writing of the text: Dr. David J. Greenblatt, Professor of Clinical Pharmacology, Division of Clinical Pharmacology, Tufts-New England Medical Center, Boston, who evaluated the method presented in this book in his department, and Dr. Ernst K. Franke, Professor of Biophysics, University of Cincinnati, Cincinnati, for his valuable advice in editing the manuscript.

If only one single patient benefits from this book, it has served its purpose.

Wolfgang A. Ritschel
1983

I INTRODUCTION TO PHARMACOKINETICS

1. WHAT IS PHARMACOKINETICS AND HOW DOES IT RELATE TO THE PHARMACOLOGIC OR CLINICAL RESPONSE?

It is generally accepted that for reversibly acting drugs, the drug concentration at the site of action will determine the intensity and duration of the pharmacologic effect. Since it is usually not possible to sample at the site of action or biophase, the next alternative is to sample whole blood, plasma or serum which is the biologic fluid which is in closest contact with the receptor site. It is generally accepted that the changes in the time course of drug concentrations in the body are related to the time course of the pharmacologic effect. The time course of the changes of drug concentrations in the body is described by the LADME-System, a system which deals with the processes of drug release from the dosage form (liberation), the uptake of the unchanged drug into systemic circulation (absorption), its distribution to various body sites including the biophase (distribution), the biotransformation of the parent drug molecule to usually less effective or ineffective metabolites (although in some cases the metabolites may be more, less or equieffective, or even more toxic) (metabolism), and the elimination of the drug from the body by any pathway, such as via kidney, liver, lung, skin, saliva, milk, etc. (elimination). Using pharmacokinetic models the time course of drug concentrations can be described as visualized for the central compartment which includes, but is not identical with systemic circulation, and for peripheral compartments. Once the distribution phase is completed the drug concentrations in the central and peripheral compartments will decline in parallel. At this point a pseudoequilibrium of distribution is obtained regardless of whether the site of action is in the central compartment or in any peripheral compartment.

Although the total drug concentration may considerably differ between central and peripheral compartments, the concentrations of free (non-bound) drug will be the same. Hence, once the pseudoequilibrium of distribution is reached, a correlation should exist between pharmacologic effect and drug concentration in blood. Usually only the total drug concentration is measured in plasma. This is quite acceptable under normal conditions because interindividual differences in plasma protein binding seem to be small (1). However, if two acidic drugs are given simultaneously and both are extensively bound, one drug may displace the other one from its binding site. The pharmacologic action of the displaced drug will increase. If the drug is extensively metabolized the increased portion of the free drug is now available for metabolism and the total drug concentration may decrease. Hence, an increased pharmacologic or even toxic effect may occur at lower total drug concentration (2).

Models for correlation between pharmacologic response and drug disposition have been described in the literature (3-7).

Pharmacokinetics deals with the quantitative aspects of a drug in the body once the drug product or dosage form is administered to the patient, and with the quantitative relationship between pharmacologic or clinical response and the fate or disposition of the drug in the body.

2. WHICH PHARMACOKINETIC FACTORS INFLUENCE BLOOD LEVELS?

Most drugs are not given as a single dose administration but according to a dosage regimen of a given dose size in specified dosing intervals throughout the entire course of drug therapy. If the repeated dosing occurs in dosing intervals shorter than it takes to eliminate the drug of the preceeding dose from the body, the drug will accumulate to a steady state where input and output are equal. The maintenance dose, DM, which is required to maintain a desired mean steady state concentration, $C_{ss\,av}$, at a given dosing interval, τ, depends on the magnitude of $C_{ss\,av}$ (the required drug concentration in blood to elicit the pharmacologic response), the pharmacokinetic parameters of drug disposition and the patient's body weight, BW. The generalized equation for DM is given in Table I.1 (8).

Table I.1: Factors determining an individualized dose size

$$DM = CL_{TOT} \bullet C^{SS}_{AV} \bullet \tau \bullet BW$$

V_d	k_e or β	Ther. Range	Interval	Body Composition
APC	Metabolism:	Receptor	Increase	Fat/lean mass
pKa	LBF	sensitivity	or	Lean BW
TBF	Enzyme	No. of receptors	No change	Total BW
Fat	activity	Neurotrans-	with	
EBP	Subcellular	mittance	reduced DM	
Protein	changes	Homeostasis		
structure	Extrahepatic			
Tissue BFR	factors			
	Excretion:			
	ERPF			
	GFR			
	Tm			
	Morphologic			
	changes			

DM = maintenance dose [mcg]
Cl_{tot} = total body clearance [ml/h]
V_d = apparent volume of distribution [ml/g]
k_e or β = overall terminal disposition rate constant [1/h]
C^{ss}_{av} = desired mean steady state conc. [mcg/ml]
τ = dosing interval [h]
BW = body weight [g]

The drug's disposition in the equation is characterized by the total clearance, Cl_{tot}, which is the product of the apparent volume of distribution, V_d, and the terminal disposition rate constant, β. The V_d in turn is influenced by several factors such as the drug's apparent lipid/water partition coefficient, APC, the total body fluid, TBF, the fat content of the body, the extent of protein binding, EPB, the protein structure and the tissue blood flow rates, BFR. The overall terminal disposition rate constant, k_e or β, is mainly influenced by the two major pathways of elimination via metabolism and urinary excretion. Regarding metabolism, the liver blood flow rate, LBF, enzyme activity (enzyme induction, enzyme inhibiton) and subcellular changes (liver diseases) are of importance. For urinary excretion the effective renal plasma flow rate, ERPF, the glomerular filtration rate, GFR, active tubular transport, T_m, and morphologic changes of the kidney (renal diseases) are the major determining factors.

The $C_{ss\,av}$ is a concentration within the therapeutic range. This range may not be constant but may be influenced by receptor sensitivity, number of receptors present, neurotransmittance and homeostasis which may be altered in infants and the aged, or due to diseases.

The dosing interval, τ, is freely chosen and may have to be increased in renal or hepatic diseases.

The body weight, BW, is not necessarily the actual body weight. In geriatric or obese patients it is more appropriate to use the lean or ideal BW rather than the actual one for some drugs.

It is easily recognized that a changed body composition such as in obesity, infancy, old age and patients with severe edemas, may in turn alter the apparent volume of distribution.

Since these pharmacokinetic parameters as derived from studies with healthy, young adult volunteers may not be constant and may not apply to an individual patient, drug monitoring seems to be a logical consequence.

3. PHARMACOKINETICS

Pharmacokinetics is the quantitative study of drug disposition in the body. Under the assumption that for most drugs a relationship can be demonstrated between the drug concentration in blood, plasma or serum, and the pharmacological or clinical response, pharmacokinetics permits one to mathematically describe the fate of a drug upon administration in a given dosage form by a given route of administration, to compare one drug with others or other dosage forms, and to predict blood levels in the same or other individuals upon single or multiple dosing under various conditions of either changed dosage regimens or disease states.

3.1. KINETIC PROCESSES

Basically, in pharmacokinetics three types of kinetic processes are used to characterize the fate of drug in the body: First-order or linear kinetics; Zero-order or nonlinear kinetics; Michaelis-Menten or saturation kinetics.

First-Order Kinetics– Most of the processes of drug uptake (= absorption), diffusion and permeation in the body (= distribution) and excretion (= urinary elimi-

nation) can be described by first-order or linear kinetics. This means that the rate of change of concentration of drug is dependent on the drug concentration. When the concentration *versus* time data are plotted on numeric or cartesian graph paper a concave curve is obtained and when plotted on semi-log paper a straight line is obtained as seen in Fig. I.1. The relationship can be expressed by equation 1:

$$dC/dt = -k \cdot C \qquad \text{Eq.1}$$

where C = concentration of drug, k = first-order rate constant, and t = time.

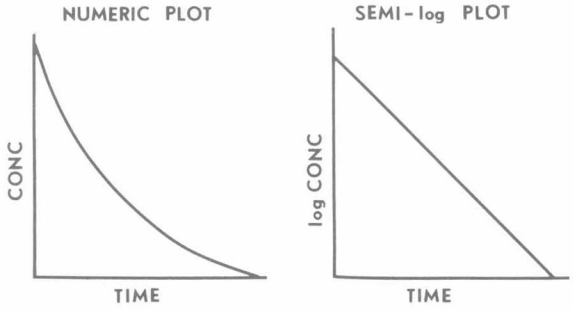

Fig. I.1. Schematic diagram of first-order kinetics.

The rate of change of drug concentration per unit of time is equal to the drug concentration multiplied by the rate constant for that particular first-order process. The minus sign indicates that the drug concentration decreases with time. (Elimination: % per unit of time). Examples of first-order elimination kinetics are all antibiotics and sulfonamides, digoxin, lidocaine, procainamide, theophylline (most drugs!).

Zero-Order Kinetics– If the rate of elimination of few compounds from the body is not proportional to the concentration of the drug then the elimination usually follows zero-order or nonlinear kinetics. This means that the rate of change of concentration is independent of the concentration of the particular drug. In other words, a constant amount of drug, rather than a constant proportion, is eliminated per unit of time. (Elimination: amount per unit of time). When the concentration *versus* time data are plotted on numeric or cartesian graph paper a straight line is obtained, whereas on semi-log paper a convex curve is obtained as shown in Fig. I.2. The classical example for zero-order kinetics is the disposition of alcohol (ethanol).

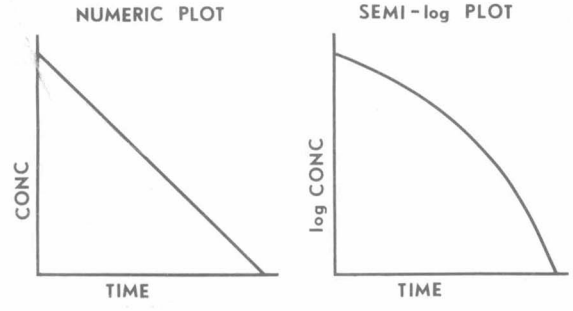

Fig. I.2. Schematic diagram of zero-order kinetics.

The relationship can be expressed by equation 2:

$$dC/dt = -k_o \qquad \text{Eq.2}$$

where the rate of change of concentration, dC/dt, is equal to the zero-order rate constant, k_o, which has the units of amount per unit of time.

Michaelis-Menten Kinetics– In metabolism nearly all biotransformation processes are catalyzed by specific enzyme systems with a limited capacity for the drug. Also in active transport of drugs across membranes the carriers have a limited capacity. Whenever the drug concentration present in a given system exceeds the capacity of the system, the rate of change of concentration is most precisely described by the Michaelis-Menten equation.

When the drug concentration *versus* time is plotted on numeric or cartesian graph paper a curve is obtained which in the upper portion is only slightly concave but becomes more concave in its lower portion. On semi-log paper the upper portion of the curve decays in a convex fashion whereas the lower portion ends in a straight line as shown in Fig. I.3.

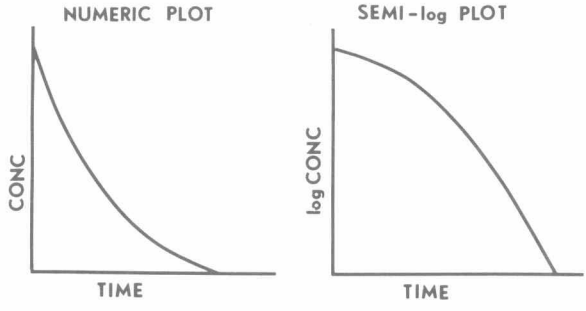

Fig. I.3. Schematic diagram of Michaelis-Menten kinetics.

The rate of change of concentration dC/dt for the Michaelis-Menten process can be expressed by equation 3:

$$dC/dt = -Vm \cdot C/(Km + C) \qquad \text{Eq.3}$$

where C is the drug concentration, t is the time, Vm is a constant representing the maximum rate of the process and Km is the Michaelis constant, the drug concentration at which the process proceeds at exactly one-half its maximal rate.

For simplification of this presentation often a Michaelis-Menten process can be approximated by either one of the following two simplifications: a) If $C \ll Km$, then C can be removed from the denominator of equation 3, and Vm and Km, being both constants, can be combined to a new constant, k. Hence, equation 3 is simplified to a first-order process as given in equation 1; b) if $C \gg Km$, then Km can be removed from the denominator of equation 3, and C cancels out. Hence, the equation is simplified to:

$$dC/dt = -Vm \qquad \text{Eq.4}$$

indicating that the rate of change of concentration is equal to a constant, i.e. follows zero-order kinetics.

Examples of saturation elimination kinetics are: phenytoin, high doses of barbiturates, and glutethimide.

Note: First-order processes of absorption and distribution, but particularly of metabolism and elimination may change from first-order to Michaelis-Menten kinetics or pseudo zero-order kinetics with increasing the dose size (usually beyond the therapeutic range), in certain disease states, or due to other drugs that are administered concomitantly.

3.2. COMPARTMENT MODELS

To describe the quantitative processes of a drug in the organism, pharmacokinetics utilizes the concept of compartments. A compartment is a unit characterized by two parameters: the drug concentration, C, and the volume, V_d. Multiplying the drug concentration by the apparent volume of distribution the amount, A, of the drug in that compartment is obtained:

$$C \cdot V_d = A \qquad \text{Eq.5}$$

A given compartment model is not necessarily specific for a given drug. For instance, a drug given I.V. is often described by a two-compartment open model whereas the same drug given P.O. or by any other extravascular route may be described by a one-compartment open model.

In reality the human body is a multimillion-compartment model. However, usually we have in the intact organism easy access to only two kinds of biological fluids, blood (serum, plasma) and urine. Being restricted to blood and/or urine specimens the fate of a drug in the body is usually described by either one- or two-compartment open models. Clinically speaking, the concept of the one- and two-compartment model is usually satisfactory for therapeutic use. The main application of pharmacokinetics in a clinical setting is to predict, monitor and adjust dosage regimens resulting in therapeutically effective and safe blood levels of the drug. Most of the mathematical procedures for these purposes are actually based on the one-compartment open model and are applicable for the two- or higher compartment models under certain conditions and assumptions. The difference between a one- and a two-compartment model is that in the first one distribution occurs instantly whereas in the latter one the distribution process needs a measurable time before pseudo-equilibrium is obtained.

Compartment models are usually visualized by block diagrams. Each compartment is characterized by the amount or volume and concentration term. The compartments are connected by arrows indicating the rate of drug transfer in units of reciprocal time. In Fig. I.4 the most important compartment models are shown listing the block diagrams with their corresponding blood level-time curves as numeric and semi-log concentration *versus* time.

3.2.1. Compartment model analysis

In the one-compartment model the intercept of the terminal k_e-slope is the fictitious zero-time concentration, C(0) (see Fig. I.5). The volume of distribution in

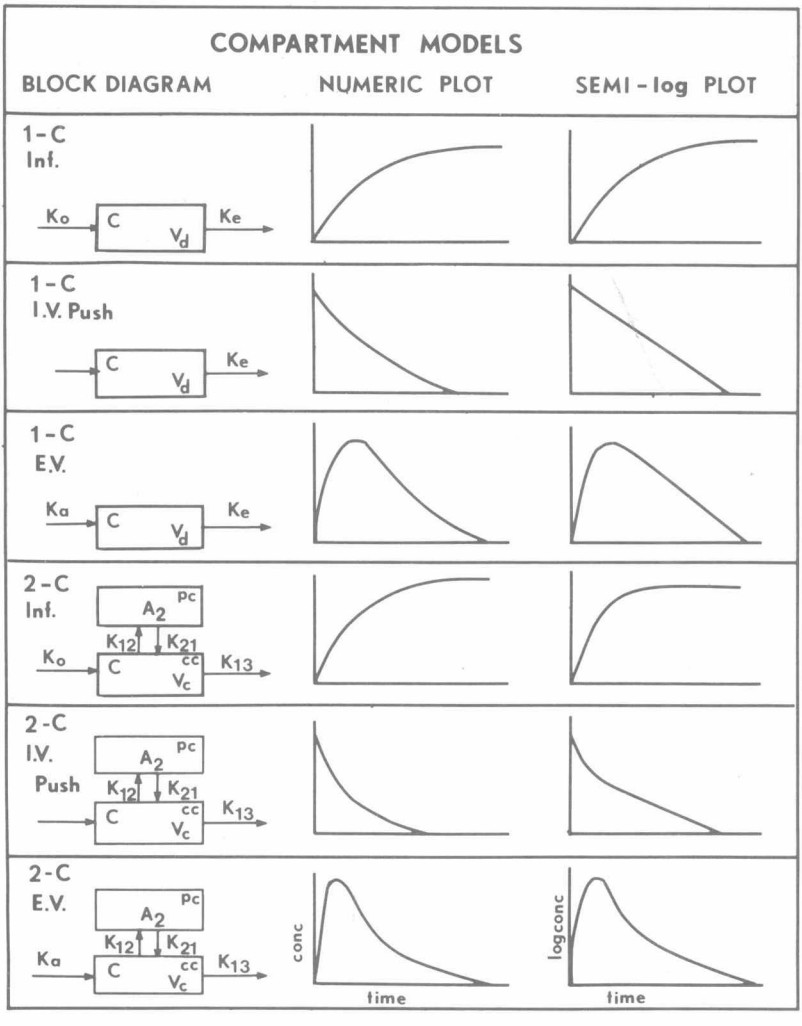

Fig. I.4. Schematic representation of pharmacokinetic models in form of block diagrams (left column), and blood level-time curves as numeric (middle column) and semilog plots (right column) for intravenous infusion, I.V. administration, and extravascular administration according to the open one-compartment model and open two-compartment model.

k_o = zero-order infusion rate
$C(t)$ = drug concentration in blood
V_d = apparent volume of distribution
k_e = overall elimination rate constant
k_a = absorption rate constant
k_{12} = distribution rate constant from the central to the peripheral compartment
k_{21} = distribution rate constant from the peripheral to the central compartment
CC = central compartment (blood and any organ or tissue which is in immediate equilibrium with the drug concentration in blood)
k_{13} = elimination rate constant for loss of drug from the central compartment
A_2 = drug amount in peripheral compartment
1-C = open one-compartment model
2-C = open two-compartment model
I.V. = intravascular
E.V. = extravascular
V_c = central compartment volume of distribution
PC = peripheral compartment

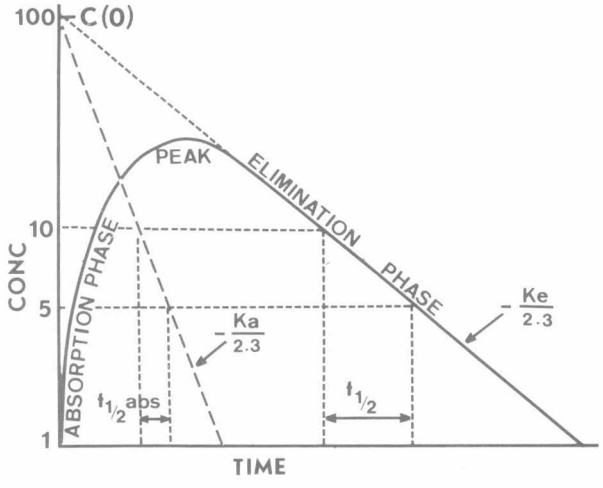

Fig. I.5. One-compartment model blood level-time curve after extravascular administration, with monoexponential slopes for elimination, k_e, and absorption, k_a.

the one-compartment model is given by equation 6:

$$V_d = D/C(0) \qquad \text{Eq.6}$$

where D is the dose and C(0) is the fictitious zero-time blood level.

The *volume of distribution* is not a real value and usually has no relationship to any physiologic space or body fluid volume. It is simply a term to make the mass-balance equation true. Upon I.V. administration we know how much (amount) drug is in the body. However, we can sample only the blood volume. Since an amount, A, equals the product of concentration and volume, the volume of distribution is that hypothetical volume which would be required to dissolve the total amount of drug at the same concentration as found in blood.

The volume of distribution is expressed in ml. If this value is divided by the patient's body weight the distribution coefficient, △', is obtained in ml/g (or l/kg).

The *elimination half-life* is the time required to reduce the blood level concentration to one-half after equilibrium is obtained. After absorption is completed it takes one half-life to eliminate 50% of the drug, 7 half-lives to eliminate 99% of the drug and 10 half-lives to eliminate 99.9% (see Table I.2).

Table I.2: Elimination half-lives

Number of Half-lives	% of Drug Remaining in the Body	% of Drug Eliminated
1	50	50
2	25	75
3	12.5	87.5
4	6.25	≃94
5	3.125	≃97
6	1.5625	≃98.5
7	0.78125	≃99.2
8	0.3906	≃99.6
9	0.195	≃99.8
10	0.097	≃99.9

Whenever a monoexponential straight line is obtained a half-life can be calculated. Other half-lives frequently used are the absorption half-life, $t_{1/2abs}$, and distribution half-life, $t_{1/2\alpha}$.

The terms half-time, half-life, plasma half-life, elimination half-life and biological half-life are often used interchangeably. Half-life refers to the total dose or amount of drug in the body and is equal to the time required for elimination of one-half of the total dose of drug from the body. The elimination half-life or plasma half-life refers to the half-time of the terminal elimination phase (k_e- or β-slope) for the drug in blood, plasma or serum. In those instances where the decline of drug concentrations in all tissues does not parallel the decline of drug concentrations in plasma, blood or serum, half-life and elimination half-life will be different. Most statements on drug disposition refer to the elimination half-life.

The elimination half-life, $t_{1/2}$, is determined as follows: Select any concentration on the *terminal* elimination phase, such as 10 in Fig. I.5. At one $t_{1/2}$ half of the drug concentration is eliminated from the body. One half of 10 = 5. Draw parallel lines to the time axis at the concentrations 10 and 5. Where these parallel lines intersect with the terminal elimination line, perpendicular lines are drawn to the abscissa (time axis). The time span read from the time axis is the elimination half-life. The rate constant for elimination, k_e (which is the slope of the elimination phase), can then be calculated by equation 7:

$$k_e = \frac{0.693}{t_{1/2}} \qquad \text{Eq.7}$$

To obtain the absorption rate constant, k_a (which is the slope of the absorption phase), needs some further mathematic manipulation. The differences of the blood concentrations during the absorption phase and the back-extrapolated elimination phase (dashed line) are plotted. Fitting a straight line through these plotted differences results in the absorption slope shown in Fig. I.5. To obtain the absorption half-life, $t_{1/2abs}$, one proceeds in the same fashion as discussed above for the elimination half-life. Substituting k_a for k_e and $t_{1/2abs}$ for $t_{1/2}$ in equation 7, the absorption rate constant, k_a, is obtained.

In Part II of this book a simple graphic solution is presented to read $t_{1/2}$, k_e, $t_{1/2abs}$ and k_a directly from a nomogram.

In the two-compartment model the fictitious zero-time concentration, C(0), is the sum of the two monoexponential processes of slow and fast disposition, i.e. the sum of the intercepts B and A obtained from the slopes β for slow disposition and α for fast disposition (see Fig. I.6).

If equation 6 is used for the two-compartment model the volume of distribution of the central compartment, V_c, is obtained.

In the two-compartment model the *terminal disposition rate constant* is called β. The rate constant β is determined in the same fashion as discussed for k_e in the one-compartment model. To determine the distribution rate constant, α, a process is used similar to that described for k_a in the one-compartment model. The differences are plotted between the actual drug conentrations on the steep downswing of the curve past the peak and the back-extrapolated concentrations read from the terminal disposition slope (dashed line). To determine the absorption rate constant, k_a, one has to determine twice differences. First the differences are calculated between the drug concentrations on the upswing of the blood level curve and the back-extrapolated terminal disposition slope. The new differences are calculated between the first dif-

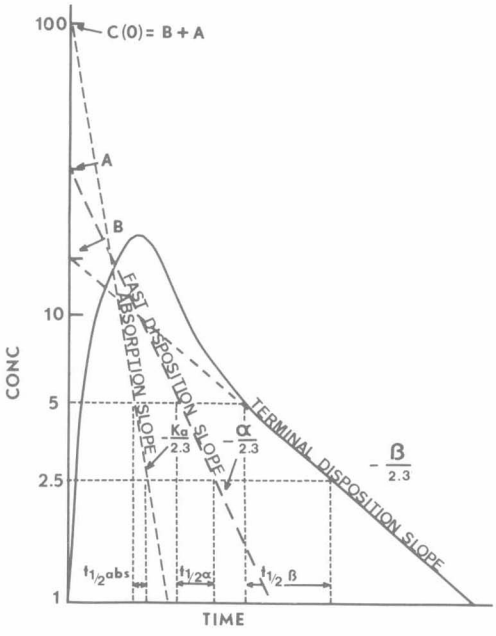

Fig. I.6. Two-compartment model blood level-time curve after extravascular administration, with monoexponential slopes for slow disposition, β, fast disposition, α, and absorption, k_a.

ferences and the α-slope. The half-lives for distribution, $t_{1/2\alpha}$, and absorption, $t_{1/2abs}$, are determined as discussed above and shown in Fig. I.6. The corresponding rate constants for distribution, α, and absorption, k_a, are then calculated according to equation 7, using α and $t_{1/2\alpha}$, or k_a and $t_{1/2abs}$, respectively instead of k_e and $t_{1/2}$.

The procedure is time-consuming. A simple graphical method is presented in Part II, where all the parameters, i.e. $t_{1/2}$, β, $t_{1/2\alpha}$, α, $t_{1/2abs}$ and k_a, can be directly read from the nomogram.

For dosage regimen calculation and prediction of steady state blood levels the volume of distribution during the β-phase or apparent volume of distribution, V_d, is used instead of V_c as given by equation 8:

$$V_d = \frac{D \cdot \alpha}{B \cdot \alpha + A \cdot \beta} \qquad \text{Eq.8}$$

If the drug is given by any extravascular route not the entire dose might be absorbed. Therefore the dose size, D, must be multiplied by the fraction of drug actually absorbed (absolute bioavailability, F).

The terminal disposition rate constant (k_e in the one-compartment model, β in the two-compartment model) can also be calculated from any two concentration-time points [C(1) at t(1) and C(2) at t(2)] from the terminal, monoexponential slope:

$$k_e \text{ or } \beta = \frac{\ln C(1) - \ln C(2)}{t(2) - t(1)} \qquad \text{Eq.9}$$

The elimination half-life, $t_{1/2}$, can then be calculated by equation 10:

$$t_{1/2} = \frac{0.693}{k_e \text{ or } \beta} \qquad \text{Eq.10}$$

The *total clearance* in pharmacokinetics describes how much of the volume of distribution is cleared of the drug per unit of time, regardless of the pathway for the loss of drug from the body. In effect it is the sum of all clearances by different pathways. The major pathways are via the liver (metabolism) and via the kidney (urinary excretion). Other nonrenal and nonhepatic pathways are via expired air (lung), sweat (skin) and milk (mammae).

The total clearance, Cl_{tot}, is the product of the apparent volume of distribution and the terminal disposition rate constant. For the one-compartment model equation 11 is used, and equation 12 for the two-compartment model.

$$Cl_{tot} = V_d \cdot k_e \qquad \text{Eq.11}$$

$$Cl_{tot} = V_d \cdot \beta \qquad \text{Eq.12}$$

For the two-compartment model one may also use the volume of the central compartment, V_c, and the corresponding elimination rate constant from the central compartment, k_{13}.

$$Cl_{tot} = V_c \cdot k_{13} \qquad \text{Eq.13}$$

k_{13} is a "micro"-constant and refers to the elimination rate of the drug from the central compartment. k_{13} can be calculated from the intercepts A and B, and the hybrid rate constants α and β:

$$k_{13} = \frac{A + B}{A/\alpha + B/\beta - C(0)/k_a} \qquad \text{Eq.14}$$

The term $C(0)/k_a$ in the denominator applies only to E.V. and is deleted for I.V. administration.

3.2.2. Compartment model-free analysis

Often it is not simple to determine which model is appropriate because there are not enough data points available, particularly for the early part of the concentration-time curve, or because the distribution phase is masked by the absorption phase. Furthermore, the calculation of microconstants (k_{12}, k_{21}, k_{13}) is sometimes bothersome and often meaningless. The most insensitive of all parameters is the total area under the concentration-time curve, AUC. Using the AUC and deriving the most important parameters, i.e. V_d and Cl_{tot}, from it, results in parameters which can be considered "robust". Furthermore, the parameters derived via the AUC are independent of the compartment model.

The terminal disposition rate constant is calculated from the terminal, monoexponential slope using equation 9. The terminal rate constant in the compartment model-free analysis is called β (regardless of any compartment model applicable). (In a newer, however not yet widely used nomenclature, the terminal rate constant is called λ_z).