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CLINICAL PHARMACOKINETICS

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INTRODUCTION

Pharmacokinetics derives its clinical utility from the fact that drug concentrations measured in plasma water correlate more predictably with pharmacologic response than standardized drug doses. This is true because the relationship between concentration of drug in plasma water and pharmacologic response is not affected by individual variation in the processes of drug absorption, distribution, and elimination that influence patient response when a given drug dose is administered. This was appreciated over 50 years ago when Wuth described serum concentration monitoring as an essential adjunct to the proper use of bromide as a sedative or anticonvulsant drug (1). General application of this approach to clinical therapy has hinged on the development of analytical methods suitable for measuring drug concentrations in body fluids and on the description of the processes of drug absorption, distribution, and elimination in mathematical terms that permit the precise analysis and design of drug regimens for individual patients. Drug metabolites must also be considered when they have pharmacologic activity that contributes to observed clinical responses (2, 3).

The term *pharmacokinetics* was coined by Dost who defined it as "the science of quantitative analysis between organism and drug" (4). However, Widmark can be credited with beginning work in this field, and his publication in 1919 defines the characteristics of drug distribution, elimination, and cumulation for a single-compartment open model (5). In 1937, Teorell laid the foundation for multicompartment pharmacokinetics by presenting a systematic analysis of plasma and tissue drug concentrations based on a two-compartment open model (6, 7). More recently, quantitative analysis

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of concentration-response relationships and drug-receptor interactions has been attempted in man, expanding the scope of pharmacokinetic investigations to the full extent of Dost's definition.

This review focuses on those aspects of pharmacokinetics that have the greatest clinical utility. We also attempt to place recent conceptual and technologic advances in pharmacokinetics in proper context with previous approaches. The reader should consult standard textbooks for a more detailed treatment of basic pharmacokinetic theory (8, 9) and Melmon & Morelli's textbook of clinical pharmacology for actual case presentations illustrating the application of pharmacokinetic principles (10). The reader is referred also to several recent symposia on pharmacokinetics (11–13).

THE SINGLE-COMPARTMENT PHARMACOKINETIC MODEL

Under certain circumstances (14) it is sufficient to regard a drug as being uniformly distributed in a single-body compartment, the volume of which determines the plasma concentration resulting from the total amount of drug contained in the body. This volume, termed the apparent volume of distribution of the drug, derives its clinical utility from the fact that drug doses (amounts) are prescribed but plasma drug concentrations are generally measured. Hence, the apparent volume of distribution of a drug (V_d) is defined by the equation,

$$V_d = X/c, \qquad 1.$$

where X is the total-body drug content and c is the plasma drug concentration. Distribution volume often is calculated from the concentration change resulting from the administration of a known drug dose, but can also be estimated from the concentration change resulting from hemodialytic removal of a measurable amount of drug (15).

Apparent distribution volumes seldom correspond to anatomic body spaces and, in fact, are often greater than total body weight on a liter per kilogram basis. This occurs because tissues may have far higher affinity for a drug than plasma. For example, the apparent volume of digoxin distribution in a 70 kg patient with normal renal function may be expected to approximate 535 liters (16, 17). This occurs because the tissue:plasma partition ratio of digoxin is much greater than 1 (18), so that tissues essentially extract digoxin from plasma, causing the distribution volume of this drug, referenced to plasma, to be far larger than anatomically possible. The same paradox would result if we placed a known quantity of drug in a 10 ml test tube containing 1 ml of plasma and 9 ml of chloroform. If the chloroform:water partition ratio of the drug was 10:1 and we attempted

to estimate the volume of the test tube from the equilibrium plasma concentration of the drug, we would arrive at the apparently absurd value of 91 ml. Nonetheless, this value would allow us to correctly predict the relationship between total drug content and plasma concentration for this particular system.

GENERAL PRINCIPLES OF DRUG DOSING

When there is an urgent need to establish therapeutically effective plasma concentrations, it is customary to begin treatment by administering a loading dose of a drug. In the case of digoxin this process is relatively straightforward. For example, it can be anticipated for our hypothetical 70 kg patient that the administration of 0.75 mg, usually given in a divided loading dose, will give a plasma concentration approximating 1.4 ng ml^{-1} after distributional equilibrium has been reached.

Distributional equilibrium is generally thought to occur when a semilogarithmic plot of plasma concentrations versus time reaches a terminal linear slope (Figure 1). Back-extrapolation of this slope, termed the elimination phase slope, yields at the y-intercept an estimate of the hypothetical plasma concentration that would have occurred had drug distribution been instan-

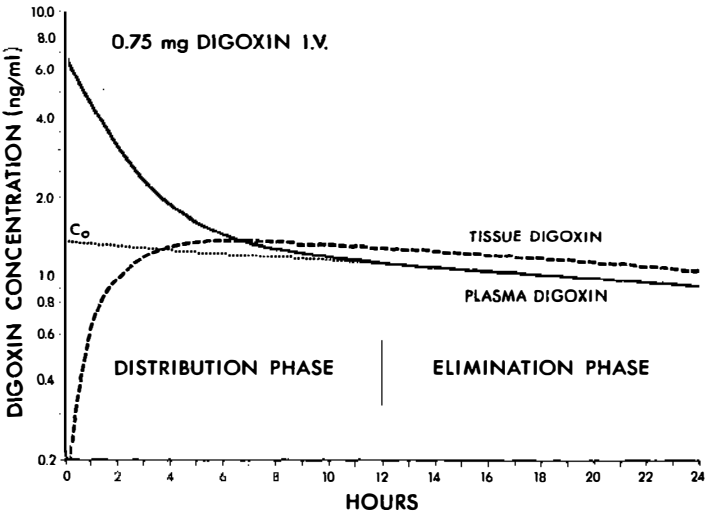

Figure 1 The pharmacokinetic model of Reuning and colleagues (17), based on data from Bloom & Nelp (19), was used to simulate plasma (*solid line*) and tissue (*broken line*) digoxin concentrations after intravenous administration of a 0.75 mg loading dose to a 70 kg patient with normal renal function. C_o is estimated from back extrapolation (*dotted line*) of elimination phase plasma concentrations.

taneous when the loading dose was administered (5). This y-intercept value (C_0) is often used to estimate distribution volume from the equation,

$$V_{d_{extrap}} = \text{Dose}/C_o. \qquad 2.$$

Plasma levels measured prior to the attainment of distributional equilibrium will lie above the back-extrapolated elimination phase slope, reflecting the distribution of drug from plasma to other tissues. Even after the elimination phase is reached, tissue drug levels do not equal plasma levels but only parallel them (Figure 1). The utility of plasma level monitoring is critically dependent on the proportionate relationship between plasma and tissue drug concentrations and on the assumption that this ratio is relatively constant from one individual to the next. For digoxin, 12 hr may be required for 99% completion of the distribution phase, as shown in Figure 1 (17). However, in practice plasma drawn 6 to 8 hr after a digoxin dose is generally regarded as satisfactory for clinical monitoring (20, 21).

After the distribution phase, plasma concentrations and tissue stores of digoxin decline in a monoexponential fashion and, at the end of 24 hr, approximately two thirds of the initial loading dose remains in a patient with normal renal function (19, 21). The goal of continued therapy then would be to maintain a steady state by replacing daily losses with a dose that is one third that of the appropriate initial loading dose or, in the example given, 0.25 mg per day. Of course, if the patient's clinical condition does not warrant immediate digitalization, this same steady state can be reached by the daily administration of this maintenance dose (22). This is easily visualized as follows:

$0.25 \text{ mg} \times \frac{2}{3} = 0.17$ mg End of Day 1
$+0.25$ mg Daily Dose
$0.42 \text{ mg} \times \frac{2}{3} = 0.28$ mg End of Day 2
$+0.25$ mg Daily Dose
$0.53 \text{ mg} \times \frac{2}{3} = 0.36$ mg End of Day 3
$+0.25$ mg Daily Dose
$0.61 \text{ mg} \times \frac{2}{3} = 0.41$ mg End of Day 4
$+0.25$ mg Daily Dose
$0.66 \text{ mg} \times \frac{2}{3} = 0.44$ mg End of Day 5
$+0.25$ mg Daily Dose
$0.69 \text{ mg} \times \frac{2}{3} = 0.46$ mg End of Day 6
$+0.25$ mg Daily Dose
0.71 mg

It can be seen that a situation is being asymptotically approached in which total body stores will reach a peak of 0.75 mg and fall in the course of each day to 0.50 mg. This is identical with the steady state reached more rapidly by administering a 0.75 mg digoxin loading dose, followed by a daily maintenance dose of 0.25 mg.

KINETICS OF DRUG ELIMINATION

Fortunately, the elimination of most drugs used in clinical practice is similar to that of digoxin and can be described by first-order kinetics. In a single-compartment model, the rate of drug elimination (dX/dt) after administration of a single drug dose is given by the equation,

$$dX/dt = -KX, \quad 3.$$

where K is the elimination rate constant and X is the total drug in the body at any time, t. This first-order differential equation is easily solved by first separating variables to give,

$$dX/X = -K dt \quad 4.$$

and then integrating from time equals zero, when a drug dose of X_o is administered, to time equals t.

$$\int_{X_o}^{X} dX/X = -K\int_{0}^{t} dt. \quad 5.$$

$$ln\ X \Big|_{X_o}^{X} = -Kt\Big|_{0}^{t}. \quad 6.$$

$$ln\ X/X_o = -Kt. \quad 7.$$

$$X = X_o e^{-Kt}. \quad 8.$$

These equations can also be expressed in terms of drug concentrations by making the appropriate substitutions given by Equation 1.

Elimination Half-Life

Elimination half-life is a commonly used indicator of the rapidity with which a drug is eliminated from the body. Elimination half-life can be defined as the time required for the amount, or concentration, of an administered drug to fall to one half its value at some previous time. Elimination half-life ($t_{1/2}$) can be calculated directly from Equation 7 by letting $X/X_o = 1/2$, so that,

$$ln\ 1/2 = -Kt_{1/2} \quad 9.$$

$$ln\ 2 = Kt_{1/2} \quad 10.$$

$$t_{1/2} = 0.69/K. \quad 11.$$

In practice, K is often conveniently estimated by determining the time for the plasma concentration of a drug to fall by half during its elimination phase, then using the value of $t_{1/2}$ to calculate K from Equation 11.

Elimination Clearance

As descriptions of the rate at which a drug is eliminated from the body, both K and $t_{1/2}$ suffer from their dependence on the apparent volume of drug distribution. The primary pharmacokinetic parameter that rigorously characterizes the kinetics of drug elimination is elimination clearance. It is generally known that clearance can be used to assess renal function, as described by the equation,

$$Cl = UV/c, \qquad 12.$$

where Cl represents clearance, c plasma concentration, and $U \cdot V$ the amount of a substance eliminated by the kidneys in a given period of time (23). This is a disguised first-order differential equation since $U \cdot V$ is actually an excretion rate (24). Hence Equation 12 can be rewritten,

$$\mathrm{d}E/\mathrm{d}t = Clc, \qquad 13.$$

where $\mathrm{d}E/\mathrm{d}t$ is, for example, the rate of creatinine appearance in urine. With a change of sign, this is equivalent to the rate of creatinine elimination from the body, $\mathrm{d}X/\mathrm{d}t$. Substituting X/V_d for C (Equation 1) then gives,

$$\mathrm{d}X/\mathrm{d}t = ClX/V_d. \qquad 14.$$

Comparison with Equation 3 thus indicates that,

$$K = Cl/V_d. \qquad 15.$$

From Equation 11 it can be seen that,

$$t_{1/2} = 0.69 V_d/Cl. \qquad 16.$$

Thus a drug may have a long elimination half-life, either because its clearance by eliminating organs is slow or because its apparent volume of distribution is large.

EFFECTS OF DISEASE ON DRUG ELIMINATION

Assessment of the effects of disease on drug elimination requires an appreciation of the interaction of parallel renal and hepatic mechanisms of drug elimination. In Equation 14, Cl is usually a composite of renal and hepatic drug clearances such that,

$$Cl = Cl_r + Cl_h. \qquad 17.$$

Wagner has provided a detailed analysis of the different components comprising renal clearance of drugs (25). It is expected that Cl_r will be reduced in patients with impaired renal function and that Cl_h will be reduced in patients with sufficiently advanced liver disease. Reductions in either one

of these parameters will prolong elimination half-life in a hyperbolic fashion (26), as is found by substituting Equation 17 into Equation 16,

$$t_{1/2} = 0.69\ V_d/(Cl_r + Cl_h). \qquad 18.$$

Hepatic blood flow is a major determinant of the hepatic clearance of some drugs, and a number of mathematical models have been proposed to relate hepatic clearance, hepatic blood flow, binding of the drug within the blood, and the intrinsic metabolizing activity of liver enzymes (27–30). One model that is compatible with existing experimental evidence predicts that

$$Cl_h = Q\left[\frac{f\,Cl_{\text{int}}}{Q + fCl_{\text{int}}}\right], \qquad 19.$$

where Q is hepatic blood flow, f is the fraction of drug in the blood that is unbound, and Cl_{int} is the intrinsic metabolic clearance of the drug (31–33). The intrinsic clearance can be thought of as the clearance that would be measured if hepatic clearance were not limited by binding or blood flow (31, 34).

In certain cases intrinsic clearance is concentration dependent and must be described by the Michaelis-Menten equation,

$$Cl_{\text{int}} = V_{\max}/(K_M + fc), \qquad 20.$$

where $V_{\max}$ and K_M denote the apparent Michaelis-Menten constants (35, 36). Estimates of these parameters made from in vivo pharmacokinetic investigations seldom correlate with the results of in vitro drug metabolism studies for reasons that have been discussed in a recent review (36). Fortunately, K_M is usually far greater than the therapeutic concentration range of most drugs, so that intrinsic clearance reduces to a constant. Hence, even hepatic elimination can be regarded generally as an apparent first-order process. There are, however, important exceptions. For example, ethyl alcohol (37) and phenytoin (38, 39) have been shown in man to have overall elimination rates described by Michaelis-Menten kinetics. Furthermore, drugs are often metabolized by several parallel pathways so that Cl_{int} comprises the sum of several Michaelis-Menten processes (34, 36, 40). Since each pathway may involve several serial steps that could include the formation of potentially toxic compounds and their subsequent deactivation, the variability with which different metabolic steps become rate limiting may be of critical importance in explaining the biochemical basis of certain adverse drug reactions that now appear to be idiosyncratic (41). In addition, inhibition or induction of many of these metabolic steps by other drugs to which patients are exposed forms the basis of many known drug interactions (42). Few of these have been the subject of formal pharmacokinetic analysis.

Therapy of Patients with Reduced Renal Drug Elimination

Considerable attention has been devoted to the design of effective and safe drug dosage regimens for patients with impaired renal function, and several excellent reviews are available (26, 43–46). Fortunately, creatinine clearance provides a valuable indicator of the adequacy of elimination for many drugs that are primarily excreted by the kidneys. Dosing recommendations have been based on experience (47), have been presented in nomographic form based on systematic empirical observations (21), and have been presented in nomographic form based on the application of pharmacokinetic principles to the results of studies in normal subjects (26, 47, 48).

Pharmacokinetic data have been critically compiled to facilitate application of this last approach (49). The elimination phase half-life and percentage drug elimination by metabolism in normal subjects is used to estimate the rate of nonrenal drug elimination, which is then taken as the overall rate of drug elimination in functionally anephric patients. A straight-line extrapolation of drug elimination rate can be made between the extremes of zero and normal creatinine clearance and serves to estimate the rate of drug elimination, and the elimination phase half-life, for a patient with a given degree of renal impairment (26). This approach has the advantage of great versatility since the appropriate data are available for many drugs. However, its validity is critically dependent on the assumptions that the renal clearance of creatinine and of the drug are proportional, and that nonrenal drug elimination is unaffected by the uremic state (45, 46). This latter assumption seems valid for many drugs metabolized by oxidation or glucuronide conjugation. However, reduction and acetylation pathways may be slowed (50, 51), and the oxidative metabolism of phenytoin appears to be enhanced (52) in uremic patients.

Therapy of Patients with Reduced Hepatic Drug Elimination

The design of dose regimens appropriate for treating patients with advanced liver disease is hampered by the fact that hepatic clearance of drugs cannot be predicted accurately from standard tests of liver function (34, 53, 54). In many cases this could reflect induction of microsomal drug metabolizing enzymes, concomitant with chemical injury (55) or in response to concurrent drug therapy (56), so that hepatic drug clearance is maintained at normal levels in many patients with liver disease (57, 58). When hepatocellular injury is more extensive, perhaps indicated to some extent by a low serum albumin or a prolonged prothrombin time (54, 56), this means of compensation may be inadequate to provide normal drug metabolic clearance (58). Even in normal subjects, the rate of hepatic drug metabolism varies widely between individuals, reflecting age (59), genetic (60, 61), and environmental (62) differences. Analysis-of-variance techniques have been

applied to population pharmacokinetic data to develop dose recommendations for therapy with one extensively metabolized drug, theophylline (63). It is likely that methods of this complexity will be required to adequately account for the major sources of individual variation in the hepatic metabolism of drugs.

Because hepatic clearance is flow dependent, drug elimination by the liver can be impaired when reduced cardiac output compromises hepatic blood flow (64). It can be seen from Equation 19 that this is particularly likely to occur when $f \cdot Cl_{int}$ is much greater than Q (34). This accounts for the finding that lidocaine clearance is greatly reduced in patients with congestive heart failure or cardiogenic shock (65, 66), and has led to the development of a nomogram for adjusting lidocaine dosage on the basis of cardiac output (67). Appreciation of the interrelationship between hepatic blood flow and hepatic clearance also provides an understanding of the basis for certain hemodynamic drug interactions (64).

Alterations in protein binding may also affect hepatic drug clearance. Such changes are prominent when Q is much greater than $f \cdot C_{int}$ (33). This includes most drugs metabolized by the liver, and clinically significant changes usually involve acidic drugs that are highly bound to serum albumin. For example, the protein binding of phenytoin is impaired in uremia (68) and in patients with hypoalbuminemia secondary to the nephrotic syndrome (69), causing Cl_h to be increased. If Cl_{int} is estimated from values of Cl_h and f published for nephrotic patients, no increase is found and free phenytoin levels are the same as in normal subjects maintained on the same dose regimen (69). On the other hand, Cl_{int} and f appear to be increased in uremia (52). Because the sum of free plus protein-bound phenytoin levels will be lower than expected in both uremic and nephrotic patients, dose adjustments based on total phenytoin levels may cause toxic reactions. Measurement of free phenytoin levels would be preferable, since they correlate best with the therapeutic and toxic effects of this drug (70). However, these measurements are not routinely available.

KINETICS OF DRUG ACCUMULATION

For many drugs therapeutically effective and toxic plasma concentrations are separated by a therapeutic index of two or more so that therapy can be initiated by administering a loading dose followed by maintenance doses that are half as large as the loading dose, given at intervals of one half-life (26). This provides a simple way of using expected half-life changes to individualize dose regimens for patients with impaired renal or hepatic drug elimination. In many cases a loading dose may not be required at all. The kinetics of drug accumulation can be predicted for both continuous intravenous infusion therapy and intermittent administration.

Continuous Infusion

When a drug is administered by continuous intravenous infusion its pharmacokinetics can be described by modifying Equation 3 as follows,

$$dX/dt = I - KX, \quad 21.$$

where I is the zero-order rate of constant drug infusion. At steady state, when $dX/dt = 0$,

$$I = KX \quad 22.$$

or substituting for K and X according to Equation 15 and Equation 1,

$$I = Clc. \quad 23.$$

Thus drug clearance can be estimated directly if the steady state concentration corresponding to a given infusion rate is known.

In this regard it is important to be able to estimate the time required to reach steady state plasma concentrations when drugs are administered by constant intravenous infusion. If a loading dose is not given, integration of Equation 21 will provide an estimate of total body drug stores at any time after the drug infusion has been started. Thus,

$$\int_0^X dX/(I - KX) = \int_0^t dt \quad 24.$$

$$ln(I - KX)\Big|_0^X = -Kt\Big|_0^t \quad 25.$$

$$X = \frac{I}{K}(1 - e^{-Kt}). \quad 26.$$

Note that when t equals infinity this gives the same relationship between infusion rate, elimination rate, and steady state total body stores as is provided by Equation 22, i.e. $X_\infty = I/K$. Although mathematically steady state is achieved only after an infinite time, we can calculate the length of time needed to reach any given percentage of that steady state (71). For clinical purposes the 90% attainment of eventual steady state ($X_{0.90}$) is usually adequate. If we designate the time needed to reach $X_{0.90}$ as $t_{0.90}$, then from Equation 26, since $X_{0.90}/X_\infty = 0.90$,

$$0.90 = 1 - e^{-Kt}0.90 \quad 27.$$

$$ln0.10 = -Kt_{0.90} \quad 28.$$

$$t_{0.90} = 2.30/K \quad 29.$$

and from Equation 11,

$$t_{0.90} = 3.3t_{1/2}. \quad 30.$$

It can be shown similarly that the time to reach any fraction of the eventual steady state total body stores or drug concentration is determined solely by the elimination half-life of the drug. This has been termed the *plateau principle* (71).

Intermittent Administration

Most drugs are administered on an intermittent rather than on a continuous basis. Hence for a patient started on a maintenance drug dose without prior administration of a loading dose, we can estimate from Equation 8 that the minimum drug concentration just before the second dose will be given by,

$$X_{\min_1} = X_o e^{-K\tau} \quad 31.$$

where X_o is the maintenance dose and τ is the dosing interval (72). Just after the second dose, letting $p = e^{-K\tau}$,

$$X_{\max_2} = X_o + X_o p. \quad 32.$$

Similarly after the nth dose,

$$X_{\max_n} = X_o(1 + p + \ldots\ldots + p^{n-1}) \quad 33.$$

$$X_{\max_n} = X_o(1 - p^n)/(1 - p). \quad 34.$$

Since p is less than 1, as n approaches ∞, p^n approaches 0, so,

$$X_{\max_\infty} = X_o/(1 - p) = X_o/(1 - e^{-K\tau}). \quad 35.$$

The fractional attainment of steady state after n doses can then be expressed as

$$X_{\max_n}/X_{\max_\infty} = 1 - e^{-K\tau n}. \quad 36.$$

From Equation 36 the number of doses needed to reach 90% of the anticipated steady state level, $n_{0.90}$, can be calculated as follows,

$$0.90 = 1 - e^{-K\tau n_{0.90}}, \quad 37.$$

$$ln 0.10 = -K\tau n_{0.90}, \quad 38.$$

$$n_{0.90} = 2.30/K\tau, \quad 39.$$

$$n_{0.90} = 3.3t_{1/2}/\tau. \quad 40.$$

This is equivalent to Equation 30 since $\tau n = t$.

Although Equation 35 estimates peak plasma levels at steady state, in clinical practice vagaries in the rate of gastrointestinal absorption of drugs make it preferable to measure minimum or "valley" drug concentrations. These can be estimated from the equation,

$$X_{\min_\infty} = X_o e^{-Kt}/(1 - e^{-Kt}). \quad 41.$$

Inspection of Equation 35 and Equation 41 indicates that the extent of drug cumulation at steady state, when compared to the first dose, is given by the accumulation factor R (73), where,

$$R = 1/(1 - e^{-Kt}). \quad 42.$$

It has been shown that mean steady state plasma concentrations under conditions of intermittent dosing are also given by Equation 22 (74). Replacing I by X_o/t, and substituting for X according to Equation 1,

$$c = X_o/(\tau K V_d). \quad 43.$$

BIOAVAILABILITY

Up to this point we have assumed that the absorption of intermittently administered drug doses is rapid and complete. This assumption may not be valid even when drugs are injected intramuscularly. For example, parenteral formulations of phenytoin precipitate at tissue pH when administered by this route (75). However, the rate and extent of absorption of oral drug formulations have received more general concern. Bioavailability is defined as the relative amount of an administered drug dose that reaches the systemic circulation unchanged and the rate at which this occurs (76). When an intravenous drug formulation is used as reference, absolute bioavailability can be determined. When two oral formulations are compared, only their relative bioavailability is estimated.

Passive nonionic diffusion is the most important mechanism of drug absorption, but the common belief that weakly acidic drugs are primarily absorbed in the stomach is probably not generally true because the absorbing surface area of the proximal small intestine is so very much larger (77). For this reason, the rate of gastric emptying greatly affects the rate at which drugs are absorbed, regardless of whether they are weak acids, weak bases, or neutral compounds (77–79). For compounds that are unstable at gastric pH, delayed gastric emptying can reduce the extent as well as the rate of drug absorption (78).

Kinetics of Drug Absorption

After drug ingestion there is a delay before any drug appears in the systemic circulation. This lag reflects the time required for the disintegration of the drug product, the dissolution of the drug into intestinal fluid, and the time required to traverse the stomach to the small intestine (80). After this delay, a plot of plasma drug concentration versus time reflects the combined operation of the processes of drug absorption, distribution, and elimination. A peak concentration is reached when drug absorption no longer exceeds

drug removal from the systemic circulation by distribution to tissues, metabolism, and excretion. It should be emphasized that drug absorption is not completed when this peak is reached.

A plot of total body drug content versus time, $X(t)$, can be thought of mathematically as being generated by the convolution of a function, $g(t)$, describing the drug absorption process, with a function, $h(t)$, describing drug elimination (81, 82),

$$X(t) = g(t) * h(t). \quad 44.$$

The operation of convolution, denoted by the asterisk, corresponds to multiplication in the domain of the subsidiary algebraic equation given by Laplace transformation of the three functions,

$$\bar{X}(s) = \bar{g}(s) \cdot \bar{h}(s). \quad 45.$$

Equation 3 defines $h'(t)$, and Laplace transformation of this equation yields

$$s\bar{X}(s) - X_o = -k\bar{X}(s). \quad 46.$$

If X_o is normalized to one,

$$\bar{h}(s) = 1/(s + k). \quad 47.$$

Despite the physiological complexity of drug absorption it frequently can be approximated mathematically by a lag followed by a simple first-order process characterized by an absorption rate, a (83). If the time axis is shifted to account for the lag, the differential equation, $g'(t)$, describing the rate of drug appearance in plasma is

$$dX/dt = a(M_o - X), \quad 48.$$

where a is the first-order absorption rate, M_o is the total drug dose that will be absorbed, and X is the amount of drug absorbed at time t. Converting to Laplace transforms,

$$\bar{g}(s) = aM_o/(s + a). \quad 49.$$

From Equation 45,

$$\bar{X}(s) = \frac{aM_o}{(s + a)(s + k)}. \quad 50.$$

Returning to the time domain by obtaining the inverse Laplace transform for a unequal to k,

$$X(t) = \frac{aM_o}{k - a}(e^{-at} - e^{-kt}). \quad 51.$$

The time required to reach peak plasma concentrations can now be estimated by taking the first derivative of Equation 51 and setting it equal to zero (84),

$$t_{max} = (a - k)^{-1} ln(a/k). \quad 52.$$

Then the value of the maximum drug concentration can be obtained by substituting t_{max} in equation 51 and dividing the result by the distribution volume,

$$c_{max} = (M_o/V_d)(a/k)^{k/(k-a)}. \quad 53.$$

Similar equations can be derived for the special case in which a and k are equal (84).

Determination of Bioavailability

Several methods are used to determine drug bioavailability (75). The plasma level versus time curve of a given drug formulation can be compared to that of a reference standard on a point by point basis, or the area under the plasma level versus time curve (AUC) of each formulation can be compared. Total drug elimination (E) is obviously equal to total drug absorption and can be estimated from Equation 13 by separating variables and direct integration to give (85)

$$E = Cl \int_0^\infty c \, dt. \quad 54.$$

The integral equals AUC so we can rewrite this expression,

$$F \cdot D = Cl \cdot AUC, \quad 55.$$

where F is the fractional absorption of the administered drug dose, D. If two drug formulations are given in sequence to the same individual, their relative bioavailability can be estimated from the AUC ratio. Total renal drug elimination (E_r) can be calculated from (86),

$$E_r = E \cdot Cl_r/Cl. \quad 56.$$

Therefore, bioavailability can also be estimated by comparing the amount of drug excreted unchanged by the kidneys when two drug formulations are given.

All of these methods estimate only the extent of drug absorption. However, absorption rate can also be estimated by deconvolution of the plasma level versus time curve after intravenous drug administration from that found after oral drug administration. In practice, this deconvolution can be carried out numerically (81, 82) but is most often accomplished with computer programs capable of iterative least squares analysis of data (87, 88).

In conventional studies, the assumption is made that the kinetics of drug distribution and elimination remain unchanged in a given individual and in the interval between sequential studies. However, this assumption can be avoided when absolute bioavailability and absorption rate are determined by simultaneous administration of an intravenous, stable isotope-labeled drug formulation and the oral drug formulation being evaluated (89).

Factors Affecting Bioavailability

Bioavailability may be incomplete not only because a drug is poorly absorbed but because it may be inactivated or interact with other substances in the gastrointestinal tract or be metabolized in the intestinal wall or on its first passage through the liver en route to the systemic circulation (77, 78, 90). Increasing attention has been focused on the importance of first-pass drug elimination by the liver as a cause of incomplete bioavailability (31, 91–93). The extent of this first-pass effect is defined by the extraction ratio, ϵ, which is equal to the ratio of hepatic drug clearance to hepatic blood flow (Cl_h/Q) (35). If drug absorption is otherwise complete,

$$\epsilon = 1 - F. \qquad 57.$$

From Equation 19 it can be seen that,

$$\epsilon = fCl_{int}/(Q + fCl_{int}). \qquad 58.$$

Thus, the first-pass effect will be particularly marked when $f \cdot Cl_{int}$ equals or exceeds Q. Oral doses of such drugs, if effective, will be several times larger than effective intravenous doses. One example is propranolol, a drug that has been used as a model compound to study the relationship between hepatic blood flow and hepatic drug clearance (94). When first-pass metabolism does not limit bioavailability, it appears that erratic and incomplete drug absorption is particularly likely to be found when the rate of drug absorption is slow (78, 95).

Formal investigation of the effects of disease on drug bioavailability has generally been limited to patients with renal disease or congestive heart failure. Drug bioavailability has been found to be unchanged (96), increased (97, 98), or variably reduced in uremic patients (95). For example, propranolol bioavailability has been found to be increased in uremia, presumably because first-pass metabolism is impaired (97, 98). Absorption of some drugs appears to be reduced in patients with congestive heart failure (99). This probably occurs because mesenteric blood flow is reduced (100), presumably reflecting intense vasoconstriction of mesenteric and iliac vascular beds in response to reduced cardiac output (101). It is likely that bioavailability will also be found to be increased for drugs with a marked first-pass effect when this effect is attenuated by hepatocellular disease or shunting

of portal venous blood (102, 103). Drug- or disease-induced alterations in gastrointestinal motility have also been shown to affect drug bioavailability (79). However, there is a need for more formal pharmacokinetic studies of factors affecting the rate and extent of drug absorption in patients.

DRUG DISTRIBUTION AND THE KINETICS OF PHARMACOLOGIC RESPONSE

Since drug distribution is not instantaneous there is often a lag between the attainment of peak plasma drug concentrations and the onset of pharmacologic effect. This lag is apt to be most prominent when drugs are administered by rapid intravenous injection, and, as is shown in Figure 1, may coincide with the time required for a drug to distribute from plasma to its site of action (17).

The single-compartment model is obviously inadequate for analysis of distribution phase data and investigators have used either multicompartment (104, 105) or perfusion (106–108) models for this purpose. The appropriate model will vary with the intent of the investigator, the general principle being to select the simplest model that is compatible with the experimental data, yet reflects physiological reality in those ways that are critical to the investigation (105, 109). For example, compartmental models are more widely used because of their simplicity. However, compartment models provide little insight into the effects of hemodynamic changes on drug distribution, so more complex perfusion models are needed (110). Considerable judgment is required because a model cannot entirely resemble reality yet remain simple. For complicated models, computers are usually used to estimate pharmacokinetic parameters from experimental data, and several satisfactory programs are widely used (87, 88).

The Effects of Drug Binding on Distribution

The pharmacokinetic aspects of plasma and tissue protein binding of drugs have been reviewed recently (111, 112). It is evident that if a drug is completely bound to plasma proteins, its apparent volume of distribution would equal that of the proteins themselves. This situation is reasonably well approximated by thyroxine which is normally 99.95% bound to plasma proteins and has a distribution volume of 15% of body weight, close to most estimates of extracellular fluid space (113). As drug binding to plasma proteins decreases, the apparent volume of drug distribution can be expected to increase with upper limits determined by the steady state partition coefficient between plasma water and various tissues (31, 35).

The compartmental distribution pattern of highly protein-bound or large molecular weight drugs (113, 114) can also be expected to approximate that

of albumin and to reflect the existence of both fast and slow equilibrating interstitial fluid spaces (111, 112). This heterogeneity probably results from the fact that slowly equilibrating tissues, such as muscle and skin, are supplied with capillaries whose surface appears to be continuous when examined by electron microscopy, whereas tissues, such as liver, have discontinuous capillaries that appear to be more rapidly penetrated by protein (115). It is possible that capillary structure as well as perfusion rate also affects distribution rate when smaller molecular weight drugs that are not protein bound are administered. In any event, it is often clinically helpful to picture a three-compartment model in which a drug distributes from plasma to its site of action, the pharmacokinetic biophase, and then to more slowly equilibrating tissues, such as skeletal muscle, where the drug has no pharmacologic activity.

Intercompartmental Clearance

Compartmental systems used to describe the kinetics of drug distribution usually incorporate first-order transfer rates between compartments (6, 7, 105). It has been emphasized recently that intercompartmental clearances are preferable since they provide a volume-independent estimate of the rate of drug distribution (116). Few rigorously controlled studies have been made of the distribution kinetics of closely related drugs, based on a comparison of intercompartmental clearances and distribution volumes (117). However, intercompartmental clearance has been found to limit the elimination of amphotericin B from the body after long-term therapy (114) and to restrict the effectiveness of hemoperfusion in removing digoxin from dogs (118). Thus drug elimination may be affected by intercompartmental clearance as well as distribution volume.

Kinetics of Pharmacologic Response

Relatively few attempts have been made to correlate the kinetics of drug distribution with the time course of pharmacologic response (119). This can be done to identify the pharmacokinetic biophase for reversibly acting drugs. Levy and his colleagues first demonstrated this approach by correlating impaired arithmetic test performance with lysergide content in the slowly equilibrating compartment of a three-compartment model (120). It has also been shown that the inotropic effects of digoxin correlate better with estimated tissue concentrations than with plasma levels (17), and it seems likely that this will also apply to antiarrhythmic drugs (121, 122).

When pharmacologic response is characterized by quantal effects, therapeutic and toxic threshold concentrations can be defined. However, responses are often graded in intensity and various nonlinear functions have

been used empirically to relate drug concentration to effect (119). One equation proposed by Wagner (123) is

$$R = R_{max}C^s/(1/Q + C^s), \quad 59.$$

where R is the intensity of pharmacologic response, and Q and s are parameters related to the concentration that corresponds to a 50% response, EC_{50},

$$EC_{50} = Q^{-1/s}. \quad 60.$$

Meffin and his colleagues have used this approach to describe plasma concentration-response relationships for the antiarrhythmic drug, tocainide, under steady state conditions (124). Under non-steady state conditions it should be possible to define biophase concentration-response relationships as well. Clinical study of concentration-response relationships should prove useful in enabling drugs with similar therapeutic effects to be characterized systematically in terms of efficacy and potency. If data are determined for toxic as well as therapeutic effects, utility functions can be constructed to evaluate rigorously the benefits and risks of a given therapeutic regimen (125).

Concentration-response studies should also provide fundamental information on the contribution of individual variation in receptor sensitivity to observed variation in pharmacologic response. The antagonism of isoproterenol tachycardia by propranolol has been studied to estimate in man the binding affinity of propranolol for its receptor (126). In this study the binding affinity constant, K_A, was calculated from the relationship,

$$K_A = (DR - 1)/(fc), \quad 61.$$

where DR is the dose ratio calculated as the isoproterenol dose required to increase resting heart rate by 25 beats per minute (I_{25}) in the presence of propranolol, divided by the control I_{25}.

The quantitative analysis of pharmacological response possibly provides the greatest challenge in clinical pharmacokinetics at this time, since the successful application of measured or predicted plasma concentration data to patient care hinges on the elucidation of concentration-response relationships.

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Literature Cited

1. Wuth, O. 1927. Rational bromide treatment: New methods for its control. *J. Am. Med. Assoc.* 88:2013–17
2. Drayer, D. E. 1976. Pharmacologically active drug metabolites: Therapeutic and toxic activities, plasma and urine data in man, accumulation in renal failure. *Clin. Pharmacokinet.* 1:426–43
3. Atkinson, A. J. Jr., Strong, J. M. 1977. Effect of active drug metabolites on plasma level-response correlations. *J. Pharmacokinet. Biopharm.* 5:95–109
4. Dost, F. H. 1953. *Der Blutspiegel: Kinetic der Konzentrationsablaufe in der Krieslaufflussigkeit,* p. 244. Leipzig, E. Germany: Thieme. 362 pp.
5. Widmark, E. M. P. 1919. Studies in the concentration of indifferent narcotics in blood and tissues. *Acta Med. Scand.* 52:87–164
6. Teorell, T. 1937. Kinetics of distribution of substances administered to the body: I. The extravascular modes of administration. *Arch. Int. Pharmacodyn.* 57:205–25
7. Teorell, T. 1937. Kinetics of distribution of substances administered to the body. II. The intravascular modes of administration, *Arch. Int. Pharmacodyn.* 57:226–40
8. Gibaldi, M., Perrier, D. 1975. *Pharmacokinetics.* New York: Dekker. 329 pp.
9. Wagner, J. G. 1975. *Fundamentals of Clinical Pharmacokinetics.* Hamilton, Ill: Drug Intelligence. 461 pp.
10. Melmon, K. L., Morelli, H. F., eds. 1978. *Clinical Pharmacology: Basic Principles in Therapeutics.* New York: Macmillan. 1146 pp. 2nd ed.
11. Teorell, T., Dedrick, R. L., Condliffe, P. G., eds. 1974. *Pharmacology and Pharmacokinetics.* New York: Plenum. 388 pp.
12. Benet, L. Z., ed. 1976. *The Effect of Disease States on Drug Pharmacokinetics.* Washington, DC: Am. Pharm. Assoc. Acad. Pharm. Sci. 252 pp.
13. Ritschel, W. A., ed. 1977. *Clinical Pharmacokinetics.* Stuttgart: Gustav Fischer. 211 pp.
14. Wagner, J. G., Northam, J. I. 1967. Estimation of volume of distribution and half-life of a compound after rapid intravenous injection. *J. Pharm. Sci.* 56:529–31
15. Atkinson, A. J. Jr., Krumlovsky, F. A., Huang, C. M., del Greco, F. 1976. Hemodialysis for severe procainamide toxicity: Clinical and pharmacokinetic observations. *Clin. Pharmacol. Ther.* 20:585–92
16. Brooker, G., Jelliffe, R. W. 1972. Serum cardiac glycoside assay based upon displacement of ^{3}H-ouabain from Na-K ATPase. *Circulation* 45:20–36
17. Reuning, R. H., Sams, R. A., Notari, R. E. 1973. Role of pharmacokinetics in drug dosage adjustment. 1. Pharmacologic effect kinetics and apparent volume of distribution of digoxin. *J. Clin. Pharmacol.* 13:127–41
18. Doherty, J. E., Perkins, W. H., Flanigan, W. J. 1967. The distribution and concentration of tritiated digoxin in human tissues. *Ann. Intern. Med.* 66:116–24
19. Bloom, P. M., Nelp, W. B. 1966. Relationship of the excretion of tritiated digoxin to renal function. *Am. J. Med. Sci.* 251:133–44
20. Chamberlain, D. A., White, R. J., Howard, M. R., Smith, T. W. 1970. Plasma digoxin concentrations in patients with atrial fibrillation. *Br. Med. J.* 3:429–32
21. Jelliffe, R. W., Brooker, G. 1974. A nomogram for digoxin therapy. *Am. J. Med.* 57:63–68
22. Marcus, F. I., Burkhalter, L., Cuccia, C., Pavlovich, J., Kapadia, G. G. 1966. Administration of tritiated digoxin with and without a loading dose: A metabolic study. *Circulation* 34:865–74
23. Smith, H. W. 1937. *The Physiology of the Kidney,* p. 52. New York: Oxford Univ. Press. 310 pp.
24. Dost, F. H. 1949. Die clearance. *Klin. Wochenschr.* 27:257–64
25. Wagner, J. G. 1967. Equations for excretion rate and renal clearances of exogenous substances not actively reabsorbed. *J. Clin. Pharmacol.* 7:89–92
26. Dettli, L. 1974. Individualization of drug dosage in patients with renal disease. *Med. Clin. N. Am.* 58:977–85
27. Nagashima, R., Levy, G. 1968. Effect of perusion rate and distribution factors on drug elimination kinetics in a perfused organ system. *J. Pharm. Sci.* 57:1991–93
28. Winkler, K., Keiding, S., Tygstrup, N. 1973. Clearance as a quantitative measure of liver function. In *The Liver: Quantitative Aspects of Structure and Function.* ed. G. Paumgartner, R. Preisig, pp. 144–55. Basel: Karger 427 pp.
29. Rowland, M., Benet, L. Z., Graham, G. G. 1973. Clearance concepts in pharmacokinetics. *J. Pharmacokinet. Biopharm.* 1:123–36

30. Pang, K. S., Rowland, M. 1977. Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma and blood cell binding, and hepatocellular enzymatic activity on hepatic drug clearance. *J. Pharmacokinet. Biopharm.* 5:625–53
31. Wilkinson, G. R., Shand, D. G. 1975. A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.* 18:377–90
32. Pang, K. S., Rowland, M. 1977. Hepatic clearance of drugs. II. Experimental evidence for acceptance of the "well-stirred" model over the "parallel tube" model using lidocaine in the perfused rat liver *in situ* preparation. *J. Pharmacokinet. Biopharm.* 5:655–80
33. Pang, K. S., Rowland, M. 1977. Hepatic clearance of drugs. III. Additional experimental evidence supporting the "well-stirred" model, using metabolite (MEGX) generated from lidocaine under varying hepatic blood flow rates and linear conditions in the perfused rat liver *in situ* preparation. *J. Pharmacokinet. Biopharm.* 5:681–99
34. Rowland, M., Blaschke, T. F., Meffin, P. J., Williams, R. L. 1976. Pharmacokinetics in disease states modifying hepatic and metabolic function. See Ref. 12, pp. 53–86
35. Gillette, J. R. 1971. Factors affecting drug metabolism. *Ann. NY Acad. Sci.* 179:43–66
36. Pang, K. S., Rowland, M., Tozer, T. N. 1978. *In vivo* evaluation of Michaelis-Menten constants of hepatic drug-eliminating systems. *Drug Metab. Dispos.* 6:197–200
37. Wagner, J. G., Patel, J. A. 1972. Variations in absorption and elimination rates of ethyl alcohol in a single subject. *Res. Commun. Chem. Pathol. Pharmacol.* 4:61–76
38. Gerber, N., Wagner, J. G. 1972. Explanation of dose-dependent decline of diphenylhydantoin plasma levels by fitting to the integrated form of the Michaelis-Menten equation. *Res. Commun. Chem. Pathol. Pharmacol.* 3: 455–66
39. Atkinson, A. J. Jr., Shaw, J. M. 1973. Pharmacokinetic study of a patient with diphenylhydantoin toxicity. *Clin. Pharmacol. Ther.* 14:521–28
40. Tsuchiya, T., Levy, G. 1972. Relationship between dose and plateau levels of drugs eliminated by parallel first-order and capacity-limited kinetics. *J. Pharm. Sci.* 61:541–44
41. Mitchell, J. R., Jollow, D. J. 1975. Metabolic activation of drugs to toxic substances. *Gastroenterology* 68:392–410
42. Matin, S. B., Rowland, M. 1973. Kinetics of drug-drug interactions. *J. Pharmacokinet. Biopharm.* 1:553–67
43. Reidenberg, M. M. 1971. *Renal Function and Drug Action.* Philadelphia: Saunders. 113 pp.
44. Welling, P. G., Craig, W. A. 1976. Pharmacokinetics in disease states modifying renal function. See Ref. 12, pp. 155–87
45. Levy, G. 1977. Pharmacokinetics in renal disease. *Am. J. Med.* 62:461–65
46. Dettli, L. 1976. Drug dosage in renal disease. *Clin. Pharmacokinet.* 1:126–34
47. Bennett, W. M., Singer, I., Golper, T., Feig, P., Coggins, C. J. 1977. Guidelines for drug therapy in renal failure. *Ann. Intern. Med.* 86:754–83
48. Welling, P. G., Craig, W. A., Kunin, C. M. 1975. Prediction of drug dosage in patients with renal failure using data derived from normal subjects. *Clin. Pharmacol. Ther.* 18:45–52
49. Pagliaro, L. A., Benet, L. Z. 1975. Critical compilation of terminal half-lives, percent excreted unchanged, and changes of half-life in renal and hepatic dysfunction for studies in humans with references. *J. Pharmacokinet. Biopharm.* 3:333–83
50. Reidenberg, M. M. 1977. The biotransformation of drugs in renal failure. *Am. J. Med.* 62:482–85
51. Gibson, T. P., Atkinson, A. J. Jr., Matusik, E., Nelson, L. D., Briggs, W. A. 1977. Kinetics of procainamide and N-acetylprocainamide in renal failure. *Kidney Int.* 12:422–29
52. Odar-Cederlöf, I., Borgå, O. 1974. Kinetics of diphenylhydantoin in uraemic patients: Consequences of decreased plasma protein binding. *Eur. J. Clin. Pharmacol.* 7:31–37
53. Branch, R. A., Shand, D. G. 1976. Hepatic drug clearance in chronic liver disease. See Ref. 12, pp. 77–86
54. Wilkinson, G. R., Schenker, S. 1976. Effects of liver disease on drug disposition in man. *Biochem. Pharmacol.* 25:2675–81
55. Hutterer, F., Klion, F. M., Wengraf, A., Schaffner, F., Popper, H. 1969. Hepatocellular adaptation and injury: Structural and biochemical changes following dieldrin and methyl butter yellow. *Lab. Invest.* 20:455–64

56. Levi, A. J., Sherlock, S., Walker, D. 1968. Phenylbutazone and isoniazid metabolism in patients with liver disease in relation to previous drug therapy. *Lancet* 1:1275–79
57. Remmer, H. 1970. The role of the liver in drug metabolism. *Am. J. Med.* 49:617–29
58. Schoene, B., Fleischmann, R. A., Remmer, H., Oldershausen, H. F. 1972. Determination of drug metabolizing enzymes in needle biopsies of human liver. *Eur. J. Clin. Pharmacol.* 4:65–73
59. Richey, D. P., Bender, A. D. 1977. Pharmacokinetic consequences of aging. *Ann. Rev. Pharmacol. Toxicol.* 17:49–65
60. Kalow, W. 1962. *Pharmacogenetics: Heredity and the Response to Drugs.* Philadelphia: Saunders. 231 pp.
61. Vesell, E. S. 1973. Advances in pharmacogenetics. In *Prog. Med. Genet.* 9:291–367
62. Univ. Mont. Found. 1977. Environmental Chemicals and Nutrition: Relationship to Metabolism, Action and Toxicity of Drugs. Proceedings of the Fourth Deer Lodge Conference on Clinical Pharmacology. *Clin. Pharmacol. Ther.* 22:623–824
63. Jusko, W. J., Schentag, J. J., Koup, J. R. 1976. *Surveillance of Factors Affecting Theophylline Body Clearances.* Presented at Ann. Meet. Am. Pharm. Assoc., New Orleans
64. Wilkinson, G. R. 1976. Pharmacokinetics in disease states modifying body perfusion. See Ref. 12, pp. 13–32
65. Stenson, R. E., Constantino, R. T., Harrison, D. C. 1971. Interrelationships of hepatic blood flow, cardiac output and blood levels of lidocaine in man. *Circulation* 43:205–11
66. Thomson, P. D., Rowland, M., Melmon, K. L. 1971. The influence of heart failure, liver disease and renal failure on the disposition of lidocaine in man. *Am. Heart J.* 82:417–21
67. Thomson, P. D., Melmon, K. L., Richardson, J. A., Cohn, K., Steinbrunn, W., Cudihee, R., Rowland, M. 1973. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. *Ann. Intern. Med.* 78:499–508
68. Odar-Cederlöf, I., Lunde, P., Sjöqvist, F. 1970. Abnormal pharmacokinetics of phenytoin in a patient with uraemia. *Lancet* 2:831–32
69. Gugler, R., Shoeman, D. W., Huffman, D. H., Cohlmia, J. B., Azarnoff, D. L. 1975. Pharmacokinetics of drugs in patients with the nephrotic syndrome. *J. Clin. Invest.* 55:1182–89
70. Booker, H. E., Darcey, B. 1973. Serum concentrations of free diphenylhydantoin and their relationship to clinical intoxication. *Epilepsia* 14:177–84
71. Goldstein, A., Aronow, L., Kalman, S. M. 1974. *Principles of Drug Action: The Basis of Pharmacology,* pp. 311–38. New York: Wiley. 854 pp. 2nd ed.
72. Gaddum, J. H. 1944. Repeated doses of drugs. *Nature* 153:494
73. Gibaldi, M., Perrier, D. 1975. See Ref. 8, pp. 105–6
74. Wagner, J. G., Northam, J. I., Alway, C. D., Carpenter, O. S. 1965. Blood levels of drug at the equilibrium state after multiple dosing. *Nature* 207:1301–2
75. Wilensky, A. J., Lowden, J. A. 1973. Inadequate serum levels after intramuscular administration of diphenylhydantoin. *Neurology* 23:318–24
76. Dittert, L. W., Cressman, W. A., Kaplan, S. A., Riegelman, S., Wagner, J. G. 1972. *Guidelines for Biopharmaceutical Studies in Man,* p. 17. Washington, DC: Am. Pharm. Assoc. Acad. Pharm. Sci. 33 pp.
77. Levine, R. R. 1970. Factors affecting gastrointestinal absorption of drugs. *Digest Dis.* 15:171–88
78. Prescott, L. F. 1974. Gastrointestinal absorption of drugs. *Med. Clin. N. Am.* 58:907–16
79. Nimmo, W. S. 1976. Drugs, diseases and altered gastric emptying. *Clin. Pharmacokinet.* 1:189–203
80. Wagner, J. G. 1961. Biopharmaceutics: Absorption aspects. *J. Pharm. Sci.* 50:359–87
81. Rescigno, A., Segre, G. 1966. *Drug and Tracer Kinetics,* pp. 102–10. Waltham, Mass: Blaisdell. 209 pp.
82. Benet, L. Z., Chiang, C.-W. 1972. The use and application of deconvolution methods in pharmaceutics. *Abstr. 13th Natl. Meet. Am. Pharm. Assoc. Acad. Pharm. Sci.,* Chicago & Washington, DC 2:169–71
83. Loo, J. C. K., Riegelman, S. 1968. New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* 57:918–28
84. Goldstein, A., Aronow, L., Kalman, S. M. 1974. See Ref. 71, pp. 335–36
85. Wagner, J. G., Nelson, E. 1963. Per cent absorbed time plots derived from blood level and/or urinary excretion data. *J. Pharm. Sci.* 52:610–11
86. Nelson, E. 1961. Kinetics of drug absorption, distribution, metabolism, and excretion. *J. Pharm. Sci.* 50:181–92

87. Berman, M., Weiss, M. F. 1967. *SAAM Manual.* Washington DC: GPO (PHS Publ. No. 1703)
88. Metzler, C. M. 1969. *NONLIN: A Computer Program for Parameter Estimation in Nonlinear Situations. Tech. Rep. No. 7292/69/7292/005.* Kalamazoo, Mich: Upjohn Co.
89. Strong, J. M., Dutcher, J. S., Lee, W.-K., Atkinson, A. J. Jr. 1975. Absolute bioavailability in man of N-acetylprocainamide determined by a novel stable isotope method. *Clin. Pharmacol. Ther.* 18:613–22
90. Koch-Weser, J. 1974. Bioavailability of drugs. *N. Engl. J. Med.* 291:233–37, 503–6
91. Gibaldi, M., Boyes, R. N., Feldman, S. 1971. Influence of first-pass effect on availability of drugs on oral administration. *J. Pharm. Sci.* 60:1338–40
92. Rowland, M. 1972. Influence of route of administration on drug availability. *J. Pharm. Sci.* 61:70–74
93. Shand, D. G., Kornhauser, D. M., Wilkinson, G. R. 1975. Effects of route of administration and blood flow on hepatic drug elimination. *J. Pharmacol Exp. Ther.* 195:424–32
94. Kornhauser, D. M., Wood, A. J. J., Vestal, R. E., Wilkinson, G. R., Branch, R. A., Shand, D. G. 1978. Biological determinants of propranolol disposition in man. *Clin. Pharmacol. Ther.* 23: 165–74
95. Huang, C. M., Atkinson, A. J. Jr., Levin, M., Levin, N. W., Quintanilla, A. 1974. Pharmacokinetics of furosemide in advanced renal failure. *Clin. Pharmacol. Ther.* 16:659–66
96. Welling, P. G., Craig, W. A., Amidon, G. L., Kunin, C. M. 1973. Pharmacokinetics of trimethoprim and sulfamethoxazole in normal subjects and in patients with renal failure. *J. Infect. Dis.* 128:S556–66
97. Lowenthal, D. T., Briggs, W. A., Gibson, T. P., Nelson, H., Cirksena, W. J. 1974. Pharmacokinetics of oral propranolol in chronic renal disease. *Clin. Pharmacol. Ther.* 16:761–69
98. Bianchetti, G., Graziani, G., Brancaccio, D., Morganti, A., Leonetti, G., Manfrin, M., Sega, R., Gomeni, R., Ponticelli, C., Morselli, P. L. 1976. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin. Pharmacokinet.* 1:373–84
99. Benet, L. Z., Greither, A., Meister, W. 1976. Gastrointestinal absorption of drugs in patients with cardiac failure. See Ref. 12, pp. 33–50
100. Crouthamel, W. G., Diamond, L., Dittert, L. W., Doluisio, J. T. 1975. Drug absorption. VII. Influence of mesenteric blood flow on intestinal drug absorption in dogs. *J. Pharm. Sci.* 64:664–70
101. Higgins, C. B., Vatner, S. F., Franklin, D., Braunwald, E. 1974. Pattern of differential vasoconstriction in response to acute and chronic low-output states in the conscious dog. *Cardiovasc. Res.* 8:92–98
102. Shand, D. G., Rangno, R. E. 1972. The disposition of propranolol. I. Elimination during oral absorption in man. *Pharmacology* 7:159–68
103. Gugler, R., Lain, P., Azarnoff, D. L. 1975. Effect of portacaval shunt on the disposition of drugs with and without first-pass effect. *J. Pharmacol. Exp. Ther.* 195:416–23
104. Riegelman, S., Loo, J. C. K., Rowland, M. 1968. Shortcomings in pharmacokinetic analysis by conceiving the body to exhibit properties of a single compartment. *J. Pharm. Sci.* 57:117–23
105. Rescigno, A., Segre, G. 1966. See Ref. 81, pp. 24–128
106. Price, H. L., Kovnat, P. J., Safer, J. N., Conner, E. H., Price, M. L. 1960. The uptake of thiopental by body tissues and its relation to the duration of narcosis. *Clin. Pharmacol. Ther.* 1:16–22
107. Bischoff, K. B., Dedrick, R. L. 1968. Thiopental pharmacokinetics. *J. Pharm. Sci.* 57:1346–51
108. Benowitz, N., Forsyth, R. P., Melmon, K. L., Rowland, M. 1974. Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. *Clin. Pharmacol. Ther.* 16: 87–98
109. Apter, J. T. 1965. Models and mathematics: Tools of the mathematical biologist. *J. Am. Med. Assoc.* 194: 269–72
110. Benowitz, N., Forsyth, R. P., Melmon, K. L., Rowland, M. 1974. Lidocaine disposition kinetics in monkey and man. II. Effects of hemorrhage and sympathomimetic drug administration. *Clin. Pharmacol. Ther.* 16:99–109
111. Jusko, W. J., Gretch, M. 1976. Plasma and tissue protein binding of drugs in pharmacokinetics. *Drug. Metab. Rev.* 5:43–140
112. Jusko, W. J. 1976. Pharmacokinetics in disease states changing protein binding. See Ref. 12, pp. 99–123
113. Larsen, P. R., Atkinson, A. J. Jr., Wellman, H. N., Goldsmith, R. E. 1970. The

effect of diphenylhydantoin on thyroxine metabolism in man. *J. Clin. Invest.* 49:1266–79

114. Atkinson, A. J. Jr., Bennett, J. E. 1978. Amphotericin B pharmacokinetics in humans. *Antimicrob. Agents Chemother.* 13:271–76
115. Courtice, F. C. 1971. Lymph and plasma proteins: Barriers to their movement throughout the extracellular fluid. *Lymphology* 4:9–17
116. Perrier, D., Gibaldi, M. 1974. Clearance and biologic half-life as indices of intrinsic hepatic metabolism. *J. Pharmacol. Exp. Ther.* 191:17–24
117. Dutcher, J. S., Strong, J. M., Lucas, S. V., Lee, W.-K., Atkinson, A. J. Jr. 1977. Procainamide and N-acetylprocainamide kinetics investigated simultaneously with stable isotope methodology. *Clin. Pharmacol. Ther.* 22: 447–57
118. Gibson, T. P., Atkinson, A. J. Jr. 1978. Effect of changes in intercompartmental rate constants on drug removal during hemoperfusion. *J. Pharm. Sci.* 67: 1178–79
119. Wagner, J. G. 1975. Relationships between drug concentration and response and kinetics of pharmacological response. See Ref. 9, pp. 307–35
120. Levy, G., Gibaldi, M., Jusko, W. J. 1969. Multicompartment pharmacokinetic models and pharmacologic effects. *J. Pharm. Sci.* 58:422–24
121. Giardina, E.-G., Bigger, J. T. Jr. 1973. Procaine amide against re-entrant ventricular arrhythmias: Lengthening R-V intervals of coupled premature depolarizations as an insight into the mechanism of action of procaine amide. *Circulation* 48:959–70
122. Galeazzi, R. L., Benet, L. Z., Sheiner, L. B. 1976. Relationship between the pharmacokinetics and pharmacodynamics of procainamide. *Clin. Pharmacol. Ther.* 20:278–89
123. Wagner, J. G. 1968. Kinetics of pharmacologic response. I. Proposed relationships between response and drug concentration in the intact animal and man. *J. Theor. Biol.* 20:173–201
124. Meffin, P. J., Winkle, R. A., Blaschke, T. F., Fitzgerald, J., Harrison, D. C. 1977. Response optimization of drug dosage: Antiarrhythmic studies with tocainide. *Clin. Pharmacol. Ther.* 22: 42–57
125. Sheiner, L. B., Tozer, T. N. 1978. Clinical pharmacokinetics: The use of plasma concentrations of drugs. See Ref. 10, pp. 71–109
126. McDevitt, D. G., Frisk-Holmberg, M., Hollifield, J. W., Shand, D. G. 1976. Plasma binding and the affinity of propranolol for a beta receptor in man. *Clin. Pharmacol. Ther.* 20:152–57