CLINICAL PHARMACOKINETICS

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Pharmacokinetics is an important tool that is used in the conduct of both basic and applied research, and is an essential component of the drug development process. In addition, pharmacokinetics is a valuable adjunctfor prescribing and evaluating drug therapy. For most clinical applications, pharmacokinetic analyses can be simplified by representing drug distribution within the body by a *single compartment* in which drug concentrations are uniform (1). Clinical applications of pharmacokinetics usually entails relatively simple calculations, carried out in the context of what has been termed *the target concentration strategy*. We shall begin by discussing this strategy.

The Target Concentration Strategy :

The rationale for measuring concentrations of drugs in plasma, serum or blood is that *concentration-response* relationships are often less variable than *dose-response* relationships (2). This is true because individual variation in the processes of drug absorption, distribution and elimination affects doseresponse relationships, but not the relationship between free (non-protein bound) drug concentration in plasma water and intensity of effect (Figure 1).

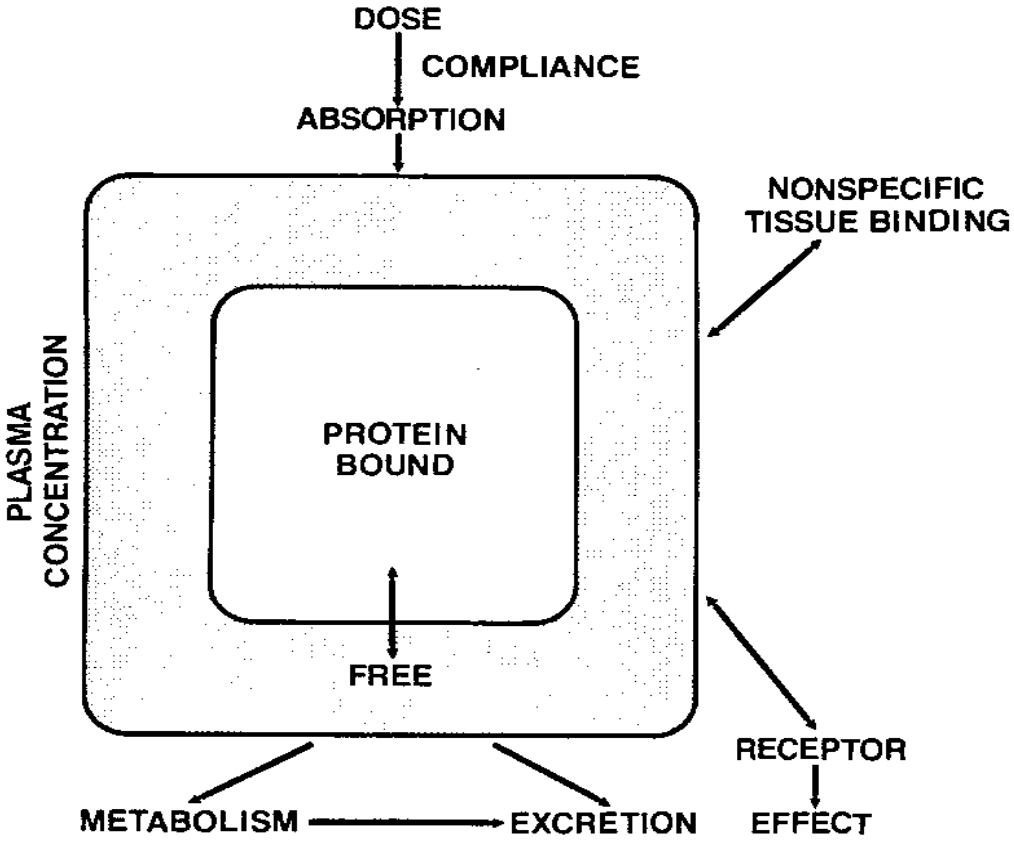
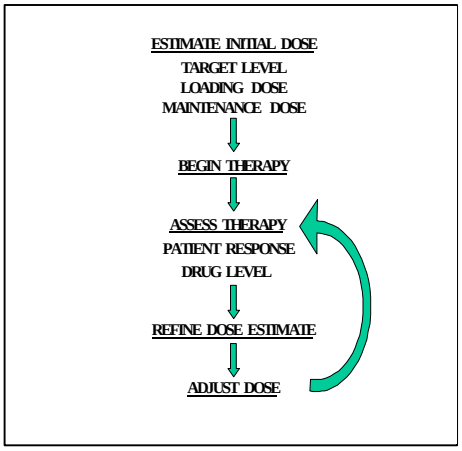


Figure 1: Diagram of factors that account for variability in observed effects when standard drug doses are prescribed. Some of this variability can be taken into account by using plasma concentration measurements to guide dose adjustments.

Because most adverse drug reactions are dose related, therapeutic drug monitoring has been advocated as a means of improving therapeutic efficacy and reducing drug toxicity (3). Drug level monitoring is most useful when combined with pharmacokinetic-based dose selection in an integrated management plan as outlined at the right. This approach to drug dosing has been termed the *target concentration strategy*.



The rationale of therapeutic drug monitoring was first elucidated over 70 years ago when Otto Wuth recommended monitoring bromide levels in patients treated with this drug (4). More widespread clinical application of the target concentration strategy has been possible only because major advances have been made over the past 30 years in developing analytical methods capable of routinely measuring drug concentrations in patient serum, plasma or blood samples, and because of increased understanding of basic pharmacokinetic principles (5). However, given the advanced state of modern chemical and immunochemical analytical methods, the greatest current challenge is the establishment of the range of drug concentrations in blood, plasma or serum that correlate reliably with therapeutic efficacy or toxicity. This challenge is exemplified by the results shown in Figure 2 that are taken from the attempt by Smith and Haber (6) to correlate serum digoxin levels with clinical manifestations of toxicity. It can be seen that no patient with digoxin levels below 1.6 ng/mL was toxic and that all patients with digoxin levels above 3.0 ng/mL had evidence of digoxin intoxication. However, there is a large intermediate range between 1.6 and 3.0 ng/mL in which patients could be either nontoxic or toxic. Additional clinical information is often necessary to interpret drug concentration measurements that are otherwise equivocal. In this study, it was found that all toxic patients with serum digoxin levels less than 2.0 ng/mL had coexisting coronary heart disease, a condition known to predispose the myocardium to the toxic effects of this drug. Conversely, 4 of the 10 nontoxic patients with levels above 2.0 ng/mL were being treated with antiarrhythmic drugs that might have suppressed electrocardiographic evidence of digoxin toxicity.

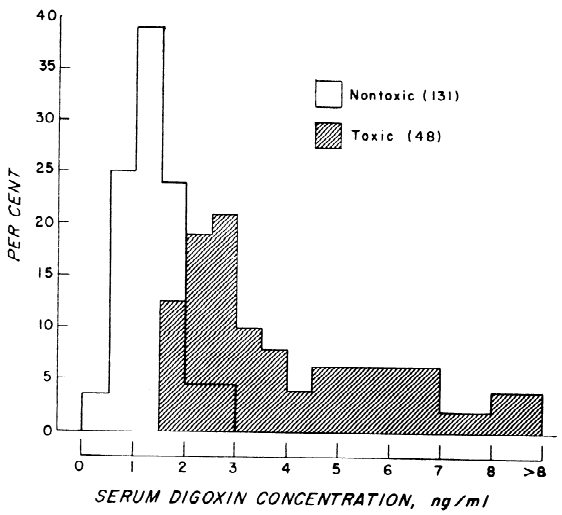


Figure 2: Superimposed frequency histograms in which serum digoxin concentrations are shown for 131 patients without digoxin toxicity and 48 patients with electrocardiographic evidence of digoxin toxicity (6).

In the final analysis the digoxin level that is therapeutic for a given patient depends on the extent to which ventricular rate needs to be slowed in patients with atrial fibrillation or on the amount of additional inotropy that is needed to compensate for congestive heart failure. Since an initial maintenance dose of 0.25 mg/day is usually prescribed for

patients with apparently normal renal function, this corresponds to a target level of 1.4 ng/mL. Accordingly, laboratory reports of digoxin concentration measurements are commonly accompanied by guidelines such as the following:

Usual therapeutic range:	0.8 – 1.6 ng/mL
Possibly toxic levels	1.6 – 3.0 ng/mL
Probably toxic levels	> 3.0 ng/mL

However, Lee and Smith (7) have reviewed clinical conditions that may affect patient response to a given digoxin level and emphasize quite properly that digoxin concentration measurements should not be the sole criterion that is used in clinical decision making.

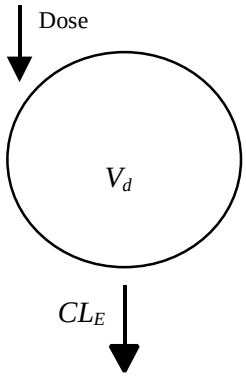
Despite the ambiguity in interpreting digoxin level results, it was demonstrated in a controlled study that routine availability of digoxin concentration measurements markedly reduced the incidence of toxic reactions to this drug (8). Unfortunately, controlled studies documenting the clinical benefit of plasma level monitoring are limited. In addition, one could not justify monitoring plasma levels of all prescribed drugs even if this technical challenge could be met. Thus plasma level monitoring is most helpful for drugs that have a low therapeutic index and that have no clinically observable effects that can be easily monitored to guide dose adjustment. Generally accepted indications for measuring plasma concentrations of these drugs are:

1. To evaluate concentration-related toxicity
   - Unexpectedly slow drug elimination
   - Accidental or purposeful overdose
   - Surreptitious drug taking
   - Dispensing errors
2. To evaluate lack of therapeutic efficacy
   - Patient adherence to prescribed therapy
   - Poor drug absorption
   - Unexpectedly rapid drug elimination
3. To ensure that the dose regimen is likely to provide effective prophylaxis
4. To use pharmacokinetic principles to guide dose adjustment

Despite these technical advances, adverse reactions still occur frequently with digoxin, phenytoin and many other drugs for which plasma level measurements are routinely available. The persistence in contemporary practice of dose-related toxicity with these drugs most likely reflects inadequate understanding of basic pharmacokinetic principles. This is illustrated by the following case history (5):

> In October, 1981, a 39 year-old man with mitral stenosis was hospitalized for mitral valve replacement. He had a history of chronic renal failure resulting from interstitial nephritis and was maintained on hemodialysis. His mitral valve was replaced with a prosthesis and digoxin therapy was initiated postoperatively in a dose of 0.25 mg/day. Two weeks later, he was noted to be unusually restless in the evening. The following day, he died shortly after he received his morning digoxin dose. Blood was obtained during an unsuccessful resuscitation attempt, and the measured plasma digoxin concentration was 6.9 ng/mL.

Concepts Underlying Clinical Pharmacokinetics:



Pharmacokinetics provides the scientific basis of dose selection, and the process of dose regimen design can be used to illustrate with a single-compartment model the basic concepts of *apparent distribution volume* (V_d), *elimination half-life* ($t_{½}$), and *elimination clearance* (CL_E). A schematic diagram of this model is shown at the right along with the two primary pharmacokinetic parameters of distribution volume and elimination clearance that characterize it.

Initiation of Drug Therapy (concept of apparent distribution volume):

Sometimes drug treatment is begun with a loading dose to produce a rapid therapeutic response. Thus, a patient with atrial fibrillation might be given a 0.75 mg intravenous loading dose of digoxin as initial therapy to control ventricular rate. The expected plasma concentrations of digoxin are shown in Figure 3.

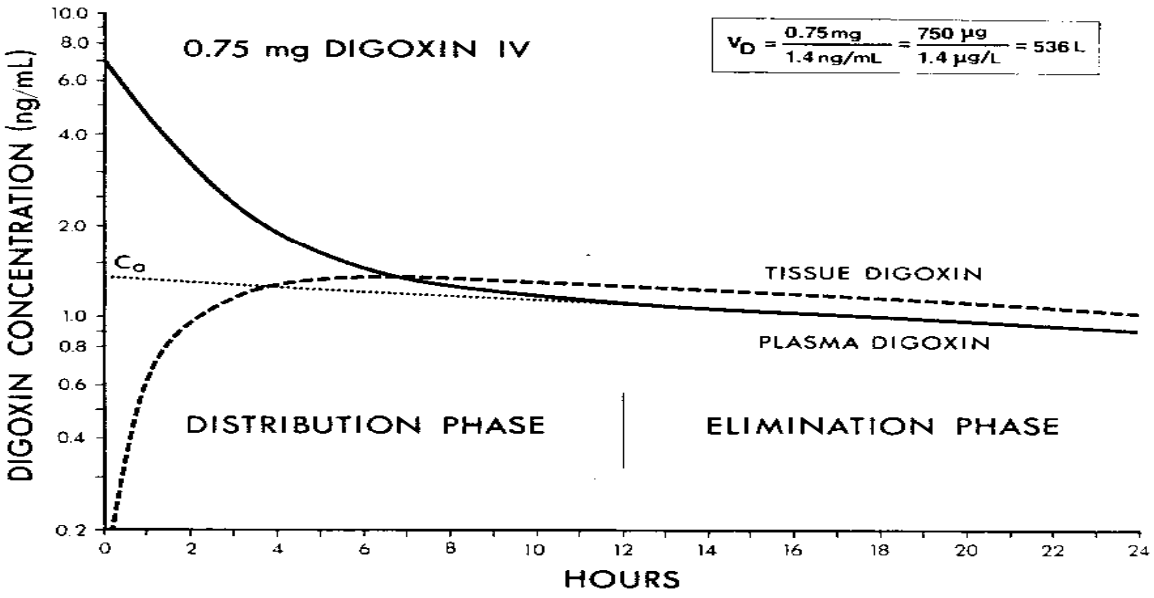


Figure 3: Simulation of plasma (solid line) and tissue (broken line) digoxin concentrations after intravenous administration of a 0.75 mg loading dose to a 70 Kg patient with normal renal function. C_0 is estimated by back extrapolation (dotted line) of elimination-phase plasma concentrations. V_d is calculated by dividing the administered drug dose by this estimate of C_0, as shown. Tissue concentrations are referenced to the apparent distribution volume

Inspection of this figure indicates that the log plasma concentration vs. time curve eventually becomes a straight line. This part of the curve is termed the *elimination phase*. By extrapolating this elimination-phase line back to time zero, we can estimate the plasma concentration (C_0) that would have occurred if the loading dose were instantaneously distributed throughout the body. Measured plasma digoxin concentrations lie above the

back extrapolated line for several hours because distribution equilibrium actually is reached only slowly after a digoxin dose is administered. This part of the plasma level-vs.-time curve is termed the *distribution phase*. This phase reflects the underlying *multicompartmental* nature of digoxin distribution from the intravascular space to peripheral tissues.

As shown in Figure 3, the back-extrapolated estimate of C_0 can be used to calculate the apparent volume ($V_{d\ (extrap.)}$) of a hypothetical single compartment into which digoxin distribution occurs:

$$V_{d\ (extrap.)} = \text{Loading Dose} \,/\, C_0 \qquad \text{Equation 1}$$

In this case, the apparent distribution volume of 536 L is much larger than anatomically possible. This apparent anomaly occurs because digoxin has a much higher binding affinity for tissues than for plasma, and the apparent distribution volume is the volume of *plasma* that would be required to provide the observed dilution of the loading dose. Despite this apparent anomaly, the concept of distribution volume is clinically useful because it defines the relationship between plasma concentration and the total amount of drug in the body. Further complexity arises from the fact that $V_{d\ (extrap.)}$ is only one of three different distribution volume estimates that we shall encounter. Because the distribution process is neglected in calculating this volume, it represents an over estimate of the sum of the individual compartments involved in drug distribution.

Because the time course of the myocardial effects of digoxin parallels the distribution of this drug to peripheral tissues, there is a delay between the attainment of peak plasma digoxin concentrations and the observation of maximum inotropic and chronotropic effects. The range of therapeutic and toxic digoxin concentrations has been derived from observations made during the elimination phase, so blood should not be sampled for digoxin assay until distribution equilibrium is nearly complete. In clinical practice, this means waiting for at least 6 hours after a digoxin dose has been administered. In a recent audit of patients with measured digoxin levels of 3.0 ng/ml or more, it was found that nearly one-third of these were not associated with toxicity but reflected procedural error in that blood was sampled less than 6 hours after digoxin administration (9).

For other drugs, such as thiopental (10) or lidocaine (11), the locus of pharmacologic action (termed the *biophase* in classical pharmacology) is in more rapid kinetic equilibrium with the intravascular space. The distribution phase of these drugs reflects their somewhat slower distribution from intravascular space to pharmacologically inert tissues, such as skeletal muscle, and serves to shorten the duration of their pharmacologic effects when single doses are administered. Plasma levels of these drugs reflect therapeutic and toxic effects throughout the dosing interval and blood can be obtained for drug assay without waiting for the elimination phase to be reached.

Continuation of Drug Therapy (concepts of elimination half-life and clearance):

After starting therapy with a loading dose, it is often necessary to maintain the desired therapeutic effect by administering maintenance drug doses to replace the amount of drug

that has been excreted or metabolized. Fortunately, the elimination of most drugs is a *first-order* process in that the rate of drug elimination is directly proportional to the drug concentration in plasma.

Elimination half-life: It is convenient to characterize the elimination of drugs with first-order elimination rates by their *elimination half-life*, the time required for half an administered drug dose to be eliminated. If drug elimination half-life can be estimated for a patient, it is often practical to continue therapy by administering half the loading dose at an interval of one elimination half-life. In this way, drug elimination can be balanced by drug administration and a steady state maintained from the onset of therapy. Because digoxin has an elimination half-life of 1.6 days in patients with normal renal function, it is inconvenient to administer digoxin at this interval. When renal function is normal, it is customary to initiate maintenance therapy by administering daily digoxin doses equal to 1/3 of the required loading dose.

Another consequence of first-order elimination kinetics is that a constant fraction of total body drug stores will be eliminated in a given time interval. Thus if there is no urgency in establishing a therapeutic effect, the loading dose of digoxin can be omitted and 90% of the eventual steady state drug concentration will be reached after a period of time equal to 3.3 elimination half-lives. This is referred to as the *Plateau Principle.* The classical derivation of this principle is provided later in this chapter but for now brute force will suffice to illustrate this important concept. Suppose that we elect to omit the 0.75 mg digoxin loading dose shown in Figure 3 and simply begin therapy with a 0.25 mg/day maintenance dose. If the patient has normal renal function, we can anticipate that 1/3 of the total amount of digoxin present in the body will be eliminated each day and that 2/3 will remain when the next daily dose is administered. As shown below, the patient will have digoxin body stores of 0.66 mg just after the 5th daily dose (3.3 x 1.6 day half-life = 5.3 days) and this is 88% of the total body stores that would have been provided by a 0.75 mg loading dose.

.25 x 2/3 = .17	Dose #1
+.25	Dose #2
.42 x 2/3 = .28	
+.25	Dose #3
.53 x 2/3 = .36	
+.25	Dose #4
.61 x 2/3 = .41	
+.25	Dose #5
.66 x 2/3 = .44	
+.25	Dose #6
.69 x 2/3 = .46	
+.25	Dose #7
.71	

The solid line in Figure 4 shows ideal matching of digoxin loading and maintenance doses. When the digoxin loading dose (called *digitalizing dose* in clinical practice) is omitted, or when the loading dose and maintenance dose are not matched appropriately, steady state levels are reached only asymptotically. However, the most important concept that this figure demonstrates is that *the eventual steady state level is determined only by*

the maintenance dose, regardless of the size of the loading dose. Selection of an inappropriately high digitalizing dose only subjects patients to an interval of added risk without achieving a permanent increase in the extent of digitalization. Conversely, when a high digitalizing dose is required to control ventricular rate in patients with atrial

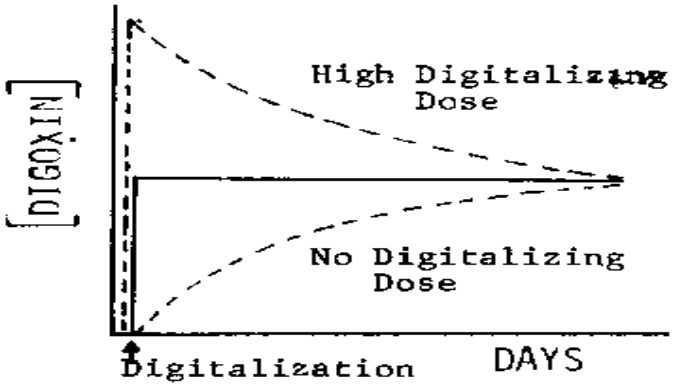


Figure 4: Expected digoxin plasma concentrations after administering perfectly matched loading and maintenance doses (solid line), no initial loading dose (bottom broken line), or a loading dose that is large in relation to the subsequent maintenance dose (upper broken line).

fibrillation or flutter, a higher than usual maintenance dose also will be required.

Elimination clearance: Just as creatinine clearance is used to quantitate the renal excretion of creatinine, the removal of drugs eliminated by first-order kinetics can be defined by an *elimination clearance* (CL_E). In fact, elimination clearance is the primary pharmacokinetic parameter that characterizes the removal of drugs that are eliminated by first-order kinetics. At steady state, the average concentration of drug in the body (C_{ss}) can be calculated from the following equation, where the drug dosing rate is given by I:

$$C_{ss} = I / CL_E \qquad \text{Equation 2}$$

Since there is a directly proportionate relationship between administered drug dose and steady state plasma level, this equation provides a straightforward guide to dose adjustment for drugs that are eliminated by first-order kinetics. Thus, to double the plasma level, the dose simply should be doubled. Conversely, to halve the plasma level, the dose should be halved. It is for this reason that Equation 2 is the most clinically important pharmacokinetic equation. Note that, as is apparent from Figure 4, this equation also stipulates that the steady state level is determined only by the maintenance dose and elimination clearance. The loading dose does not appear in the equation and does not influence the eventual steady state level.

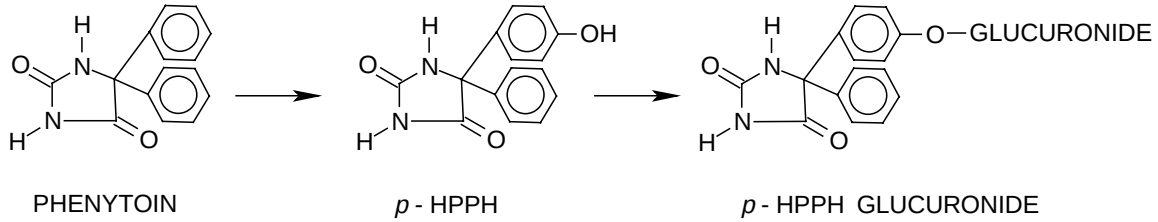
In contrast to elimination clearance, elimination half-life ($t_{½}$) is not a primary pharmacokinetic parameter because it is determined by distribution volume as well as by elimination clearance.

$$t_{1/2} = \frac{0.693\, V_{d\,(area)}}{CL_E} \qquad \text{Equation 3}$$

The value of V_d in this equation is not $V_{d(extrap.)}$ but represents a second estimate of distribution volume, referred to as $V_{d(area)}$ or $V_{d(\beta)}$ that generally is estimated from measured elimination half-life and clearance. The similarity of these two estimates of distribution volume reflects the extent to which drug distribution is accurately described by a single compartment model, and obviously varies from drug to drug (12).

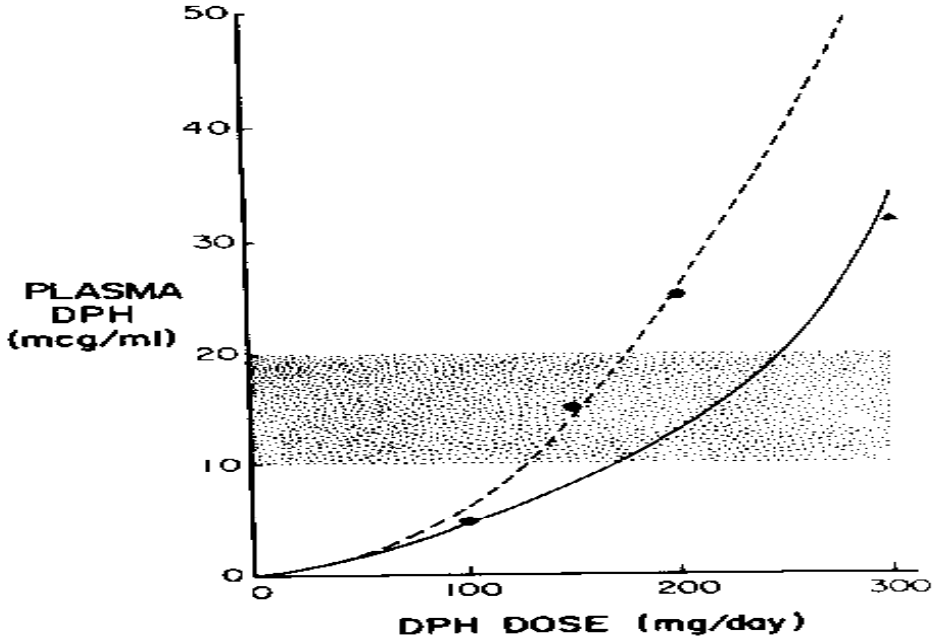
<u>Drugs not eliminated by first-order kinetics</u>:

Unfortunately, the elimination of some drugs does not follow first-order kinetics. For example, the primary pathway of phenytoin (Dilantin, PHT or DPH) elimination entails initial metabolism to form 5-(*p*-parahydroxyphenyl)-5-phenylhydantoin (*p*-HPPH), followed by glucuronide conjugation (Figure 5). The metabolism of this drug is not



<u>Figure 5</u>: Metabolism of phenytoin to form *p*-HPPH and *p*-HPPH glucuronide. The first step in this enzymatic reaction sequence is rate limiting and follows Michaelis-Menten kinetics, showing progressive saturation as plasma concentrations rise within the range that is required for anticonvulsant efficacy.

first order but follows *Michaelis-Menten* kinetics because the microsomal enzyme system that forms *p*-HPPH is partially saturated at phenytoin concentrations of 10 – 20 μg/mL that are therapeutically effective. The result is that phenytoin plasma concentrations rise hyperbolically as dosage is increased (Figure 6).



<u>Figure 6</u>: The lines show the relationship between dose and steady state plasma phenytoin (DPH) concentrations predicted for two patients who became toxic after initial treatment with 300 mg/day. Measured steady state plasma concentrations are shown by the dots. The shaded area shows the usual range of therapeutically effective phenytoin plasma concentrations.

For drugs eliminated by first-order kinetics, the relationship between dosing rate and steady state plasma concentration is given by rearranging Equation 2 as follows:

$$I = CL_E \bullet C_{ss} \qquad \text{Equation 4}$$

The corresponding equation for phenytoin is:

$$I = \frac{V_{max}}{K_m + C_{ss}} \bullet C_{ss} \qquad \text{Equation 5}$$

Where V_{max} is the maximum rate of drug metabolism and K_m is the apparent Michaelis-Menten constant for the enzymatic metabolism of phenytoin.

Although phenytoin plasma concentrations show substantial interindividual variation when standard doses are administered, they average 10 μg/mL when adults are treated with a 300-mg total daily dose but rise to an average of 20 μg/mL when the dose is increased to 400 mg (13). This non-proportional relationship between phenytoin dose and plasma concentration complicates patient management, and undoubtedly contributes to the many adverse reactions that are seen in patients treated with this drug. Although several pharmacokinetic approaches have been developed for estimating dose adjustments, it is safest to change phenytoin doses in small increments and to rely on careful monitoring of clinical response and phenytoin plasma levels. The pharmacokinetics of phenytoin were studied in both patients shown in Figure 6 after they became toxic when treated with the 300 mg/day dose that is routinely prescribed as initial therapy for adults (13). The figure demonstrates that the entire therapeutic range is traversed in these patients by a dose increment of less than 100 mg/day.

Even though many drugs in common clinical use are eliminated by drug metabolizing enzymes, fortunately few of them have Michaelis-Menten elimination kinetics (e.g. aspirin and ethyl alcohol). The reason for this is that K_m for most drugs is much greater than C_{ss}. Hence for most drugs, C_{ss} can be ignored in the denominator of Equation 5 and this equation reduces to:

$$I = \frac{V_{max}}{K_m} \bullet C_{SS}$$

where the ratio V_{max}/ K_m is equivalent to CL_E in Equation 4 Thus for most drugs, a change in dose will change steady state plasma concentrations proportionately, a property that is termed *dose proportionality*.

Mathematical Basis of Clinical Pharmacokinetics:

In the following sections we will review the mathematical basis of some of the important relationships that are used in applying pharmacokinetic principles to the care of patients. The reader also is referred to other literature sources that may be helpful (1, 12, 14).

First-order elimination kinetics: For most drugs, the amount of drug eliminated during any time interval is proportional to the total amount of drug present in the body. In

pharmacokinetic terms, this is called *first-order* elimination and is described by the equation:

$$dX/dt = -k\,X \qquad \text{Equation 6}$$

where X is the total amount of drug present in the body at any time (t) and k is the elimination rate constant for the drug. This equation can be solved by separating variables and direct integration to calculate the amount of drug remaining in the body at any time after an initial dose:

Separating variables: $dX/X = -k\,dt$

Integrating from zero time to time = t: $\int_{X_0}^{X} dX/X = -k\int_{0}^{t} dt$

$$\ln X\Big|_{X_0}^{X} = -k\,t\Big|_{0}^{t}$$

$$\ln\frac{X}{X_0} = -k\,t \qquad \text{Equation 7}$$

$$X = X_0\,e^{-k\,t} \qquad \text{Equation 8}$$

Although these equations deal with total amounts of drug in the body, the equation $C = X/V_d$ provides a general relationship between X and drug concentration (C) at any time after the drug dose is administered. Therefore, C can be substituted for X in Equations 7 and 8 as follows:

$$\ln\frac{C}{C_0} = -k\,t \qquad \text{Equation 9}$$

$$C = C_0\,e^{-k\,t} \qquad \text{Equation 10}$$

Equation 9 is particularly useful since it can be rearranged in the form of the equation for a straight line (y = mx + b) to give:

$$\ln C = -k\,t + \ln C_0 \qquad \text{Equation 11}$$

Now when data is obtained after administration of a single drug dose and C is plotted on base 10 semilogarithmic graph paper, a straight line is obtained with 0.434 times the slope equal to k (log x/ln x = 0.434) and an intercept on the ordinate of C_0. In practice C_0 is never measured directly because some time is needed for the injected drug to distribute throughout body fluids. However, C_0 can be estimated by back-extrapolating the straight line given by Equation 11 (Figure 7).

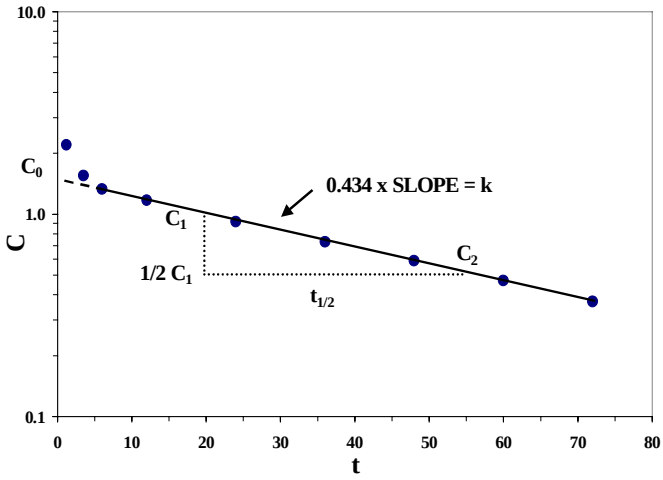


Figure 7: Plot of drug concentrations vs. time on semilogarithmic coordinates. Back extrapolation (*broken line*) of the elimination phase slope (*solid line*) provides and estimate of C_0. The elimination half-life ($t_{1/2}$) can be estimated from the time required for concentrations to fall from some point on the elimination-phase line (C_1) to C_2 = ½ C_1 , as shown by the *dotted lines*. In the case of digoxin, C would be in units of ng/mL and t in hours.

Concept of elimination half-life: If the rate of drug distribution is rapid compared with rate of drug elimination, the terminal exponential phase of a semilogarithmic plot of drug concentrations vs. time can be used to estimate the elimination half-life of a drug as, shown in Figure 7. Because Equation 9 can be used to estimate *k* from any two concentrations that are separated by an interval *t*, it can be seen from this equation that when $C_2 = ½\ C_1$:

$$\ln 1/2 = -k\,t_{1/2}$$

$$\ln 2 = k t_{1/2}$$

So: $t_{1/2} = \dfrac{0.693}{k}$, and $k = \dfrac{0.693}{t_{1/2}}$ Equation 12

For digoxin, $t_{1/2}$ is usually 1.6 days for patients with normal renal function and $k = 0.43\ \text{day}^{-1}$ (0.693/1.6 = 0.43). As a practical point, it is easier to estimate $t_{1/2}$ from a graph such as Figure 7 and to then calculate *k* from Equation 12, than to estimate *k* directly from the slope of the elimination-phase line.

The relationship of *k* to elimination clearance: In our introductory lecture, we pointed out that the creatinine clearance equation:

$$CL_{CR} = \frac{U\,V}{P}$$

could be re-written in the form of the following first-order differential equation:

$$dX/dt = -CL_{CR} \bullet P$$

If this equation is generalized by substituting CL_E for CL_{CR}, it can be seen from Equation 6 that, since $P = X/V_d$:

$$k = \frac{Cl_E}{V_d}$$ Equation 13

Equation 3 is derived by substituting of Cl_E / Vd for *k* in Equation 12. Although V_d and Cl_E are the two primary parameters of the single compartment model, confusion arises because *k* is initially calculated from experimental data. However, *k* is influenced by changes in distribution volume as well as clearance and does not reflect just changes in drug elimination.

The cumulation factor: In the steady state condition, the rate of drug administration is exactly balanced by the rate of drug elimination. Under conditions of intermittent administration, there is a continuing periodicity in maximum ("peak") and minimum ('trough") drug levels so that only a quasi steady state is reached with repeated dosing. However, in clinical pharmacokinetics no distinction generally is made between the true steady state that is reached when an intravenous infusion is administered continuously and the quasi steady state that results from intermittent administration.

Gaddum (15) first demonstrated that the maximum and minimum drug levels that are expected at steady state (quasi steady state) can be calculated for drugs that are eliminated by first-order kinetics. Assume that just maintenance doses of a drug are administered without a loading dose (Figure 4, lowest curve). Starting with Equation 8:

$$X = X_0 e^{-kt}$$

where X_0 is the maintenance dose and X is the amount of drug remaining in the body at time t. If t^* is the dosing interval, let:

$$p = e^{-kt^*}$$

Therefore, just before the 2nd dose: $X_{1(min)} = X_0\, p$

Just after the 2nd dose: $X_{2(max)} = X_0 + X_0\, p = X_0(1 + p)$

Similarly, after the 3rd dose $X_{3(max)} = X_0 + X_0 p + X_0 p^2 = X_0(1 + p + p^2)$

and after the nth dose: $X_{n(max)} = X_0(1 + p + \ldots\ldots + p^{n-1})$

or, $$X_{n(\max)} = X_0 \frac{(1-p^n)}{(1-p)}$$

Since $p < 1$, as $n \rightarrow \infty$, $p^n \rightarrow 0$. Therefore,

$$X_{\infty(\max)} = X_0 / (1-p)$$

or, substituting for p: $$X_{\infty(\max)} = \frac{X_0}{\left(1 - e^{-kt^*}\right)}$$

The value of X_∞ is the maximum *total body content* of the drug that is reached during a dosing interval at steady state. The maximum *concentration* is determined by dividing this value by V_d. The *minimum* value is given by multiplying either of these maximum values by e^{-kt^*}.

Note that the respective maximum and minimum drug concentrations after the first dose are:

Maximum:	C_0
Minimum:	$C_0 e^{-kt^*}$

The expected steady state counterparts of these initial concentration values can be estimted by multiplying them by the *cumulation factor* (*CF*):

$$CF = 1 \Big/ \left(1 - e^{-kt^*}\right) \qquad \text{Equation 14}$$

<u>The plateau principle</u>: Although the time required to reach steady state can not be calculated explicitly, the time required to reach *any specified fraction of the eventual steady state* can be estimated. For dosing regimens in which drugs are administered at a constant interval, Gaddum (15) showed that the number of drug doses (n) required to reach a fraction (f) of the eventual steady state amount of drug in the body can be calculated as follows:

$$f = \frac{X_n}{X_\infty} = \frac{X_0\left(1 - p^n\right)}{(1-p)} \bullet \frac{(1-p)}{X_0} = 1 - p^n \qquad \text{Equation 15}$$

In clinical practice, $f = 0.90$ is usually a reasonable approximation of eventual steady state. Substituting this value into Equation 15 and solving for *n*:

$$0.90 = 1 - e^{-nkt^*}$$

$$e^{-nkt^*} = 0.1$$

$$n = -\frac{\ln 0.1}{kt^*}$$

$$n = \frac{2.3}{kt^*}$$

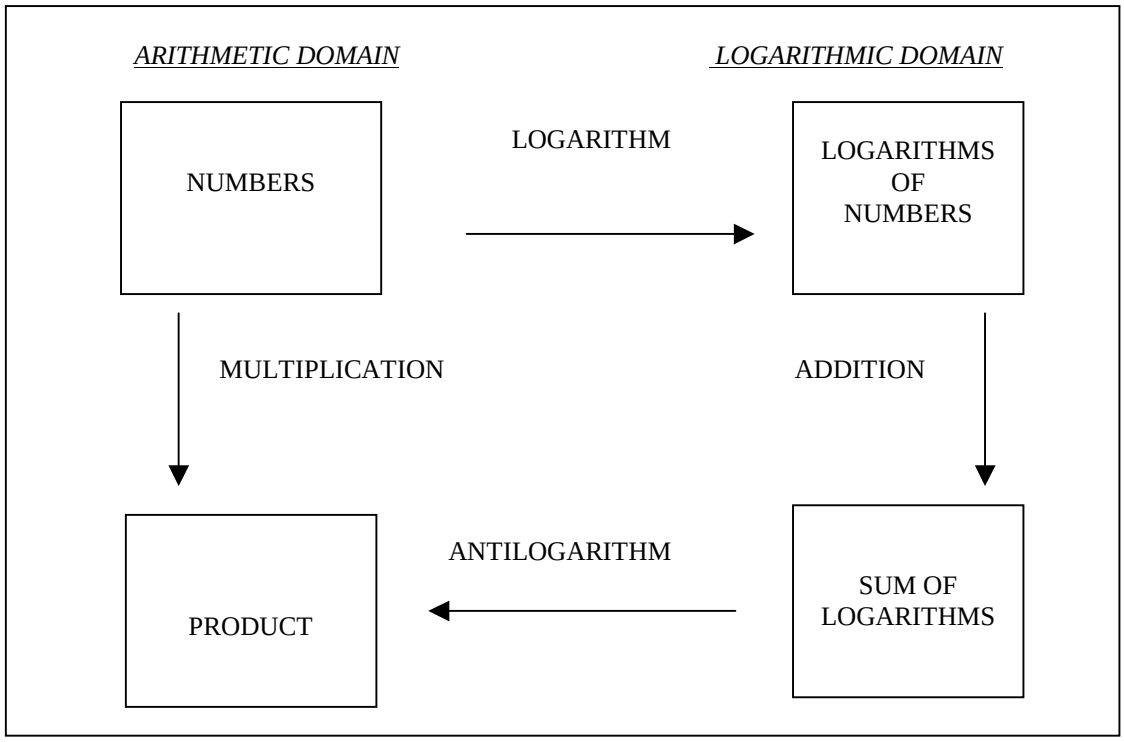
From Equation 12: $k = 0.693 / t_{1/2}$

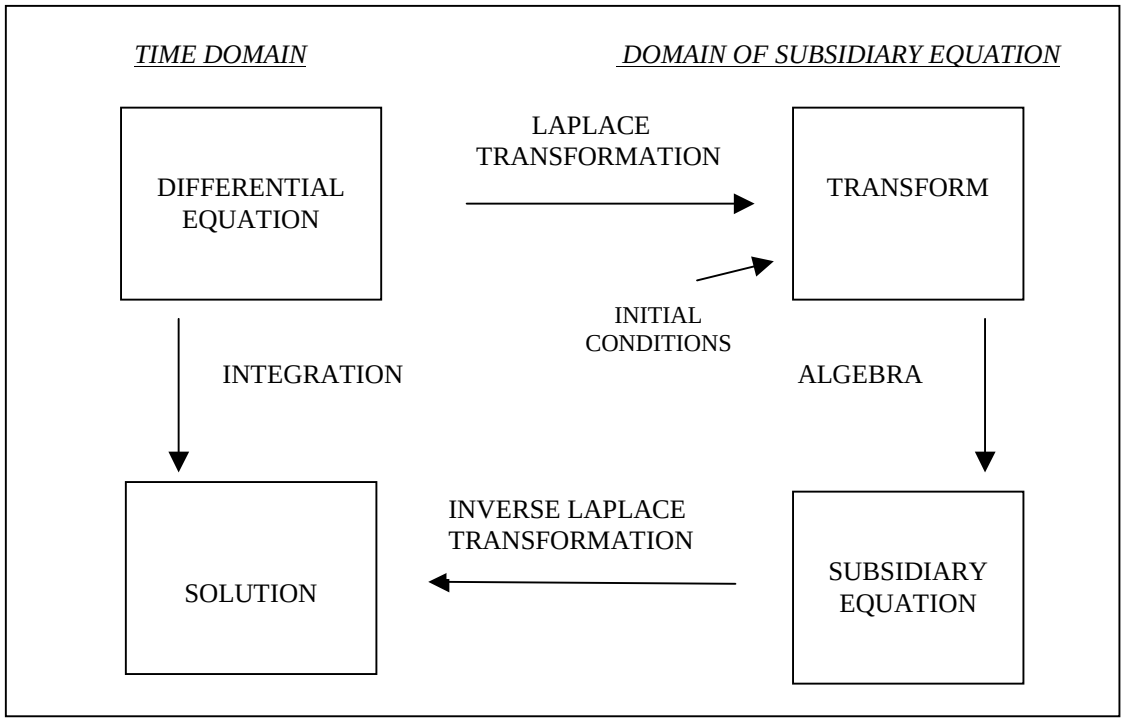
Therefore: $n = 3.3\, t_{1/2}$ Equation 16

Not only are drug accumulation greater and steady state drug levels higher in patients with a prolonged elimination half-life but an important consequence of Equation 16 is that it takes these patients longer to reach steady state. For example, the elimination half-life of digoxin in patients with normal renal function is 1.6 days, so that 90% of the expected steady state is reached in 5 days when daily doses of this drug are administered. However, the elimination half-life of digoxin is approximately 4.3 days in functionally anephric patients, such as the one described in the case history, and 14 days would be required to reach 90% of the expected steady state. This explains why this patient's adverse reaction occurred two weeks after starting digoxin therapy.

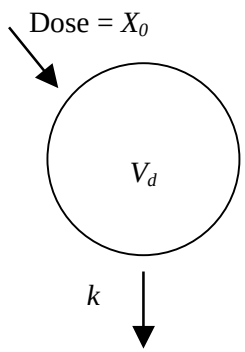
Application of Laplace transforms to pharmacokinetics:

The Laplace transformation method of solving differential equations falls into the area of *operational calculus* that is finding increasing utility in pharmacokinetics. Operational calculus was invented by an English engineer, Sir Oliver Heaviside (1850-1925), who had an intuitive grasp of mathematics (16). Although Laplace provided the theoretical basis for the method, some of Sir Oliver's intuitive contributions remain (e.g. the Heaviside Expansion Theorem). The idea of operational mathematics and Laplace transforms perhaps is best understood by comparison with the use of logarithms to perform arithmetic operations. This comparison is diagrammed in the flow charts shown below:


ARITHMETIC DOMAIN
LOGARITHMIC DOMAIN
NUMBERS
LOGARITHM
LOGARITHMS OF NUMBERS
MULTIPLICATION
ADDITION
PRODUCT
ANTILOGARITHM
SUM OF LOGARITHMS


TIME DOMAIN
DOMAIN OF SUBSIDIARY EQUATION
DIFFERENTIAL EQUATION
LAPLACE TRANSFORMATION
TRANSFORM
INITIAL CONDITIONS
INTEGRATION
ALGEBRA
SOLUTION
INVERSE LAPLACE TRANSFORMATION
SUBSIDIARY EQUATION

Just as there are tables of logarithms, there are tables to aid the mathematical process of obtaining Laplace transforms ($\mathcal{L}$) and inverse Laplace transforms ($\mathcal{L}^{-1}$)*. We can illustrate the application of Laplace transforms by using them to solve the simple differential equation that we have used to describe the single compartment model shown at the right.



Starting with the differential equation for this model (Equation 6):

$$dX / dt = - k X$$

We can use a table of Laplace transform operations (Appendix I) to take Laplace transforms of each side of this equation to create the *subsidiary equation*:

For X on the right side of the equation: $\mathcal{L} F(t) = f(s)$

For dX/dt on the left side of the equation: $\mathcal{L} F'(t) = s f(s) - F(0)$

Since $F(0)$ represents the *initial condition*, in this case the amount of drug in the model compartment at time zero, X_0, the subsidiary equation can be written:

$$s f(s) - X_0 = - k f(s)$$

This can be rearranged to give: $$(s + k) f(s) = X_0$$

Or, $$f(s) = \frac{X_0}{s + k}$$

A table of *inverse Laplace transforms* indicates: $\mathcal{L}^{-1} \frac{1}{s - a} = e^{at}$

Therefore, the solution to the differential equation is: $X = X_0 e^{-kt}$

and this is the same result that we obtained as Equation 8.

In other words, the Laplace operation transforms the differential equation from the time domain to another functional domain represented by the subsidiary equation. After algebraic simplification of this subsidiary equation, the inverse transformation is used to return the solved equation to the time domain. We have selected a simple example to illustrate the use of Laplace transform methods. A more advanced application is given in the next lecture in which equations are derived for a two-compartment model. It will be shown subsequently that Laplace transform methods also are helpful in pharmacokinetics when convolution/deconvolution methods are used to characterize drug absorption processes.

* Note that Laplace transforms can also be calculated directly from the integral:

$$\mathcal{L}[F(t)] = f(s) = \int_0^\infty F(t) e^{-st} dt$$

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APPENDIX I - ABBREVIATED TABLE OF LAPLACE TRANSFORMS:

TABLE OF OPERATIONS ($\mathcal{L}$):

TIME DOMAIN	LAPLACE DOMAIN
$F(t)$	$f(s) = \int_0^\infty F(t)e^{-st}\,dt$
1	$1/s$
A	A/s
$F'(t)$	$s\,f(s) - F(0)$
$F''(t)$	$s^2\,f(s) - s\,F(0) - F'(0)$

TABLE OF INVERSE OPERATIONS ($\mathcal{L}^{-1}$):

LAPLACE DOMAIN	TIME DOMAIN
$\frac{1}{s}$	1
$\frac{1}{s-a}$	e^{at}
$\frac{1}{(s-a)^2}$	te^{at}
$\frac{1}{s(s-a)}$	$\frac{1}{a}\left(e^{at}-1\right)$
$\frac{1}{(s-a)(s-b)}$ $\quad a \neq b$	$\frac{1}{a-b}\left(e^{at} - e^{bt}\right)$