A Nonlinear Physiologic Pharmacokinetic Model: I. Steady-State

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The two-compartment model of Rowland et al., (2) has been extended by replacing first order elimination with Michaelis-Menten elimination kinetics. All of the equations for steady-state concentrations and clearances for zero order (constant rate) input orally (into compartment ≠2) and intravenously (into compartment ≠1) are derived and reported. The steady-state concentration in compartment ≠1, following intravenous administration, is shown to be a nonlinear function of maximal velocity of metabolism, V_m, the Michaelis constant, K_m, and liver blood flow, Q; and, following oral administration is dependent only upon V_m and K_m and is independent of Q. However, oral bioavailability is a function of V_m, K_m, and Q. The model allows physiologic pharmacokinetic interpretation of both linear and nonlinear data; and, together with simple modification of the model, can explain much observed pharmacokinetic data to date particularly for first-pass drugs. Future articles in the series will be concerned with single doses, evaluation of literature data in terms of the model, application of the theory in toxicology and in clinical pharmacokinetics and therapeutics.
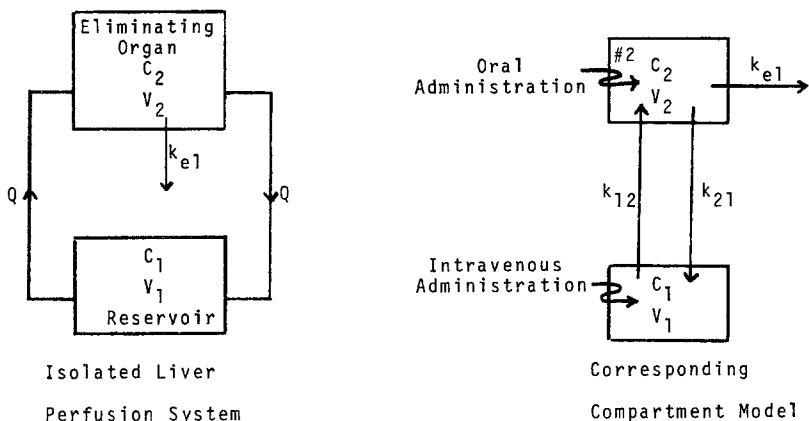
INTRODUCTION

Two types of well-defined quantitative models have been developed which attempt to describe the elimination of flowing substrates in the intact liver. One of these models has been termed the venous equilibration or "well-stirred" model (1-13) and has been developed mainly by Rowland (1, 2, 11, 12), Pang and Rowland (5-7), and Wilkinson (3, 4, 8). The other has been termed the sinusoidal perfusion or "parallel-tube" model (14-31)

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Eliminating
Organ
C_2
V_2

k_{el}

Q

C_1
V_1
Reservoir

Isolated Liver

Perfusion System

Oral
Administration

#2 C_2 k_{el}
V_2

k_{12} k_{21}

Intravenous
Administration

C_1
V_1

Corresponding

Compartment Model

Scheme I.

and has been mainly developed by Bass *et al.*, (14, 16, 18–23, 25–27) and Keiding *et al.*, (15, 17, 24, 28, 29).

The principal parts of the venous equilibration or "well-stirred" model were developed from the model of an isolated perfused organ system containing a reservoir and an eliminating organ and from the two-compartment open model with elimination from the peripheral compartment as depicted in Scheme I, but using the symbolism later used in this article rather than that of Rowland *et al.* (2). Hence, in reality there are really three models, two of which are the so-called "well-stirred" model and the specific compartment model of Scheme I and these two are equivalent mathematically. In the "well-stirred" model one measures concentrations in the reservoir or compartment #1 of Scheme I, following either oral administration into compartment #2, or intravenous administration into compartment #1.

Tucker (32) published a hydrodynamic analogue to the model of Scheme I and showed that all of the expectations of modern physiological pharmacokinetics may be derived from the analogue to the two-compartment model *providing first order kinetics are obeyed.*

We have extended the model of Rowland *et al.* (2) by replacing first order elimination by Michaelis–Menten elimination. We treat the steady-state in this article; a future article will consider single doses of drug given intravenously and orally. In subsequent articles we will show that considerable literature data on first-pass drugs may be explained by the simple models of Schemes I and II or obvious extensions of them.

The primary purpose of this article was to derive nonlinear equations involving Michaelis–Menten elimination to use in interpretation of literature
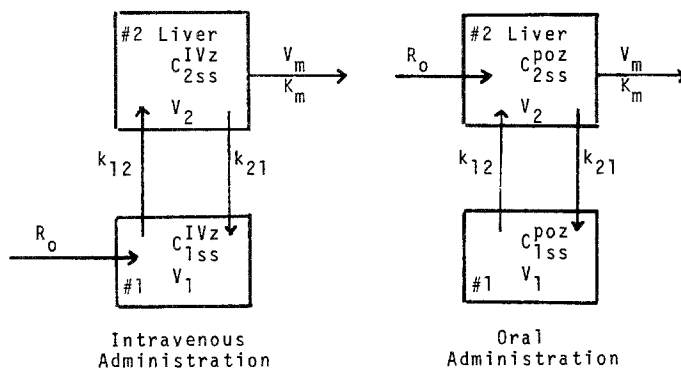
Scheme II.

data and new data available to the authors. With the exception of one article (25) all the other articles involving the sinusoidal perfusion model (14–24, 26–29) apply to the steady-state. Hence, a secondary purpose of this article was to derive equations extending the venous equilibration model (5–7) to the steady-state so comparisons could be made between the venous equilibration model and the sinusoidal perfusion model with respect to the steady-state. However, the latter comparisons are not made in this article.

THEORY

Compartment Model

The model is a modification of the "upside-down" two-compartment open model of Rowland *et al.* (2), altered to include Michaelis–Menten elimination kinetics. In this article, we discuss only the steady-state situation following administration of the drug at a zero order (constant) rate, R_o, either orally or intravenously, The equations developed assume complete availability of drug to the liver (i.e., $F_L = 1$); if not, then F_L would be less than unity and would multiply R_o when oral administration was considered. Since we are considering the steady-state then any number of other "tissue" or other compartments could be connected to compartments #1 and #2 by first order rate constants and the kinetic situation would not be changed. It is assumed that whole blood concentrations of drug are measured in compartment #1, hence the equations developed contain the liver blood flow, designated as Q. If plasma concentrations were measured in compartment #1, then the Q in this article would represent rQ where r is the blood/plasma concentration ratio of drug. The model of Scheme I considers

only the formation of a single metabolite according to Micheaelis–Menten kinetics with maximal velocity, V_m, and Michaelis constant, K_m. However, in the general model (not shown) there may be parallel Michaelis-Menten and/or first order paths and parallel elimination of unchanged drug according to first order kinetics. In the latter case equations developed later would have to be modified.

Symbolism

Note that "1" refers to compartment #1, ss refers to steady-state, po refers to oral administration, IV refers to intravenous administration, z refers to zero order (constant rate) input. "Concentration" refers to whole blood concentration when Q is actually liver blood flow, and to plasma concentration when Q is equal to $rQ(1)$. Symbols are arranged alphabetically.

$(AUC\ 0\text{-}\infty)_{IV}$:	The area under the concentration-time curve from zero to infinite time after a single dose of drug given intravenously.
$(AUC\ 0\text{-}\infty)_{po}$:	The area under the concentration-time curve from zero to infinite time after a single dose of drug given orally.
C_{1ss}^{IVz}:	The measurable constant steady-state concentration in compartment #1 during an intravenous infusion at the zero order rate, R_o, to steady-state.
C_{1ss}^{poz}:	The measurable constant steady-state concentration in compartment #1 during an oral input at the zero order rate, R_o, to steady-state.
$\overline{C_{1ss}^{poz}}$:	The average steady-state concentration in compartment #1 after oral administration during a dosage interval, defined as the area under the concentration-time curve divided by the dosage interval.
C_{2ss}^{IVz} and C_{2ss}^{poz}:	Corresponding concentrations for compartment #2.
C_i:	The input concentration of drug to the liver compartment equivalent to C_{1ss}^{IV} or C_{1ss}^{poz} for intravenous or oral administration, respectively.
C_o:	The output concentration of drug from the liver compartment—equivalent to C_{2ss}^{IVz} or C_{2ss}^{poz} for steady-state intraveneous or oral administration, respectively.
CL_H:	The systemic or hepatic clearance $= QCL_i/(Q+CL_i)$.
CL_i:	The intrinsic clearance of total drug for the model of Scheme II. Intrinsic clearance of free drug is CL_i/f_u.
CL_{1ss}^{IVzf}:	The steady-state hepatic or systemic clearance of free drug for the model of Scheme II.

CL_{1ss}^{pozf}: The steady-state oral clearance of free drug for the model of Scheme II.

CL_H / F_i: Equivalent to CL_i.

CL_R: The renal clearance of unchanged drug.

CL_{1ss}^{poz}: The steady-state clearance of total drug for oral administration (Scheme II) at rate R_o.

CL_{1ss}^{IVz}: The steady-state clearance of total drug for intravenous administration (Scheme II) at rate R_o.

D_{IV}: The dose of drug given intravenously.

D_{po}: The dose of drug given orally.

E_i: The intrinsic extraction ratio of the drug at a specified liver blood flow, Q (defined by Eq. 47).

E_{ss}: The steady-state hepatic extraction ratio of the drug (defined by Eq. 46) at a specified liver blood flow.

F_i: The intrinsic bioavailability of the drug according to the model of Schemes I and II at a specified liver blood flow (see Eq. 44).

F_L: Bioavailability of drug to the liver.

F_{ss}: The bioavailability of the drug under steady-state conditions for the model of Scheme II (defined by Eq. 41).

f_u: The fraction of drug free (unbound) in blood. Equations derived assume linear plasma protein and tissue binding.

k_{12}, k_{21}: First order distribution rate constants (see Schemes I and II).

k_e: Rate constant for renal excretion of unchanged drug.

k_{e1}: The first order elimination rate constant $= V_m / V_2 K_m$ when relating models of Schemes I and II.

K_m: The Michaelis constant for the model of Scheme II, equivalent to the concentration, C_2, when the rate of metabolism is equal to one-half of V_m.

r: The whole blood/plasma drug concentration ratio.

Q: The liver blood flow (vol/time) if whole blood drug concentration is measured or rQ_H if plasma is measured, where Q_H is true hepatic liver blood flow; in Schemes I and II $Q = V_1 k_{12} = V_2 k_{21}$.

R_o: The constant (zero order) input rate.

v: The velocity of metabolism at steady-state.

V_m: The maximal velocity of metabolism (Scheme II).

V_1: The volume of compartment #1 in the models of Schemes I and II. In applications this is an apparent volume.

V_2: The volume of compartment #2 in the models of Schemes I and II. Note that $V_2 = (k_{12}/k_{21}) V_1$.

First Order Model of Scheme I

Equal intercompartmental clearances (equivalent to our $V_1 k_{12} = V_2 k_{21}$) were assumed by Dedrick and Forrester (33), Perrier and Gibaldi (34), and Strong et al. (35). The model of Dedrick and Forrester (33) is identical with the model of Scheme II. The derivations to follow clearly show that to obtain the accepted expressions for the systemic and oral clearances (2,3) using the classical method of writing the differential equations (shown below), one must assume that the intercompartmental clearances in the model of Schemes I and II are equal.

Intravenous Administration to Steady-State

The differential equations are as follows.

$$V_1 \left(\frac{dC_{1ss}^{IVz}}{dt} \right) = R_o - V_1 k_{12} C_{1ss}^{IVz} + V_2 k_{21} C_{2ss}^{IVz} = 0 \tag{1}$$

$$V_2 \left(\frac{dC_{2ss}^{IVz}}{dt} \right) = V_1 k_{12} C_{1ss}^{IVz} - V_2 k_{21} C_{2ss}^{IVz} - V_2 k_{e1} C_{2ss}^{IVz} = 0 \tag{2}$$

From Eq. (1) we get:

$$R_o = V_1 k_{12} C_{1ss}^{IVz} - V_2 k_{21} C_{2ss}^{IVz} \tag{3}$$

Substituting from Eq. (3) into Eq. (2) gives:

$$V_2 \left(\frac{dC_{2ss}^{IVz}}{dt} \right) = R_0 - V_2 k_{e1} C_{2ss}^{IVz} = 0 \tag{4}$$

Now, the intrinsic clearance of compartment #2 of the model of Scheme I is the product of the volume, V_2, and the first order elimination rate constant, k_{e1}. Hence, from Eq. (4) we obtain Eq. (5):

$$R_o = V_2 k_{e1} C_{2ss}^{IVz} = CL_i C_{2ss}^{IVz} \tag{5}$$

Solving for C_{2ss}^{IVz} in Eq. (3) we get:

$$C_{2ss}^{IVz} = \frac{V_1 k_{12} C_{1ss}^{IVz} - R_0}{V_2 k_{21}} \tag{6}$$

Substituting from Eq. (6) into Eq. (5) yields:

$$R_o = CL_i \left(\frac{V_1 k_{12} C_{1ss}^{IVz} - R_o}{V_2 k_{21}} \right) \tag{7}$$

To obtain the accepted expression for hepatic clearance (2, 3, 5) from Eq.

(7) requires one to assume that:

$$Q = V_1 k_{12} = V_2 k_{21} \tag{8}$$

Substituting from Eq. (8) into Eq. (7) gives:

$$R_o = CL_i \left(\frac{QC_{1ss}^{IVz} - R_o}{Q} \right) = CL_i \left(C_{1ss}^{IVz} - \frac{R_0}{Q} \right) = CL_i C_{1ss}^{IVz} - \frac{R_o CL_i}{Q} \tag{9}$$

Equation (9) may be rearranged to:

$$R_o(1 + CL_i/Q) = CL_i C_{1ss}^{IVz} \tag{10}$$

Now,

$$CL_{1ss}^{IVz} = \frac{R_o}{CL_{1ss}^{IVz}} = \frac{CL_i}{1 + \dfrac{CL_i}{Q}} = \frac{QCL_i}{Q + CL_i} \tag{11}$$

which is the accepted hepatic clearance after intravenous administration.

Oral Administration to Steady-State

The differential equations are as follows.

$$V_1 \left(\frac{dC_{1ss}^{poz}}{dt} \right) = -V_1 k_{12} C_{1ss}^{poz} + V_2 k_{21} C_{2ss}^{poz} = 0 \tag{12}$$

$$V_2 \left(\frac{dC_{2ss}^{poz}}{dt} \right) = R_o + V_1 k_{12} C_{1ss}^{poz} - V_2 k_{21} C_{2ss}^{poz} - V_2 k_{e1} C_{2ss}^{poz} = 0 \tag{13}$$

From Eq. (12) we get:

$$V_1 k_{12} C_{2ss}^{poz} = V_2 k_{21} C_{2ss}^{poz} \tag{14}$$

Substituting from Eq. (14) into Eq. (13) gives:

$$R_o = V_2 k_{el} C_{2ss}^{poz} = CL_i C_{2ss}^{poz} \tag{15}$$

To obtain the accepted clearance one has to assume that Eq. (8) applies. Substituting from Eq. (8) into Eq. (14) gives:

$$C_{1ss}^{poz} = C_{2ss}^{poz} \tag{16}$$

Substituting from Eq. (16) into Eq. (15) gives:

$$R_o = CL_i C_{1ss}^{poz} \tag{17}$$

whence,

$$CL_{1ss}^{poz} = \frac{R_o}{C_{1ss}^{poz}} = CL_i = V_2 k_{e1} \tag{18}$$

Nonlinear Model of Scheme II

Intravenous Administration to Steady-State

The differential equations are as follows.

$$V_1\left(\frac{dC_{1ss}^{IVz}}{dt}\right) = R_o - V_1 k_{12} C_{1ss}^{IVz} + V_2 k_{21} C_{2ss}^{IVz} = 0 \tag{19}$$

$$V_2\left(\frac{dC_{2ss}^{IVz}}{dt}\right) = V_1 k_{12} C_{1ss}^{IVz} - V_2 k_{21} C_{2ss}^{IVz} - \frac{V_m C_{2ss}^{IVz}}{K_m + C_{2ss}^{IVz}} = 0 \tag{20}$$

From Eqs. (8) and (19) one obtains for across the liver:

$$R_o = Q(C_{1ss}^{IVz} - C_{2ss}^{IVz}) \tag{21}$$

Substituting from Eqs. (8) and (21) into Eq. (20) yields Eq. (22).

$$R_o = \frac{V_m C_{2ss}^{IVz}}{K_m + C_{2ss}^{IVz}} \tag{22}$$

Solving for C_{2ss}^{IVz} in Eq. (22) yields Eq. (23).

$$C_{2ss}^{IVz} = \frac{K_m R_o}{V_m - R_o} \tag{23}$$

Substituting from Eq. (23) into Eq. (21) gives Eq. (24).

$$R_o = Q\left(C_{1ss}^{IVz} - \frac{K_m R_o}{V_m - R_o}\right) \tag{24}$$

Solving for C_{1ss}^{IVz} in Eq. (24) yields Eq. (25).

$$C_{1ss}^{IVz} = \left(\frac{1}{Q}\right)R_o + \left(\frac{K_m}{V_m - R_o}\right)R_0 \tag{25}$$

It should be noted that Eq. (22) through (25) require that $V_m > R_o$ and are invalid when $R_o \geq V_m$.

Equation 25 is new and indicates that measurement of C_{1ss}^{IVz}'s for four different R_o values would allow nonlinear estimation of the variables Q, V_m and K_m with one degree of freedom remaining. If Q was measured independently, such as by indocyanine clearance or another method, then V_m and K_m could be determined following two or three different infusions.

Oral Administration to Steady-State

The differential equations are:

$$V_1\left(\frac{dC_{1ss}^{poz}}{dt}\right) = -V_1 k_{12} C_{1ss}^{poz} + V_2 k_{21} C_{2ss}^{poz} = 0 \tag{26}$$

$$V_2\left(\frac{dC_{2ss}^{poz}}{dt}\right) = R_o - V_2 k_{21} C_{2ss}^{poz} + V_1 k_{12} C_{1ss}^{poz} - \frac{V_m C_{2ss}^{poz}}{K_m + C_{2ss}^{poz}} = 0 \qquad (27)$$

Equations 8 and 26 give Eq. (16), that is:

$$C_{1ss}^{poz} = C_{2ss}^{poz} \qquad (16)$$

Hence it follows in the oral case that:

$$CL_{2ss}^{poz} = CL_{1ss}^{poz} \qquad (28)$$

Equations 8, 16, and 27 give Eq. (29).

$$R_o = \frac{V_m C_{1ss}^{poz}}{K_m + C_{1ss}^{poz}} = CL_{1ss}^{poz} \cdot C_{1ss}^{poz} \qquad (29)$$

Solving for C_{1ss}^{poz} in Eq. (29) yields Eq. (30).

$$C_{1ss}^{poz} = \frac{K_m R_o}{V_m - R_o} = \frac{R_o}{CL_{1ss}^{poz}} \qquad (30)$$

From eqs. (29) and (30) it follows that:

$$\frac{R_o}{C_{1ss}^{poz}} = CL_{1ss}^{poz} = \frac{V_m}{K_m + C_{1ss}^{poz}} = \frac{V_m - R_o}{K_m} \qquad (31)$$

As before, Eqs. (29–31) require that $V_m > R_o$ and are invalid if $R_o \geqslant V_m$. It should also be noted that the steady-state clearance is always less than the intrinsic clearance, except when first order kinetics are operating.

Now, from Eq. (31):

$$CL_i = \lim_{R \to 0} CL_{1ss}^{poz} = \frac{V_m}{K_m} \qquad (32)$$

where CL_i is the intrinsic clearance, or the maximal ability of the liver to irreversibly remove drug by hepatic metabolism in the absence of flow limitations (3).

By expanding the right-hand side of Eq. (31) and utilizing Eq. (32) we obtain:

$$CL_{1ss}^{poz} = CL_i - \frac{1}{K_m} R_o \qquad (33)$$

Equation (33) indicates that a plot of CL_{1ss}^{poz} (i.e., R_o/C_{1ss}^{poz}) vs. dose rate R_o, will yield a straight line with intercept equal to the intrinsic clearance, CL_i, and slope equal to $-1/K_m$. Parameter estimates may be made with Eqs. (34) and (35).

$$K_m = 1/|\text{Slope}| \qquad (34)$$

where the bars represent "absolute value of."

$$V_m = K_m CL_i \tag{35}$$

Equation (31) was first reported for the one-compartment open model by Sawchuk and Rector (36), but has been shown to be applicable to the two-compartment open model in this article.

Equations (29) through (33) have been derived in this article when input to the liver is truly zero order. This can be accomplished in an animal by infusing the drug at a constant rate into the portal vein. It can be accomplished approximately in man by administering an aqueous solution of a drug in small increments to steady-state, or by giving repetitive doses first at a high dose rate then switching to a slower dose rate (37). However, Eqs. (29) through (33) often apply when oral input is not zero order and when R_o is replaced by D_{po}/τ and C_{1ss}^{poz} is replaced by the average steady-state concentration, $\overline{C_{1ss}^{poz}}$, defined as the area under the concentration-time curve at steady-state divided by the dosage interval τ. An example of one such application recently is verapamil (38), but there are many others. Use of Eq. (33) will introduce some bias into estimates of CL_i, V_m, and K_m since it is a linear transformation of a nonlinear equation. To obtain better estimates of these parameters one should use Eq. (30) and either nonlinear least squares regression or a modification of Wilkinson's method (39).

If one substitutes from Eq. (31) into Eq. (25) one obtains Eq. (36).

$$C_{1ss}^{IVz} = R_0/Q + C_{1ss}^{poz} \tag{36}$$

Hence, if the rate R_0 is the same intravenously and orally, then:

$$Q = R_o/(C_{1ss}^{IVz} - C_{1ss}^{poz}) \tag{37}$$

Solving for K_m in Eq. (33) gives Eq. (38).

$$K_m = \frac{R_o}{CL_i - CL_{1ss}^{poz}} \tag{38}$$

Solving for V_m in Eq. (33) gives Eq. (39).

$$V_m = K_m CL_i = \frac{R_0}{1 - \dfrac{CL_{1ss}^{poz}}{CL_i}} \tag{39}$$

Equations (38) and (39) were given formerly by Wagner (38).

In applying Eqs. (38) and (39) one can give a single low oral dose so that kinetics are first order and make an estimate of CL_i as the ratio of the dose to the total area under the concentration-time curve in the usual manner.

Bioavailability and Extraction Ratios

Using the definition of bioavailability corresponding to input rate R_o, namely F_{ss}, given under symbolism above, and using Eqs. (25, 30, 31) we obtain:

$$\frac{1}{F_{ss}} = \frac{C_{1ss}^{IVz}}{C_{1ss}^{poz}} = \frac{\dfrac{R_o}{Q} + \dfrac{K_m R_o}{V_m - R_o}}{\dfrac{K_m R_o}{V_m - R_o}} = \frac{V_m - R_o}{Q K_m} + 1 = \frac{CL_{1ss}^{poz}}{Q} + 1 \tag{40}$$

Inverting both sides of Eq. (40) gives Eq. (41).

$$F_{ss} = \frac{1}{1 + \dfrac{CL_{1ss}^{poz}}{Q}} = \frac{Q}{Q + CL_{1ss}^{poz}} = \frac{1}{1 + \dfrac{V_m - R_o}{Q K_m}} \tag{41}$$

Rearrangement of Eq. (41) gives Eq. (42).

$$\frac{1 - F_{ss}}{F_{ss}} = \frac{V_m}{Q K_m} - \frac{1}{Q K_m} R_o \tag{42}$$

Equation (42) indicates that a plot of $1 - F_{ss}/F_{ss}$ vs. R_o will be a straight line with intercept equal to $V_m/Q K_m$ (or CL_i/Q) and a slope equal to $-1/Q K_m$. Thus an estimate of V_m is given by Eq. (43).

$$V_m = \frac{\text{Intercept}}{|\text{Slope}|} \tag{43}$$

To estimate the parameters V_m, K_m, and Q it is preferable to fit 4 or more F_{ss} values corresponding to 4 or more different R_o values, by nonlinear least squares regression using Eq. (41). Equations (33, 42) and (43) are useful to obtain preliminary estimates of the parameters.

It follows from Eq. (41) that the intrinsic bioavailability, corresponding to blood flow Q, is given by Eq. (44).

$$F_i = \lim_{R_o \to 0} (F_{ss}) = \frac{1}{1 + \dfrac{CL_i}{Q}} = \frac{Q}{Q + CL_i} \tag{44}$$

The steady-state extraction ratio, E_{ss}, across the liver, is given by Eq. (45) in conventional symbolism and by Eq. (46)

$$E_{ss} = \frac{C_i - C_o}{C_i} = 1 - \frac{C_o}{C_i} \tag{45}$$

in the symbolism of this article.

Utilizing Eqs. (28), (37), and (41) one obtains:

$$E_{ss} = 1 - F_{ss} = 1 - \frac{Q}{Q + CL_{1ss}^{poz}} = \frac{CL_{1ss}^{poz}}{Q + CL_{1ss}^{poz}} = \frac{C_{1ss}^{IVz} - C_{1ss}^{poz}}{C_{1ss}^{IVz}} \qquad (46)$$

And, from Eq. (46) the intrinsic extraction ratio, corresponding to blood flow, Q, is:

$$E_i = \lim_{R \to 0} (E_{ss}) = \frac{CL_i}{Q + CL_i} \qquad (47)$$

Analogously, from Eq. (25) we obtain Eq. (48), and

$$CL_{1ss}^{IVz} = \frac{R_o}{C_{1ss}^{IVz}} = \frac{1}{\dfrac{1}{Q} + \dfrac{K_m}{V_m - R_o}} = \frac{1}{\dfrac{1}{Q} + \dfrac{1}{CL_{1ss}^{poz}}} \qquad (48)$$

the intrinsic hepatic clearance, corresponding to blood flow Q, is given by:

$$CL_H = QE_i = \lim_{R \to 0} CL_{1ss}^{IVz} = \frac{1}{\dfrac{1}{Q} + \dfrac{K_m}{V_m}} = \frac{1}{\dfrac{1}{Q} + \dfrac{1}{CL_i}} = \frac{QCL_i}{Q + CL_i} \qquad (49)$$

Equations (44), (45), (47), and (49) were originally reported by Rowland *et al.* (2) and Wilkinson and Shand (3). These equations are the limits of the nonlinear equations derived in this article; hence, the nonlinear equations are consistent with classical first order physiologic pharmacokinetics. This is emphasized by the equations in Table I.

Effect of Protein Binding and Red Cell Binding in Blood

All the previous equations have been written in terms of total (bound + free) drug concentrations in whole blood, but may equally as well be written in terms of free (unbound) drug concentrations. In the latter case CL_{1ss}^{poz} and CL_{1ss}^{IVz} are replaced by $f_u CL_{1ss}^{pozf}$ and $f_u CL_{1ss}^{IVzf}$, respectively, where f_u is the fraction unbound in blood and the clearances are the corresponding clearances of free (unbound) drug. CL_i would be replaced by $f_u CL_i^f$, where CL_i^f is the intrinsic clearance of unbound drug. Levy and Yacobi (40) experimentally showed that the total clearance of warfarin in rats was directly proportional to the free fraction, f_u. This relationship is readily derived from the two mass balance Eqs. (50) and (51) and Eq. (49) as shown formerly (30).

$$F_i D_{po} = CL_H (AUC\ 0 - \infty)_{po} \qquad (50)$$

$$D_{IV} = CL_H (AUC\ 0 - \infty)_{IV} \qquad (51)$$

Table I. Comparison of First-Order and Nonlinear Model Expressions

Parameter	Route	First order model	Nonlinear model
Steady-state concn.	oral	$C_{1ss}^{poz} = \dfrac{R_o}{CL_i} = \dfrac{R_o}{V_2 K_{e1}}$	$C_{1ss}^{poz} = \dfrac{R_o}{CL_{1ss}^{poz}} = \dfrac{K_m R_o}{V_m - R_o}$
Steady-state clearance	oral	$CL_i = V_2 k_{e1}$	$CL_{1ss}^{poz} = \dfrac{V_m - R_o}{K_m}$
Steady-state concn.	i.v.	$C_{1ss}^{IVz} = R_o\left(\dfrac{1}{Q} + \dfrac{1}{CL_i}\right)$	$C_{1ss}^{IVz} = R_o\left(\dfrac{1}{Q} + \dfrac{K_m}{V_m - R_o}\right)$
Steady-state clearance	i.v.	$CL_{1ss}^{IVz} = \dfrac{QCL_i}{Q + CL_i} = \dfrac{1}{\dfrac{1}{Q} + \dfrac{1}{CL_i}}$	$CL_{1ss}^{IVz} = \dfrac{1}{\dfrac{1}{Q} + \dfrac{K_m}{V_m - R_o}}$
Bioavailability	oral	$F_i = \dfrac{Q}{Q + CL_i} + \dfrac{1}{1 + \dfrac{CL_i}{Q}}$	$F_{ss} = \dfrac{Q}{Q + CL_{1ss}^{poz}}$ $= \dfrac{1}{1 + \dfrac{V_m - R_o}{QK_m}}$

Equation (49) may also be written as eq. (52).

$$CL_H = \frac{Qf_u CL_i^f}{Q + f_u CL_i^f} \tag{52}$$

Equation (50) may also be written as Eq. (53).

$$D_{po} = CL_i(AUC\ 0-\infty)_{po} \tag{53}$$

where,

$$CL_i = \frac{CL_H}{F_i} \tag{54}$$

which is a fundamental equation of classical physiological pharmacokinetics (3).

Effect of Tissue Binding

As stated earlier, tissues may be attached to either compartments #1 or #2 by a pair of first-order rate constants like k_{12} and k_{21}, and such tissues may bind the drug; such binding at steady-state would not change the kinetic situation described. However, the volumes, V_1 and V_2, would change since the tissues would hold some of the drug. The clever hydrodynamic analogue of Tucker (32) has compartments 1 and 2 of Scheme I as fluid compartments with goldfish (the analogy to tissues) swimming in the fluids

in the two compartments. Nonlinear tissue binding could also be added to the basic model.

Dependence of Oral Bioavailability on Liver Blood Flow

It should be carefully noted that all the oral bioavailabilities, namely F_i and F_{ss}, are dependent upon liver blood flow, Q, even though the oral steady-state concentration and clearance are independent of liver blood flow.

Urinary Excretion of Unchanged Drug

If there were urinary excretion of unchanged drug according to first-order kinetics Schemes I and II would be modified by showing an exit rate constant with rate constant, k_e, off of compartment #1. Thus, the renal clearance of unchanged drug would be $CL_R = V_1 k_e$. This would modify Eq. (19) by the addition of a term, $-Cl_R C_{1ss}^{IVz}$, on the right-hand side. The net effect is that Eqs. (21) through (25) would have R_o replaced by $R_o - CL_R C_{1ss}^{IVz}$. Both the intravenous and oral cases are covered in the Appendix.

DISCUSSION

The models of Schemes I and II and obvious descendents, brought about by modification, appear to explain much of the clinical phar- macokinetic and physiologic observations made with first-pass drugs and reported in the literature. The senior author has surveyed the literature and believes most, if not all, first-pass drugs obey Michaelis-Menten elimination kinetics when given orally, and linear pharmacokinetics when administered intravenously. This is most likely the result of the difference in doses and the higher concentrations (as a result of both higher dose and lower volumes) when the drugs are given orally than when they are given intravenously. Pond and Tozer (13) did an excellent job of explaining this concentration difference with their Fig. 1.

The most important equations derived in this article are Eqs. (25), (30), (33), (38), (39), (41), and (42) and Eqs. (62) and (69) of the Appendix. In applying the equations, measurement of whole blood drug concentrations are preferred, but plasma concentrations may also be measured (see under r and Q in Symbolism). To determine whether one or more of the equations apply the following are guidelines. On rectilinear graph paper plot the steady-state concentrations vs. dose rate. If the steady-state concentration increases more than proportionately with increase in dose rate then applica- bility of the equations is feasible. If the concentrations were measured after oral administration then plot R_o / CL_{1ss}^{poz} (i.e., CL_{1ss}^{poz}) vs. R_o according to Eq. (33); if the data appear linear then obtain the least squares line and apply Eqs. (34) and (35) to obtain preliminary estimates of V_m and K_m. Then use

these initial estimates to fit the data by nonlinear least squares using Eq. (30) or use Wilkinson's method (39) to obtain final estimates of V_m and K_m. If steady-state concentrations are also available following intravenous infusion at different rates try fitting the data by nonlinear least squares to Eq. (25) using as initial estimate of Q the average liver blood flow of 1.5 L/min in man. Since you need at least one degree of freedom, fitting to Eq. (30) requires a minimum of three pairs of C_{1ss}^{poz}, R_o points. For application of Eqs. (38) and (39) see Wagner (38).
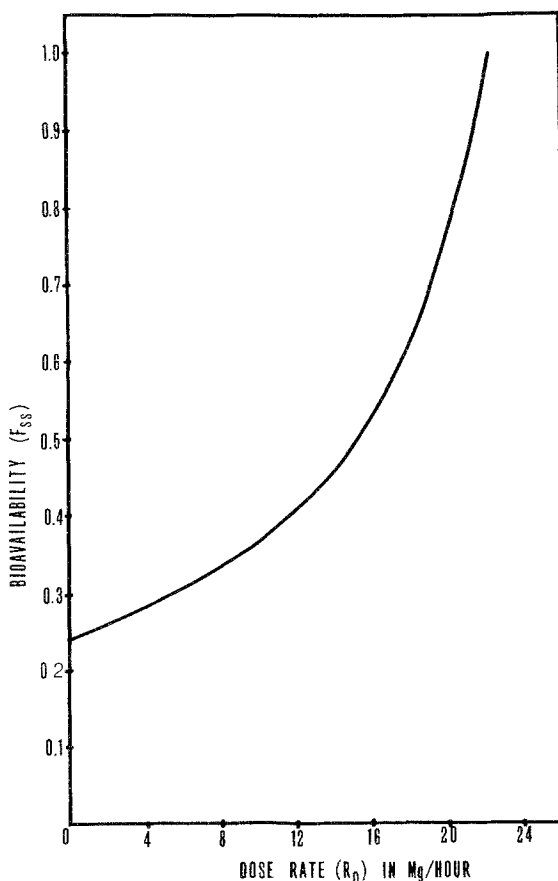

Fig. 1. Projected bioavailability of verapamil as a function of dose rate. Mean V_m, K_m, and Q values of six subjects, obtained from the data of Freedman et al. (41), were $V_m =$ 536 mg/day = 21.33 mg/hr, $K_m = 103$ ng/ml = 0.103 mg/L and $Q = 1.15$ L/min = 69 L/hr. Substitution of these values into Eq. (41) gave $F_{ss} = 1/(1 + (22.33 - R_o)/7.107)$ from which the plot was prepared.

Equation (41) indicates that the steady-state bioavailability increases more than proportionately with increase in dose rate. When F_{ss} is plotted vs. R_o on rectilinear graph paper the intercept on the ordinate scale is F_i (Eq. 44) then the plot curves upward and $F_{ss} \to 1$ as $R_o \to V_m$. An example is shown in Fig. 1 for verapamil, where the values of V_m, K_m, and Q were estimated from the data of Freedman *et al.* (41). Linearity of a plot of $(1 - F_{ss})/F_{ss}$ vs. R_o, based on Eq. (42) will indicate applicability of the nonlinear model. Using the V_m estimate obtained with Eq. (43), assuming $Q = 1.5 \, L/\text{min}$ initially, then an initial estimate of K_m may be obtained from the intercept of the above plot. With these initial estimates the F_{ss}, R_o data may be fitted to Eq. (41) by nonlinear least squares.

The model of Scheme II is readily modified by including first order metabolism parallel to Michaelis–Menten elimination. If there are two or more parallel Michaelis–Menten paths leading to two or more metabolites, then one often estimates pooled parameter values as discussed by Sedman and Wagner (42). Sometimes a parallel Michaelis–Menten and first order path also "pool" as shown by Wagner (43). This is simply the result of a lack of sufficient information in the concentration-time data. However, such pooled parameter estimates are still useful for making clinical pharmacokinetic predictions.

An additional useful component may be built into a human or animal protocol. Concentrations can be continued to be measured after input has ceased so that fall-off data are collected. If applicable, such downslope concentration-time data may be fitted to the integrated form of the Michaelis–Menten equation via numerical integration of the Michaelis–Menten equation. This procedure provides estimates of K_m and $V'_m = V_m/V_2$ as performed by the senior author and his coworkers (44, 45), where the V_m is obtained from the steady-state data as indicated above. An estimate of V_2 is then given by $V_2 = V_m/V'_m$.

Future articles in the series will be concerned with single doses, evaluation of literature data according to the derived equations, and application of the model in toxicology and clinical pharmacokinetics and therapeutics.

ACKNOWLEDGMENTS

APPENDIX

Model modification when there is urinary excretion of unchanged drug according to first order kinetics is shown in Fig. 1A.
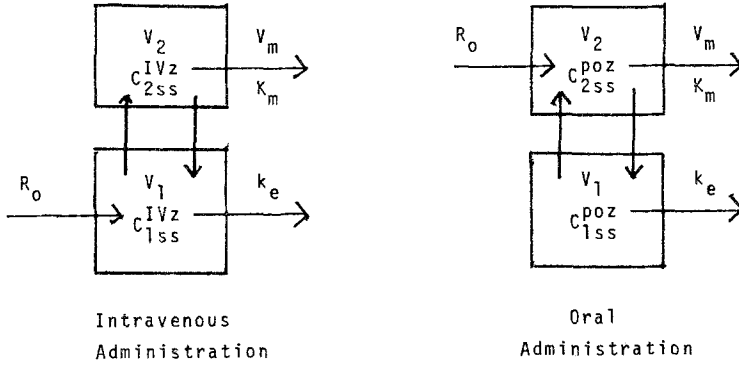
Intravenous
Administration

Oral
Administration

Fig. 1A. Modified nonlinear model when there is first-order renal excretion of drug.

Intravenous Administration

Utilizing Eq. (8) and $CL_R = V_1 k_e$ the differetial equations are:

$$V_1\left(\frac{dC_{1ss}^{IVz}}{dt}\right) = R_o - CL_R C_{1ss}^{IVz} - Q(C_{1ss}^{IVz} - C_{2ss}^{IVz}) = 0 \tag{55}$$

$$V_2\left(\frac{dC_{2ss}^{IVz}}{dt}\right) = Q(C_{1ss}^{IVz} - C_{2ss}^{IVz}) - \frac{V_m C_{2ss}^{IVz}}{K_m + C_{2ss}^{IVz}} = 0 \tag{56}$$

From Eq. (55) one obtains:

$$R_o - CL_R C_{1ss}^{IVz} = Q(C_{1ss}^{IVz} - C_{2ss}^{IVz}) \tag{57}$$

From Eq. (56) one obtains:

$$Q(C_{1ss}^{IVz} - C_{2ss}^{IVz}) = \frac{V_m C_{2ss}^{IVz}}{K_m + C_{2sss}^{IVz}} \tag{58}$$

From Eq. (57) and (58) one obtains Eq. (59).

$$R_o - CL_R C_{1ss}^{IVz} = \frac{V_m C_{2ss}^{IVz}}{K_m + C_{2ss}^{IVz}} \tag{59}$$

Solving for C_{2ss}^{IVz} in Eq. (59) gives:

$$C_{2ss}^{IVz} = \frac{K_m[R_o - CL_R C_{1ss}^{IVz}]}{V_m - [R_o - CL_R C_{1ss}^{IVz}]} \tag{60}$$

Substituting for C_{2ss}^{IVz} from Eq. (60) into Eq. (57) gives:

$$R_o - CL_R C_{1ss}^{IVz} = QC_{1ss}^{IVz} - \frac{QK_m[R_o - CL_R C_{1ss}^{IVz}]}{V_m - [R_o - CL_R C_{1ss}^{IVz}]} \tag{61}$$

Solving for C_{1ss}^{IVz} in Eq. (61) gives Eq. (62).

$$C_{1ss}^{IVz} = \left(\frac{1}{Q}\right)(R_0 - CL_R C_{1ss}^{IVz}) + \frac{Km[R_0 - CL_R C_{1ss}^{IVz}]}{V_m - [R_o - CL_R C_{1ss}^{IVz}]} \tag{62}$$

Oral Administration

The differential equations are:

$$V_1\left(\frac{dC_{1ss}^{poz}}{dt}\right) = -Q(C_{1ss}^{poz} - C_{2ss}^{poz}) - CL_R C_{1ss}^{poz} = 0 \tag{63}$$

$$V_2\left(\frac{dC_{2ss}^{poz}}{dt}\right) = R_o + Q(C_{1ss}^{poz} - C_{2ss}^{poz}) - \frac{V_m C_{2ss}^{poz}}{K_m + C_{2ss}^{poz}} \tag{64}$$

From Eq. (63) one obtains:

$$-CL_R C_{1ss}^{poz} = Q(C_{1ss}^{poz} - C_{2ss}^{poz}) \tag{65}$$

Equations (64) and (65) yield:

$$R_o - CL_R C_{1ss}^{poz} = \frac{V_m C_{2ss}^{poz}}{K_m + C_{2ss}^{poz}} \tag{66}$$

Solving for C_{2ss}^{poz} in Eq. (66) gives:

$$C_{2ss}^{poz} = \frac{K_m[R_o - CL_R C_{1ss}^{poz}]}{V_m - [R_o - CL_R C_{1ss}^{poz}]} \tag{67}$$

Substituting for C_{2ss}^{poz} from Eq. (67) into Eq. (65) gives:

$$-CL_R C_{1ss}^{poz} = QC_{1ss}^{poz} - \frac{QK_m[R_0 - CL_R C_{1ss}^{poz}]}{V_m - [R_o - CL_R C_{1ss}^{poz}]} \tag{68}$$

Rearrangement of Eq. (68) gives Eq. (69).

$$C_{1ss}^{poz} = \left(\frac{Q}{Q + CL_R}\right)\left(\frac{K_m[R_0 - CL_R C_{1ss}^{poz}]}{V_m - [R_o - CL_R C_{1ss}^{poz}]}\right) \tag{69}$$

Equation (30) indicates that in the absence of urinary excretion of unchanged drug the steady-state concentration after oral administration is independent of liver blood flow, Q. However, Eq. (69) indicates that when there is first-order elimination of unchanged drug (from compartment #1 of the model of Scheme II) then the steady-state concentration after oral administration is dependent upon liver blood flow, Q.

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