Gompertz Pharmacokinetic Model for Drug Disposition

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Purpose. Disposition of drugs among compartments of the body usually occurs at changing rates that are commonly modeled as sums of exponential terms with different rate constants. This paper describes an alternative, Gompertz kinetics, in which the rates can change systematically.

Methods. Differential equations were developed and solved that fit typical examples taken from the literature. The three or four constants required for a visually satisfactory fit to data could readily be found by successive adjustment "by hand," but strategies and results are presented for computer fitting of the data.

Results. In four examples, the amount remaining in the blood decreases as an exponentially declining fraction of the amount present at any moment, but the antecedent processes responsible for that amount differ as follows: (a) In simple i.v. disposition (e.g., lidocaine) concentration falls as a decelerated exponential decay. (b) Delayed i.v. disposition (e.g., hexobarbital) requires, as well, a decelerated exponential growth function. (c) In simple disposition after oral administration, the concentration in the blood initially increases at a decelerating rate. (d) In biphasic oral disposition (e.g., Li^+ carbonate), the initial Gompertz growth is followed by decelerated exponential decay.

Conclusions. Gompertz kinetics provides an accurate and parsimonious mathematical model describing drug disposition.

KEY WORDS: drug disposition; Gompertz kinetics; noncompartmental analysis.

INTRODUCTION

Pharmacokinetics is concerned with the mathematical description of the way substances introduced into the body are distributed (1). The concentration of a substance is monitored in blood samples taken at intervals after oral or intravenous (i.v.) delivery to the subject. The disposition of infused or ingested substances does not proceed at a constant rate of loss from the circulation, but instead the rate changes with time. Commonly, this change is modeled by sums of simple exponential terms intended to correspond to real or imagined spaces or compartments of the body (2).

In this study, pharmacokinetic phenomena are described in terms of *Gompertz kinetics* (3-7). The special feature of Gompertz kinetics is that, when appropriate, the rate coefficient, r, of an exponential process, y(t), is allowed to change exponentially during the process. So, in general, $\pm dy/dt = ry$, where $\pm dr/dt = kt$. Thus, in the models for drug disposition, the change in the rate of change of drug concentration is built into the original differential equations.

METHODS

As a modeling tool, Gompertz kinetics is not generally well known except by researchers concerned with growth and survival of organisms. Derivations of the equations used in the present unconventional application to four examples of drug disposition are therefore shown in some detail (see Table I for differential equations and their solutions).

Fit of Equations to Data

The model is validated by direct fit of the equations to published data of other authors. With practice, one can obtain in a few minutes excellent fits "by hand." For example, the original figure, scanned into the WINDOWS PAINT program (Microsoft), can be matched against successively adjusted predictions in MATHCAD (MATHSOFT) until a visually satisfactory fit is obtained. The present results, however, without reference to the hand-fit estimates, were obtained by means of SCIENTIST (MicroMath), which allows user specification of the mathematical function. Like many programs, it finds the constants by maximizing the sum of the squares of the differences between prediction and data.

Data were obtained by digitization of the points from enlargements of published figures. Disposition curves are commonly plotted as logarithm of concentration in the blood versus time, but for curve fitting, the digitizing software was allowed to transform the data back to arithmetical scale.

For each example, suggestions are given for finding reasonable initial values for the fitting program. In general, if there are more than three free parameters, fix the rest for the first run and then release them successively thereafter. In this way, the best fit can usually be found after only three or four trials, each of which requires a second or less of computer time. Best-fit parameter values for figures, listed in Table II, were obtained with routines shown in Table III.

Models for Intravenous Administration

Simple i.v. Disposition (Fig. 1)

When a substance is introduced directly into the bloodstream by i.v. injection, the diffusion gradient of the substance between blood and tissues is initially infinitely high. Not surprisingly then, the initial concentration in the blood decreases rapidly as the substance quickly succumbs to the host of specific and nonspecific affinities in its environment. The rate of removal from the circulation during this process is proportional to the amount present, i.e., is exponential, according to the differential equation:

$$-dy'/dt = y' \cdot r' \qquad (1)$$

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ABBREVIATIONS: Plain lower-case symbols stand for decelerated growth (as y, r, k), primed symbols for decelerated decay (r′, r′, k′); r, specific rate of change of concentration = dy/y·dt; primed, r′, when associated with decrease (at t = 0, r = r_o, and r′ = r'_o); k, specific rate at which r changes with time = dr/rdt; b = r_o/k; y_o, initial level of substance in blood; y, concentration of substance during decelerated growth; y′, for decelerated decay; y_m, level (theoretical) of y as $t \to \infty$ (y'_m for y′); R, rate of exponential decline of substance in the blood; K, rate constant for exponential decay of R; W(t), time course of disposition of substance; C_p = W = concentration of substance in the plasma; i.v., intravenous.

Table I. Differential Equations and Their Solutions in Gompertz Model of Drug Disposition[a]

Differential equation		Solutions	
Simple exponential decay, $dR/dt = -KR$		$R = \exp(-K \cdot t)$	(Eq. 4)
Decelerated exponential growth			
$dy/dt = y \cdot r$	(Eq. 7A)	$y = \exp((r_o - r)/k)$	(Eq. 8)
where $-dr/dt = r \cdot k$	(Eq. 7B)	*where* $r = r_o\exp(-kt)$	
Decelerated exponential decay,			
$-dy'/dt = y' \cdot r'$	(Eq. 1)	$y' = \exp(-(r'_o - r')/k')$	(Eq. 3)
where $-dr'/dt = r' \cdot k'$	(Eq. 2A)	where $r' = r'_o\exp(-k' t)$	
Simple i.v. Fig. 1,			
$-dC_p/dt = C_p(r' + K)$	(Eq. 6)	$C_p = C_o \cdot y' \cdot R$	(Eq. 5)
Delayed i.v. Fig. 2,			
$-dC_p/dt = C_p(r' - r + K)$	(Eq. 9A)	$C_p = C_o \cdot y' \cdot y \cdot R$	(Eq. 9)
Simple oral Fig. 3,			
$dC_p/dt = C_p (r - K)$	(Eq. 10A)	$C_p = C_o \cdot y \cdot R$	(Eq. 10)
Biphasic oral Fig. 4,			
$dC_p/dt = C_p(r - r' - K)$	(Eq. 9A)	$C_p = C_o \cdot y \cdot y' \cdot R$	(Eq. 11A)

[a] Prime, as in y′ (t), indicates the equation or parameter concerns decelerated *decay,* in contrast to unadorned y(t), concerned with decelerated *growth.*

The *rate* r′ decreases toward zero (Fig. 1, panel r′), as the concentration falls toward a finite level (Fig. 1, panel y′). Thus, r′ in Eq. 1 is not constant, as it would be in a simple exponential decay function; instead it decreases with time, and Eq. 1 represents decelerated exponential *decay* (with primed y′ to distinguish from *growth,* plain y). The coefficient r′ decreases exponentially:

$$-dr'/dt = r' \cdot k' \quad \text{and} \quad r' = r'_o \cdot \exp(-k' \cdot t) \qquad (2A,B)$$

and where k′ is the rate of decrease of the specific decay rate, r′.

When Eq. 2B is substituted into Eq. 1, and the result integrated between the initial value y'_o at $t_o = 0$ and y′ at t, we obtain (Fig. 1, panel y′) the solution to Eq. 1:

$$y' = y'_o \cdot \exp[-(r'_o - r')/k' \qquad (3)$$

Functioning by itself, the process represented by Eq. 3 would bring the concentration down to a level, y'_m, defined by setting $t \to \infty$ in Eq. 3. The further reduction that actually occurs is due to slower but simultaneous metabolic and ex-

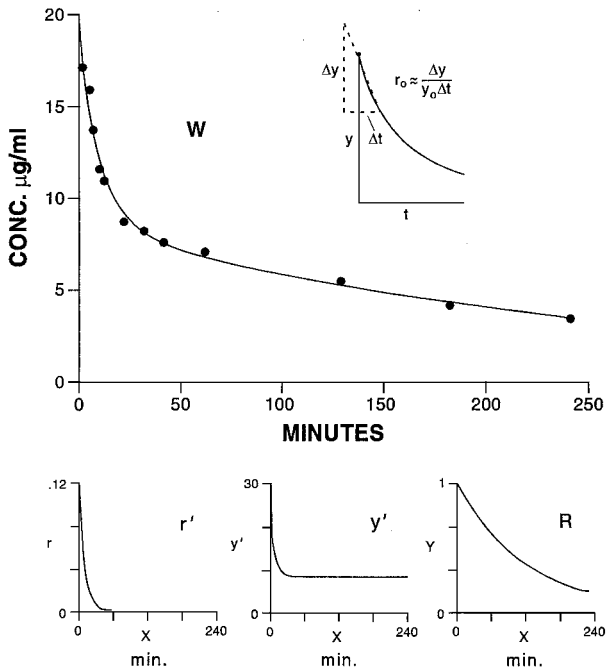

Fig. 1. Simple disposition after intravenous injection (lidocaine). Top: points digitized from Fig. 1 of Thomson *et al.* (8) and then transformed to arithemtical scale. Line fit by Eq. 5. Bottom: r′ (Eq. 2AB) drives y′ (Eq. 1, 3), which in turn is decreased by simple exponential decay (Eq. 4), R(t), to yield W(t).

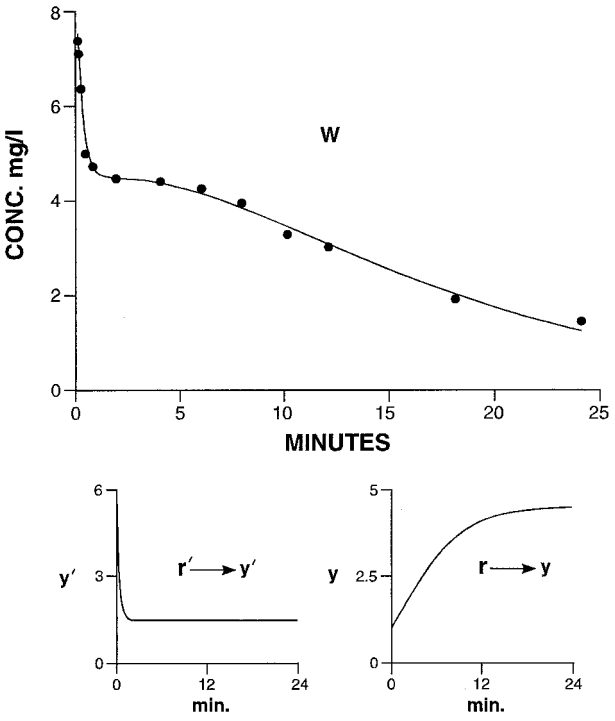

Fig. 2. Delayed disposition after intravenous injection (hexobarbital). Points digitized from Fig. 15b of van Rossum *et al.* (2), after Breimer (9). Top: arthmetical plot of disposition, Eq. 9, W(t). Bottom: disposition, W(t), is determined by decelerated exponential decay (Eq. 3), y′ driven by r′ (lower left), and growth, y driven by r (Eq. 8), together with simple exponential decay R (Eq. 4).

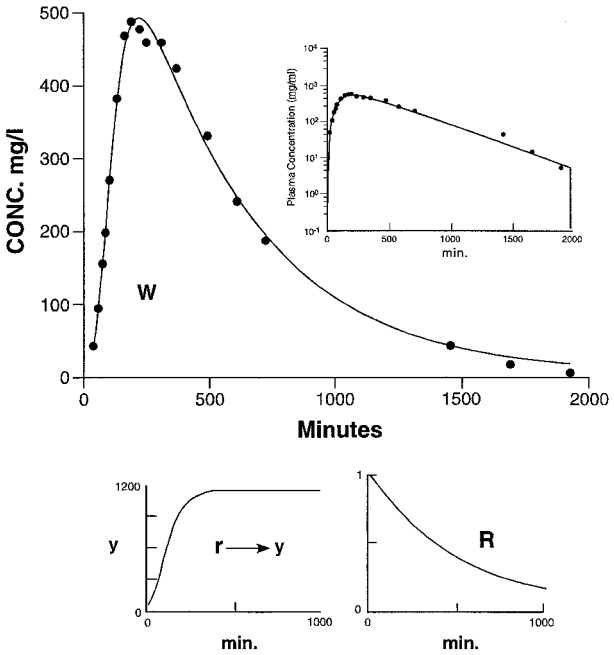

Fig. 3. Simple disposition after oral intake (extended-release product). Points digitized from Fig. 5 of Weiss (10). On them has been superimposed the prediction from log Eq. 10. Bottom: r (Eq. 2AB) drives decelerated exponential growth, y (Eq. 8), which in turn is decreased by simple exponential decay R(t) (Eq. 4) to yield net loss W(t) (Eq. 10).

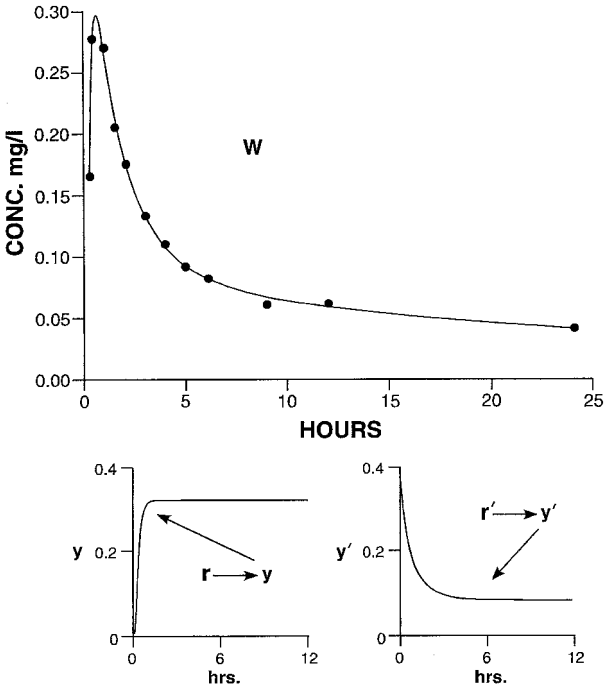

Fig. 4. Biphasic disposition following oral intake (Li^+ carbonate). Top: points digitized from Fig. 16b of Kruger-Thiemer (1), after Caldwell *et al.* (11). On them has been superimposed the arithmetic prediction. Bottom: Initial upward limb is a Gompertz growth function, decelerated exponential growth, y(t), Eq. 8. Subsequent fall is decelerated exponential decay, Eq. 3, y′(t). The net concentration of the substance in the blood is W(t) (Eq. 11), the product of y, y′, and the exponentially declining proportion R (Eq. 4).

cretory processes recruited to dispose of the substance. Their collective action diminishes the concentration by the exponentially decreasing fraction, R (Fig. 1, panel R):

$$R = \exp(-K \cdot t) \tag{4}$$

Thus the net concentration, W, at any time is the product of y′ (Eq. 3) and R (Eq. 4; Fig. 1, panel W):

$$W = y' \cdot R \tag{5}$$

The differential equation for the entire process can be obtained from the first derivative of Eq. 5:

$$dW/dt = (dt'/dt)\,R + (dr/dt)y' = -y'\,r''R - KRy' \tag{5A}$$

In conventional symbolism, and to emphasize the initial decrease in concentration, C_p, the drug in plasma:

$$-dC_p/dt = C_p\,(r' + K) \tag{6}$$

Equation 6 states that, in simple i.v. disposition, the concentration of the drug in the blood decreases in proportion to decreasing rate r′ and constant rate K.

Figure 1 shows graphically the Gompertz model addressed specifically to prediction of the disposition of injected lidocaine. The points were digitized and transformed from an enlargement of the original Fig. 1 of Thomson *et al.* (8). On the points in arithmetic scale has been superimposed the "best fit" obtained by machine fitting. Equally satisfactory conformity of prediction and data has been obtained with other similar instances from other sources.

Figure 1 displays (lower panels) the components: r′ defines the proportional diminishment of y′ (Eqs. 2B, 3), which is acted on by R, signaling final disposition. Parameter initial estimates for computer fitting of Fig. 1:

C_o: datum value at t = 0
K: estimate from logarithm of terminal limb of data plot
r'_o: estimate from specific slope at t = 0 (Fig. 1A)
k: any small positive value (say, 1).

Delayed i.v. Disposition (Fig. 2)

The initial phase of delayed i.v. disposition (Fig. 2) is described by Eq. 3, but the subsequent time course is not of the simple form shown in Fig. 1. For example, if the capacity to eliminate a drug has been reached, there may be a plateau or hesitation in the elimination curve before the final simple exponential decay (Fig. 2). In that case, the fractional diminishment of the concentration, as by Eq. 4, appears to be post-

Table II. Parameter Values

Symbols in text equations	Corresponding symbol in computer fitting program and Table III	Fig. 1	Fig. 2	Fig. 3	Fig. 4
C_o	CO	18.916	10.045	4.4266	0.00432
r_o	RFO		0.189	0.0883	26.180
k	KF		0.321	0.0166	5.432
r'_o	RSO	0.6609	2.66		0.744
k′	KS	0.075	2.774		0.400
K	K	0.00374	0.069	0.0021	0.0318

Table III. Routines for Fitting Figs. 1–4[a]

//pharmkin1 (Fig. 1)	//pharmkin3 (Fig. 3)
IndVars: T	IndVars: T
DepVars: C	DepVars: C
Params: RSO,KS,K,CO	Params: RFO,KF,K,CO
RS = RSO*EXP(-KS*T)	RF = RFO*EXP(-KF*T)
R = EXP(-K*T)	R = EXP(-K*T)
YS = EP(-(RSO-RS)/KS)	YF = EXP((RFO-RF)/KF)
C = CO*YS*R	C = CO*YS*R
//pharmkin2 (Fig. 2)	//pharmkin4 (Fig. 4)
IndVars: T	IndVars: T
DepVars: C	DepVars: C
Params: RSO,RFO,KS,KF, K,CO	Params: RSO,RFO,KS,KF, K,CO
RF = RFO*EXP(-KF*T)	RF = RFO*EXP(-KF*T)
RS = RSO*EXP(-KS*T)	RS = RSO*EXP(-KS*T)
R = EXP(-K*T)	R = EXP(-K*T)
YF = EXP((RFO-RF)/KF)	YF = EXP((RFO-RF)/KF)
YS = ESP(-(RSO-RS)/KS)	YS = ESP(-(RSO-RS)/KS)
C = CO*YS*YF*R	C = CO*YS*YF*R

[a] Equations written in the text and in Table I are here presented in the symbolism suitable for the curve-fitting program SCIENTIST (MicroMath). See Table II for symbol equivalents. Routine 1 uses decelerated exponential decay (YS) and routine 3 uses decelerated exponential growth (YF). In routine 2, r'_o (= RSO) > ro (= RFO), and k′ (= KS) > k (= KF), whereas the reverse is the case for routine 4, but the routines themselves are identical.

poned. The required "delay" can be accommodated by a decelerated exponential *growth* function:

$$(7A)\quad dy/dt = ry \quad \text{where} \quad (7B)\quad r = r_o\exp(-k \cdot t)$$

Equation 7 can be integrated to yield (Fig. 2, lower right panel):

$$y = y_m\exp(-r/k) \tag{8}$$

where y_m is the theoretical level approached by y(t) in the absence of final disposition R (see below). Equation 8 provides the delay in the plot Fig. 2. Thus, the complete process, taking account also of the initial decelerated exponential drop, y′, Eq. 3 (Fig. 2, lower left panel), and the final exponential fall, R, Eq. 4, is the product W(t), illustrated in Fig. 2, upper panel:

$$W = y' \cdot y \cdot R \tag{9}$$

The differential equation for the entire process can be obtained by differentiation of Eq. 9:

$$\begin{aligned} dW/dt &= (dy'/dt)y \cdot R + (dy/dt) \cdot y' \cdot R + (dR/dt) \cdot y' \cdot y \\ &= -yr' \; yR + yry'R = KRy'y \end{aligned} \tag{9A}$$

Thus (see Eq. 6)

$$-dC_p/dt = C_p(r' - r + K) \tag{9B}$$

Opposition (y(t) Eq. 8) to elimination during i.v. disposition (i.e., delay) develops in proportion to changing rate r, Eq. 2B. Fig. 2 is an example of delayed i.v. disposition, based on data from Breimer (9) cited by van Rossum *et al.* (2). The best fit (Eq. 9) has been superimposed on the arithmetical plot of data points in Fig. 2A. Parameter initial estimates for Fig. 2:

C_o, K, r'_o: see text description relating to Fig. 1.

Enter starting values for program: k′(1) > k(0.1), $r'_o > r_o$. With only three free parameters, the program will easily find a tentative best fit. Then release the preliminarily fixed parameters to refine the fit.

Models for Oral Administration

Simple Oral Disposition (Fig. 3)

Subsequent to oral administration, the concentration, y, increases in the bloodstream to the extent that the substance is transported from the digestive tract into the blood. The disposition can be predicted as the product of two terms: First, the level of the substance in the blood increases as a Gompertz growth function [Eq. 7, Fig. 3, lower left, y(t)]. As the rate of increase goes toward zero, the theoretically possible concentration that could be reached in the bloodstream approaches a maximum, y_m, set by the dose. By rearrangement of Eq. 7, the specific rate of growth is r = dy/ydt (Fig. 3, r → y); the coefficient r describes the changing specific slope of the theoretical rise in concentration y of the substance in the blood. Second, because of the processes that utilize or dispose of the substance, the concentration in the blood falls as an exponentially diminishing fraction, R, of the level in the blood, as predicted by Eq. 4 and illustrated by panel R in Figs. 1 and 3.

The complete differential equation for simple oral disposition is of the same form as Eq. 5, governing i.v. disposition, except it concerns a decelerated exponential growth rather than decay process. Thus:

$$W = y \cdot R \tag{10}$$

where y is defined by Eq. 8 and R by Eq. 4. The differential equation, from Eq. 10, is:

$$dW/dt = Wr - Wk \tag{10A}$$

In conventional symbols

$$dC_p/dt = C_p(r - K) \tag{10B}$$

i.e., during simple disposition after oral administration, the concentration in the blood increases in proportion to changing rate r and decreases proportional to constant rate K. An instance illustrating simple disposition following oral administration is presented in Fig. 3, based on data from Weiss (10, Fig. 5).

Parameter initial estimates for Fig. 3:

C_o, K: see text description relating to Fig. 1.

Enter starting values for program: r'_o: 0.1, k: 0.1.

"Biphasic" Oral Disposition (Fig. 4)

Disposition following oral intake can be biphasic, as in the case of Li^+ carbonate, shown in Fig. 4, based on Fig. 16b of Kruger-Thiemer (1), after Caldwell *et al.* (11). In this instance, the steep rise in concentration (Eq. 10, Fig. 4, lower left) is immediately followed by diminishment due to y′ (Eq. 3, Fig. 4, lower right). At the same time, the slow exponential decay in disposition is provided by R (Eq. 4), and the net result is the product of these three terms, i.e.,

$$W = y \cdot y' \cdot R \tag{11}$$

where y′ here is Eq. 3, with $y_o = 1$.

The differential equation representing biphasic oral dis-

position can be obtained from Eq. 11 in the same manner as Eq. 9B, but

$$dW/dt = wr - wr' - wK \quad (11A)$$

Compared to simple oral disposition (Fig. 3), biphasic (Fig. 4) is accelerated disposition. The increased rate of disposition proceeds proportional to changing rate r′. Thus the term -Wr′ is added to Eq. 10A.

Then,

$$dC_p/dt = C_p(r - r' - K) \quad (12)$$

Parameter initial estimates for Fig. 4:

K, r'_o: see text description relating to Fig. 1.

For r_o, a definition in terms of K and r'_o can be helpful. At the peak of Eq. 11, the first derivative is zero. Thus, at zero, $r - r' = K$. Then, substituting and rearranging, obtain

$$r_o = (K + r'p) \exp(ktp) \quad (13)$$

where $rp = r'_o \exp(-k'tp)$, and tp = time to peak

For first run, enter as temporary fixed values, K, r'_o, tp, together with Eq. 13. Enter initial estimate value C_o from plot; enter $k = 1$, $k' = 0.1$.

Other Predictions

The result of multiple dosing can be predicted with an appropriate program applied to any instance of drug disposition modeled by the Gompertz method. For example, the full time course of concentration change that results from each successive dose can be added to the previous profile by use of the range variable feature in MATHCAD. Figure 5A shows the increasing concentration in the blood during successive i.v. injections of a drug that exhibits delayed disposition as in Fig. 2. Amount of material in a sample is the product concentration times volume, so, with MATHCAD's convenient summing operation, the concentrations in equal successive volumes (Fig. 5A) can be cumulated to yield (Fig. 5B) AUC, the area under the curve, the total amount as a function of time.

Enterohepatic Recycling

Consider primary oral disposition of the form in Fig. 6. If enterohepatic recycling occurs, a second peak is observed following the first. The second wave will appear with a delay due to the recycling time, it will broaden because of dispersion during the recirculation, and it will be lower in amplitude than the first wave. The recirculation time specifies the delay, smaller k and k′ will determine the dispersion, and the amplitude Y_m will be less.

Whatever the concentration, at any moment, because of the primary and secondary y and y′ functions, the final disposition will be terminated by R. The measured concentration at any moment can therefore be predicted by

$$C = C_o \cdot (y_1 \cdot y'_1 + y_1 \cdot y'_2) \cdot R \quad (14)$$

Figure 6 shows a theoretical example.

Intravenous vs. Oral Disposition

Whether a drug is administered by intravenous or oral route, the mechanism of disposition must be the same once the drug is in the blood stream (and of unchanged identity).

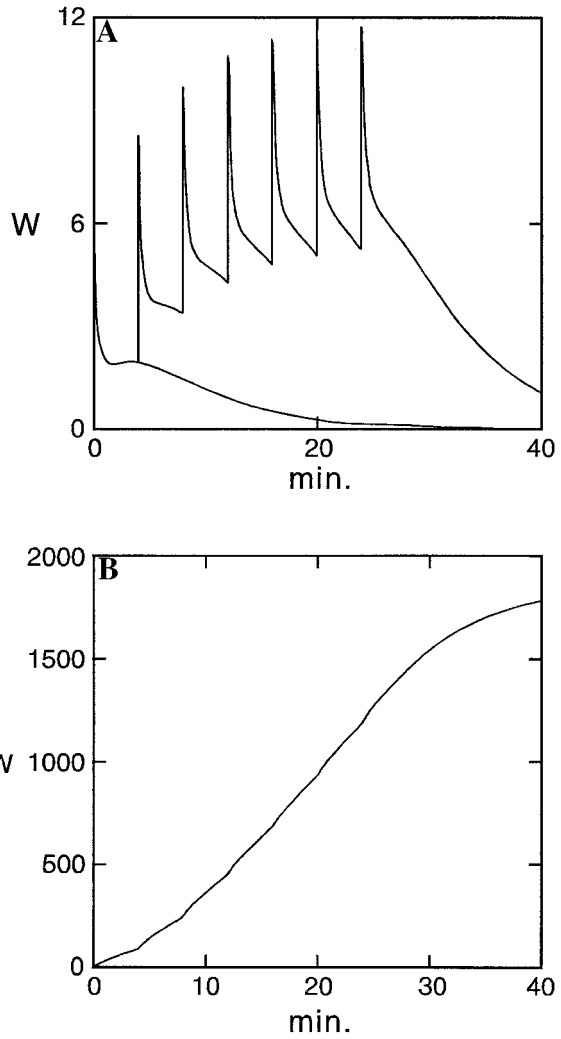

Fig. 5. Multiple dosing. A. Example of delayed disposition (Fig. 2, Eq. 9B) is repeated at regular intervals. Successive doses are added by use of MATHCAD range variable feature. Eq. 9B, with substitutions Eq. 3, 8, 4, was written for each injection; delay in each instance corresponded to the time of injection. The separately computed results were then added by MATHCAD to yield the running total. Ordinate, concentration of drug in blood. Abscissa, min. B. Equal small increments of volume (assessed at equal small increments of time), computed as Fig. 5A, were cumulated by use of the MATHCAD summing operation, to yield AUC, the area under the curve of Fig. 5A. Ordinate, amount of drug in blood. Abscissa, min.

The important difference is the absorption step from the gut after oral intake. The situation is illustrated in Fig. 7, where (middle row) the equations and constants appropriate to an i.v. bolus (A) have been used to generate the expected result from oral administration (B) of the same drug. In the latter instance, a term descriptive of adsorption (Eq. 8) has been added to the i.v. model. The top row shows the components of the model in each instance. The bottom row shows the consequence of i.v. infusion and of oral timed-release delivery. In both the latter two instances, the amount of drug available for disposition increases directly with time.

DISCUSSION

Note that all the various Gompertz functions are independent of dose. The initial value y_o (or C_o) is essentially an

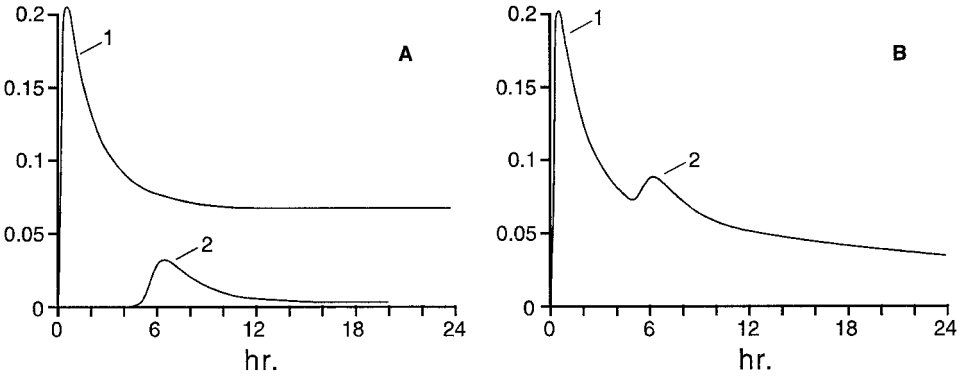

Fig. 6. Model for double-peaked disposition (as in enterohepatic recycling). At left, separate initial (1) and delayed (2) peaks of concentration of drug in the blood, following oral dose. At right, the two peaks have been summed. Peak 1 was generated with the same constants as in Fig. 1 (see also Table II). For peak 2, the rate parameters and the maximum value were assumed to be 0.3x the values for peak 1. The result is plotted with an arbitrary delay of 5 min.

amplifying factor in every instance. This situation contrasts with that in which the fit is obtained as a sum of exponential terms. For example, biphasic i.v. disposition illustrated in Fig. 4 was fit by the original author as the sum of three terms, each with its own theoretical initial value and rate constant. By this "peeling" technique, simple i.v. disposition requires a separate initial value (at $t = 0$) for each of the two exponential decay terms. In the Gompertz model, there is, more realistically, only one actual starting value of concentration, at $t = 0$, and the rate parameters are independent of concentration.

Rates of exponential change in real processes frequently change with time; Gompertz kinetics builds that assumption into the differential equation describing the process. In the present instance, two Gompertz functions, decelerated growth and decelerated decay, together with a simple exponential decay function, yield a global model of drug disposition. For convenience in the model, one function can be considered "primary," on which the second (and third) act in a proportionate way. For example, in the simplest i.v. instance, the concentration in component y′ in an i.v. dose initially falls at a high rate, r'_o, but r′ declines at rate k′ as the concentration approaches a (theoretical) plateau level, y′m (Eq. 3, Figs. 1, 2). Increasing r'_o lowers the plateau; increasing k′ raises it. The plateau level is determined by the affinities of sites other than those responsible for the simple exponential elimination. Acting simultaneously with y, the simple exponential elimination process, R, at each moment diminishes the concentration proportionately.

A delay in the appearance of the final simple exponential phase (Fig. 2) of i.v. disposition has been explained as due to capacity limitation of enzymes (12). The progress toward saturation is described by a decelerated exponential growth function (Eq. 8, Fig. 2).

Following an oral dose, the concentration in the blood rises along a path described by a decelerated exponential growth function (Eq. 8, Fig. 3). Figure 3 purports to show a simple instance in which elimination proceeds as an exponentially decreasing fraction R (Eq. 4) of the level of the substance in the blood, which is otherwise growing exponentially at a rate that decreases with time (Eq. 8). With the continuous i.v. infusion or time-release oral dose, equal additional amounts of a drug are made available to the blood during successive small equal time intervals. Thus, in the absence of removal mechanisms, the concentration in the blood would increase. The removal mechanisms are the same in either instance, but the disposition of the oral dose is delayed according to the time required to pass from gut to bloodstream. Fig. 7 (bottom) suggests how different infusion or release rates determine the steady level of drug concentration in the blood. The concentration in the blood increases exponentially at decreasing rate (concentration in the infusion sets the theo-

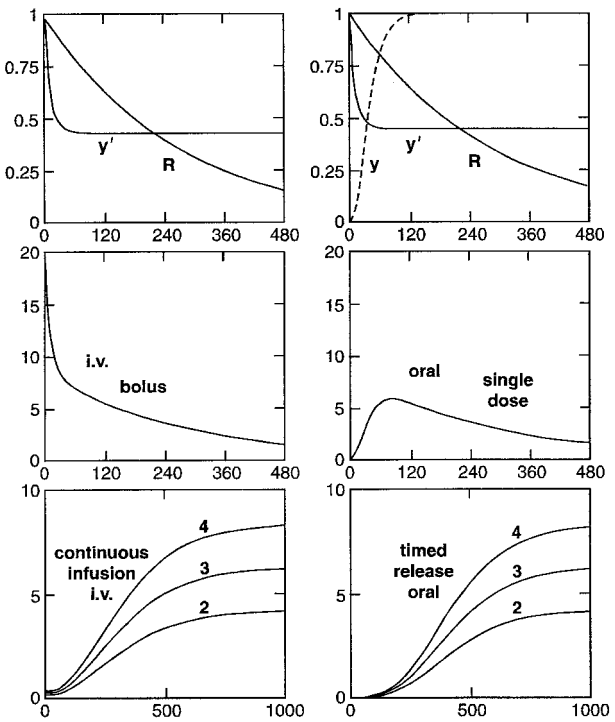

Fig. 7. Oral vs. i.v. intake. Middle row, at left, same as in Fig. 1, Eq. 5 (see Table II for parameter values). At right, Eq. 5 has been augmented by Eq. 2, with, arbitrarily, $r_o = 0.2$, $k = 0.05$, to define the uptake from oral dose. Top row, at left, components y′, R, for i.v. disposition; at right, same, but with component y (dashed line) added for uptake. Bottom row, prediction for continuous infusion (i.v.) or timed release (oral). The amount of administered drug made available by these methods of delivery was in each instance assumed to increase with time in a decelerated exponential fashion.

retical maximum) while removal proceeds at a decelerated exponential rate.

Computer power makes possible the fitting of disposition data with almost any number of simple exponential terms required in a compartmental model. Number of constants is not therefore usually an important consideration in compartmental model building. Nevertheless, it is well to note that the (noncompartmental) Gompertz model is reasonably parsimonious. Among the instances cited, none required more than four independent rate constants plus an initial value of the concentration. In contrast, if there are three rate constants in a compartmental model, three more initial values (constants) are required, if the model is to be complete (e.g., Fig. 4).

Pharmacokinetics presents a global picture of how substances introduced into the body are handled: a "mathematical treatment of concentration changes" (1). Those changes proceed at rates that are not constant with time. The elaborate complexities of many descriptions reflect that fact (2, 10). In Gompertz kinetics, the rate change is written into the original differential equations that define the processes. In the few examples described here, the equations have been successfully fit directly to data, in a way that suggests the approach can provide results that are not only rational but also exact and easy to obtain.

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