Laplace transform. Hopefully, that paper and this response will allow the uninitiated reader to understand better the use of such functions. However, once the reader becomes initiated (*i.e.*, not confused), I suggest he or she define b as the time of infusion rather than the time when infusion ends and use the anti-Laplace techniques and equations presented in my 1972 publication. They really are easier to use.

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Time-Dependent Kinetics VI: Direct Relationship between Equations for Drug Levels during Induction and Those Involving Constant Clearance

Keyphrases □ Pharmacokinetics—time dependent, equations for drug levels during induction and during constant clearance □ Models, pharmacokinetic—equations for drug levels during induction and during constant clearance

To the Editor:

In a previous report (1), equations were derived to describe the time course of drug levels during enzyme induction under various drug input conditions: single-dose intravenous (Case I) and oral (Case II) administration, constant rate intravenous infusion (Case III), and multiple-dose intravenous (Case IV) and oral (Case V) administration. These equations were based on the following assumptions:

1. Drug distribution is instantaneous (one compartment of volume V).
2. Drug is excreted unchanged by first-order processes.
3. Metabolism occurs by several first-order pathways, with one being controlled by a single inducible enzyme.
4. Metabolic clearance (pre- and postinduction) approaches intrinsic clearance.
5. Total body drug clearance increases during induction from a preinduction value $Q(t \leq \lambda)$ to a maximum Q' according to (2):

$$Q(t) = Q' - (Q' - Q)\exp[-k'(t - \lambda)] \qquad \text{(Eq. 1)}$$

where k' represents the first-order degradation rate constant of the induced enzyme, $k' < 0.1\ Q'/V$, and λ is the time at which induction begins.

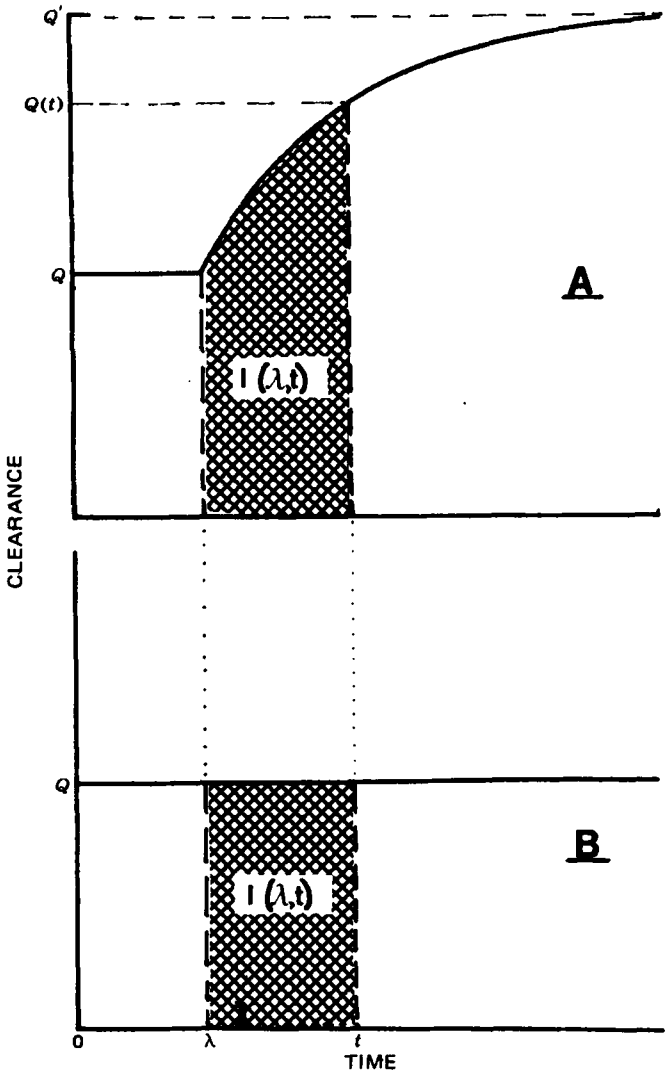

Figure 1—*Exponent* I(λ, t) *in time-dependent kinetics (A) and in linear kinetics (B). Whereas in linear kinetics (constant clearance) the area term* I(λ, t) *increases proportionately with time, in time-dependent kinetics the increase in area is more than proportional.*

To date, equations based on an exponentially increasing clearance have been validated only to the extent that the time course of blood levels that they predict is compatible with some experimental observations (3–7). In this report, a mathematical proof is presented to show that these equations are consistent with the corresponding equations of the classical one-compartment model with constant clearance. In fact, the latter represent a particular case of the former.

Table I presents solutions for Cases I–V with corresponding solutions for the one compartment with constant clearance.

Figure 1 is a plot of $Q(t)$ *versus* time. The term $I(\lambda, t)$ in every equation involving a time-dependent clearance (Table I) is defined as:

$$I(\lambda, t) = \int_{\lambda}^{t} Q(u)\,du \qquad \text{(Eq. 2)}$$

and, therefore, represents the area under the $Q(t)$ *versus*

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Table I—Equations [a] for Blood Concentration at Any Time When Clearance Increases Exponentially (A) and When Clearance Is Constant (B)

Case	A. Time-Dependent Clearance	B. Constant Clearance
I: Intravenous single dose	$C = \frac{X_0}{V}\exp\{-[Q\lambda + I(\lambda, t)]/V\}$ (Eq. I-1)	$C = \frac{X_0}{V}\exp(-Qt/V)$ (Eq. I-2)
II: Oral single dose	$C = \frac{FX_0k_a}{k_aV - Q}\exp\{-[Q\lambda + I(\lambda, t)]/V\} - \frac{FX_0k_a}{k_aV - Q(t)}\exp(-k_at)$ (Eq. II-1)	$C = \frac{FX_0k_a}{Vk_a - Q}\left[\exp\left(-\frac{Qt}{V}\right) - \exp(-k_at)\right]$ (Eq. II-2)
III: Constant rate infusion	$C = \frac{R}{Q(t)} - \frac{R}{Q}\exp\{-[Q\lambda + I(\lambda, t)]/V\}$ (Eq. III-1)	$C = \frac{R}{Q} - \frac{R}{Q}\exp(-Qt/V)$ (Eq. III-2)
IV: Intravenous multiple dose	$C = \frac{X_0}{V}\left\{\left[\frac{1 - \exp(-Q\lambda/V)}{1 - \exp(-Q\tau/V)}\right]\exp\{-[Q\tau + I(\lambda, t)]/V\} + \sum_{j=m}^{n-1}\exp[-I(j\tau, t)/V]\right\}$ (Eq. IV-1)	$C = \frac{X_0}{V}\left[\frac{1 - \exp(-n\tau Q/V)}{1 - \exp(-Q\tau/V)}\exp(-Qt'/V)\right]$ (Eq. IV-2)
V: Oral multiple dose	$C = \frac{FX_0k_a}{Vk_a - Q}\frac{1 - \exp(-Q\lambda/V)}{1 - \exp(-\tau Q/V)}\exp\{-[Q\tau + I(\lambda, t)]/V\} + \frac{FX_0k_a}{V}\left[\sum_{j=m}^{n-1}\frac{\exp[-I(j\tau, t)/V]}{k_a - Q(j\tau)/V} - \frac{\exp(-k_at')[1 - \exp(-n\tau k_a)]}{k_a - Q(t)/V[1 - \exp(-k_a\tau)]}\right]$ (Eq. V-1)	$C = \frac{FX_0k_a}{Vk_a - Q}\left[\frac{1 - \exp(-n\tau Q/V)}{1 - \exp(-\tau Q/V)}\exp(-Qt'/V) - \frac{1 - \exp(n\tau k_a)}{1 - \exp(-\tau k_a)}\exp(-k_at')\right]$ (Eq. V-2)

[a] X_0 = dose, V = single-compartment volume of distribution, F = fraction of dose absorbed, k_a = first-order absorption rate constant, τ = fixed dosing interval, n = number of doses, and:

$$I(\lambda, t) = Q'(t - \lambda) - \frac{(Q' - Q)}{k'}\{1 - \exp[-k'(t - \lambda)]\}$$

$$I(j\tau, t) = Q'\{t' + [n - (j + 1)]\tau\} - \frac{(Q' - Q)}{k'}(\exp[-(j - m)\tau k'] - \exp[-k'\{t' + [n - (m + 1)]\tau\}])$$

All other symbols are as defined in the text.

time plot between λ and t (Fig. 1A). The term $Q\lambda + I(\lambda, t)$ is equal to the total area under the $Q(t)$ *versus* time plot from 0 to t.

When $Q(t)$ is defined by Eq. 1, $I(\lambda, t)$ is given by:

$$I(\lambda, t) = Q'(t - \lambda) - \frac{(Q' - Q)}{k'}\{1 - \exp[-k'(t - \lambda)]\} \quad \text{(Eq. 3)}$$

For the one-compartment model with a constant clearance Q, the term $I(\lambda, t)$ as defined in Eq. 2 becomes:

$$I(\lambda, t) = \int_\lambda^t Q\,du = Q(t - \lambda) \quad \text{(Eq. 4)}$$

In this latter case, $I(\lambda, t)$ is equal to the area under the rectangle with height Q and width $t - \lambda$ (Fig. 1B).

For Case I, the term Qt in Eq. I-2 (Table I) can be written as:

$$Qt = Q\lambda + Q(t - \lambda) \quad \text{(Eq. 5)}$$

Using the definition of $I(\lambda, t)$ in Eq. 4, Qt becomes:

$$Qt = Q\lambda + I(\lambda, t) \quad \text{(Eq. 6)}$$

and, therefore:

$$C = \frac{X_0}{V}\exp(-Qt/V) = \frac{X_0}{V}\exp\{-[Q\lambda + I(\lambda, t)]/V\} \quad \text{(Eq. 7)}$$

Similarly in Case II, Eq. II-1 reduces to Eq. II-2 by substitution of Qt for $[Q\lambda + I(\lambda, t)]$ in the first term and Q for $Q(t)$ in the second term. In Case III also, Eq. III-1 reduces to Eq. III-2 by substitution of Q for $Q(t)$ in the first term and Qt for $[Q\lambda + I(\lambda, t)]$ in the second term.

In Cases IV and V, the relationships between Eqs. IV-1 and V-1 and between Eqs. V-1 and V-2 become apparent only after a few substitutions:

1. The term $I(j\tau, t)$, which appears in Eqs. IV-1 and V-1, is also defined by Eq. 2 with $j\tau$ as the lower bound of the integral ($\lambda \leq j\tau \leq t$). When the clearance is constant, it is given by:

$$I(j\tau, t) = Q(t - j\tau) = Q\{t' + [n - (j + 1)]\tau\} \quad \text{(Eq. 8)}$$

where $t' = t - (n - 1)\tau$.

2. The term $Q\tau + I(\lambda, t)$ can also be expressed in terms of t':

$$Q\tau + I(\lambda, t) = Q(t' + n\tau - \lambda) = Q[t' + (n - m)\tau] \quad \text{(Eq. 9)}$$

where $\lambda = m\tau$.

3. By using Eqs. 8 and 9, Eq. IV-1 can be written as:

$$C = \frac{X_0}{V}\exp(-Qt'/V)\frac{\exp[-(n - m)\tau Q/V] - \exp(-n\tau Q/V)}{1 - \exp(-Q\tau/V)} + \frac{X_0}{V}\sum_{j=m}^{n-1}\exp(-Q\{t' + [n - (j + 1)]\tau\}/V) \quad \text{(Eq. 10)}$$

4. The second term in Eq. 10 is a geometric series and, therefore, multiplication by:

$$1 = \frac{1 - \exp(-Q\tau/V)}{1 - \exp(-Q\tau/V)}$$

results in the following expression for Eq. IV-1:

$$C = \frac{X_0}{V}\exp(-Qt'/V)\left[\frac{\exp[-(n - m)\tau Q/V] - \exp(-n\tau Q/V)}{1 - \exp(-Q\tau/V)}\right] + \frac{X_0}{V}\exp(-Qt'/V)\left[\frac{1 - \exp[-(n - m)\tau Q/V]}{1 - \exp(-Q\tau/V)}\right] \quad \text{(Eq. 11)}$$

Equation 11 yields Eq. IV-2 after addition of its two terms.

5. Substitution of Q for $Q(j\tau)$ in Eq. V-1 shows that the sum of its first two terms becomes identical to Eq. IV-1, except for the difference between $FX_0k_a/(Vk_a - Q)$ and X_0/V. Correspondingly, the first term in Eq. V-2 is equal to Eq. IV-2 (except for $X_0/V \neq FX_0k_a/(Vk_a - Q)$. The third term in Eq. V-1 becomes the second term in Eq. V-2 after substitution of Q for $Q(t)$.

Thus, it appears that for all of the input modes considered, the equations commonly used for the one-compartment model with constant clearance represent only particular cases of the corresponding equations involving a time-dependent clearance. This direct correspondence provides further validation of the equations proposed to describe drug levels when metabolic clearance increases exponentially.

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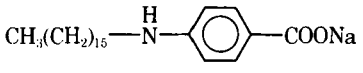
Cetaben Sodium, an Antiatherosclerotic Agent

Keyphrases □ Cetaben sodium—synthesis, antiatherosclerotic activity □ Antiatherosclerotic agents—cetaben sodium, synthesis □ Sodium 4-(hexadecylamino)benzoate—synthesis, antiatherosclerotic activity

To the Editor:

We wish to report the synthesis of cetaben sodium [sodium 4-(hexadecylamino)benzoate], a substance that shows promise as an antiatherosclerotic agent.

Ethyl 4-(hexadecylamino)benzoate (mp 85–86°) was prepared (yield 65–85%) from hexadecyl bromide or mesylate and 2 moles of ethyl 4-aminobenzoate at 135° in hexamethylphosphoric amide. Of the liquid amides, hexamethylphosphoric amide was the best reaction solvent (faster rate and fewer by-products); however, some dialkylation did occur. With dimethylformamide or *N,N*-dimethylacetamide at 135–150° as solvents, *N*-formyl and *N*-acetyl products were obtained as well as some 4-(hexadecylamino)-*N,N*-dimethylbenzamide by-product. Among various alternative synthetic methods, the diborane reduction of ethyl 4-(hexadecanoylamino)benzoate gave ethyl 4-(hexadecylamino)benzoate in good yield and can be used for preparing various isomers and analogs.



cetaben sodium

Cetaben sodium can be obtained directly from the quantitative alkaline hydrolysis of the ester but is generally prepared from 4-(hexadecylamino)benzoic acid (double mp 108–110 and 126–128°) since the latter is more easily purified. This salt, which is moderately soluble (about 2%) in 75% alcohol, is crystallized from a solution of the acid and a slight sodium hydroxide excess in aqueous ethanol in 95% yield.

The 4-(alkylamino)benzoic acids (1) are substantially less toxic and more hypolipidemic than the 4-alkoxybenzoic acids (2, 3) and 4-alkylbenzoic acids (3). Extensive studies have elucidated the structure–activity relationships in the aminobenzoic acid series, which are different from those in the alkoxybenzoic acids. The tabulated data show the hypolipidemic activity of representative aminobenzoic acids as well as of clofibrate under the same test conditions (Table I). The hypocholesterolemic activity falls off as the alkyl chain is increased to 20 or decreased to eight carbon atoms (1). However, the hypotriglyceridemic activity is relatively unaffected by the alkyl chain length. Cetaben is also the most effective member of the series in inhibiting ^{14}C-acetate and ^{3}H-glycerol incorporation into liver triglycerides, phospholipids, and cholesterol in rats. It is not esterogenic, and its hypocholesterolemic mechanism of action does not involve inhibition of a late stage in cholesterol biosynthesis. Hypocholesterolemic activity has been demonstrated also in the rabbit and monkey.

The considerable therapeutic potential of cetaben is suggested by its activity in two experimental atherosclerosis models in laboratory animals. First, cetaben sodium was shown to possess antiatherosclerotic activity in a rabbit model (4). Average reductions of 32–73% in the incidence of atherosclerotic lesions and of 24–28% in abdominal aortic cholesterol accumulation were observed in treated animals at doses below those that were hypolipidemic[1]. The reductions in aortic cholesterol were essentially all due to the decreases in cholesterol ester.

Second, Hollander *et al.* (5) reported on the antiatherosclerotic activity of cetaben sodium in the cynomolgus monkey. Serum cholesterol concentrations were reduced by 37% in the treated animals as compared to controls fed the atherogenic diet alone. This change was reflected in an altered lipoprotein distribution with decreases in very low density lipoproteins (by 30%) and low density lipoproteins (by 38%) but an increase in high density lipoproteins (by 96%). Such a shift in lipoprotein concentrations in humans is considered to be antiatherogenic (6, 7). Antiatherosclerotic activity was manifested by changes in the disease incidence and severity as well as in the chemical composition of the lesions present in the drug-treated monkeys.

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