Time-Dependent Kinetics IV: Pharmacokinetic Theory of Enzyme Induction

Keyphrases □ Kinetics, time dependent—enzyme induction, pharmacokinetic theory □ Enzyme induction—drug induced, time-dependent kinetics, pharmacokinetic theory

To the Editor:

The phenomenon of enzyme induction by drugs and foreign chemicals is well established. Many drugs stimulate their own metabolism (autoinduction) as well as that of other drugs administered concurrently (heteroinduction) (1). These phenomena have serious therapeutic implications.

In humans, experimental evidence for the enzyme-inducing abilities of a drug is generally based on decreases in plasma concentrations of the induced species. However, it is our observation that no general theory or quantitative approach has been proposed to describe the time course of plasma drug concentrations in conjunction with the phenomenon of auto- or heteroinduction. We have developed a pharmacokinetic theory able to predict the rate and extent of auto- or heteroinduction during chronic drug administration. This theory is based on biochemical models governing changes in enzyme levels in the body.

Berlin and Schimke (2) first proposed a model to describe the change in intracellular enzyme concentration following induction. They showed that when an inducer causes an increase in the rate of synthesis from S to S' and/or a decrease in the rate constant of degradation from k to k', the kinetics of the shift in enzyme level, $E(t)$, are governed by k':

$$E(t) = \frac{S'}{k'} - \left(\frac{S'}{k'} - \frac{S}{k}\right)e^{-k't} \qquad \text{(Eq. 1)}$$

where S/k and S'/k' represent the basal and induced steady-state enzyme concentrations, respectively, and $S/k \leq E(t) \leq S'/k'$ (Fig. 1). This model assumes that enzyme synthesis is zero order, that degradation is first order, and that the increase from S to S' and/or the decrease from k to k' are rapid relative to the enzyme half-life, $\ln 2/k'$.

By using the Michaelis–Menten model with steady-state approximation (3), an expression similar to Eq. 1 can be obtained to describe the change in maximum velocity, V_m, during induction:

$$V_m(t) = V'_m - (V'_m - V_m)e^{-k't} \qquad \text{(Eq. 2)}$$

where $V_m = k_2S/k$, $V'_m = k_2S'/k'$, and k_2 is the rate constant for dissociation of the enzyme–substrate complex to product and free enzyme. Equation 2 can be extended to describe drug disposition in the whole body during induction. Metabolic clearance, Cl, was defined by Rane *et al.* (4) as:

$$Cl = V_m/K_m \qquad \text{(Eq. 3)}$$

where V_m (amount time^{-1}) is a macroscopic maximal rate of metabolism, K_m (amount volume^{-1}) is a macroscopic Michaelis constant, and the substrate concentration is less than 0.1 K_m. If it is assumed that the inducer has no effect on K_m and free fraction and that clearance is not blood-flow limited, induction will result in an exponential increase in metabolic clearance. In the case of metabolism by one enzyme (single enzymatic site), the increase in Cl is given by:

$$Cl(t) = Cl' - (Cl' - Cl)e^{-k't} \qquad \text{(Eq. 4)}$$

Let us assume that the drug under consideration is also eliminated from the body through other metabolic pathways controlled by noninducible enzymes (each with its first-order clearance, M_j) and through excretion of unchanged drug by several routes (each with its first-order clearance, R_k). Prior to induction, total body clearance is given by:

$$Q = Cl + \sum M_j + \sum R_k \qquad \text{(Eq. 5)}$$

After induction, overall drug elimination from the body is controlled by a time-dependent clearance, $Q(t)$:

$$Q(t) = Q' - (Q' - Q)e^{-k't} \qquad \text{(Eq. 6)}$$

where:

$$Q' = Cl' + \sum M_j + \sum R_k \qquad \text{(Eq. 7)}$$

Equation 6 shows that the rate of change of clearance is also governed by k', the induced enzyme degradation rate constant (Fig. 1).

In the case of multiple-enzyme induction, Eq. 4 can be written for each induced enzyme. For the general case of a drug eliminated from the body by metabolism through inducible ($Cl_i \rightarrow Cl'_i$) as well as noninducible pathways (M_j), simultaneous with first-order unchanged drug excretion (R_k), $Q(t)$ is given by:

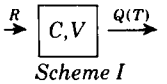
$$Q(t) = Q' - \sum_{i=1}^{n} (Cl'_i - Cl_i)e^{-k't} \qquad \text{(Eq. 8)}$$

where:

$$Q' = \sum_{i=1}^{n} Cl'_i + \sum M_j + \sum R_k \qquad \text{(Eq. 9)}$$

and n represents the number of induced enzymes.

Equation 6 (or Eq. 8) can be incorporated into the differential equations of a one-compartment pharmacokinetic model with appropriate input conditions to derive equations for the drug level time course during induction. The effect of an increase in clearance on drug levels is best illustrated (Fig. 1) when the induced species is administered by constant-rate intravenous infusion (Scheme I).



Scheme I

where C represents the plasma concentration of the induced agent, V is its apparent volume of distribution, R is its infusion rate, $T = t - \lambda$, λ is the time from the commencement of the induced agent infusion to the beginning of the increase in clearance, $Q(T)$ is as given in Eq. 6 where t is replaced by T, and the other terms are as previously defined. A solution[1] of the differential equation for Scheme I is:

$$C = \frac{R}{Q(T)} - \frac{R}{Q}\exp\left[\frac{-Q'}{V}(t - \lambda) + \frac{Q' - Q}{Vk'}\{1 - \exp[-k'(t - \lambda)]\}\right]\exp\left(\frac{-Q\lambda}{V}\right) \qquad \text{(Eq. 10)}$$

where all of the terms are as previously defined. In Fig. 1,

[1] A derivation of this equation is available from the corresponding author.

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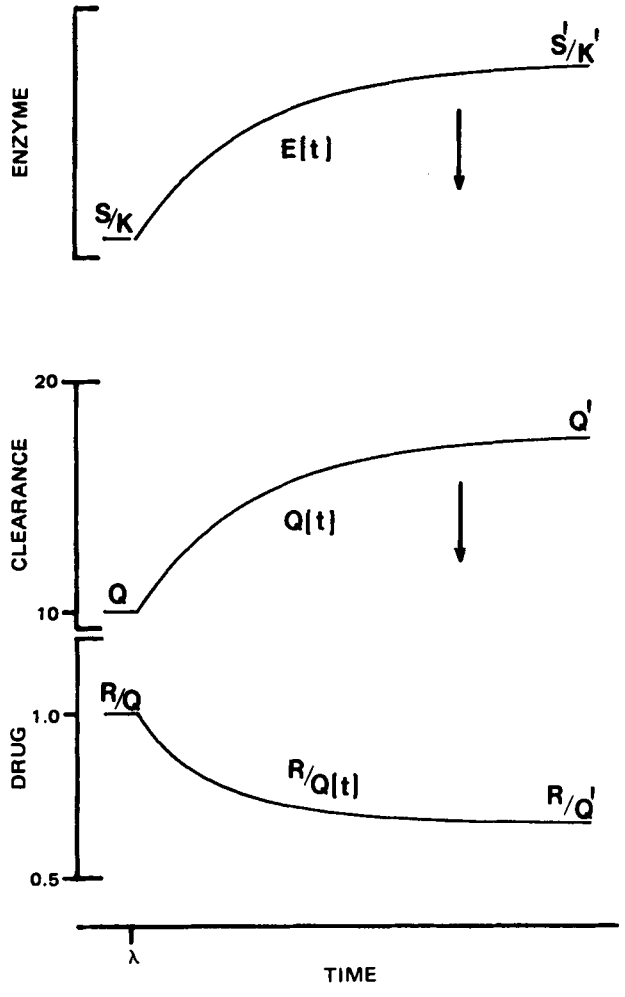

Figure 1—*Relationship between increase in enzyme level, E(t), and the corresponding increase in clearance, Q(t), and decrease in blood concentration. The drug administered by constant rate intravenously reached a steady state R/Q prior to the beginning of the increase in clearance, λ, since λ > 5 ln 2V/Q. The following parameter values were used:* S'/k' = *1.66* S/k, k' = *0.0577 hr*$^{-1}$, Q = *10.69 liters/hr*, Q' = *17.72 liters/hr, and* R = *12.4 mg/hr.*

it was assumed that $\lambda > 5[(\ln 2V)/Q]^2$ and, therefore, C is at a steady state (R/Q) prior to the beginning of induction. For $t > \lambda$, drug concentration decreases and reaches a lower steady state given by R/Q'.

The applicability of this theory is supported by a series of experimental observations:

1. In preliminary studies, three rhesus monkeys were given carbamazepine by intravenous infusion as an inducer and two other antiepileptic drugs, valproic acid and ethosuximide, as the induced agents (5, 6). Following addition of carbamazepine, plasma levels of these two drugs decreased exponentially to a lower steady state, as predicted from Eq. 10. Computer regression analysis of experimental data to Eq. 10 gave correlation coefficients (r) ranging from 0.886 to 0.996.

2. Follow-up studies in four rhesus monkeys with clonazepam (7) as the induced agent showed that the experimental decrease in clonazepam levels was consistent with model predictions (least-squares fit to Eq. 10, r = 0.924–0.993).

3. The model of Berlin and Schimke (2) also predicts that, following removal of an inducer, the return of the enzyme level to basal conditions is described by Eq. 1[3]. According to Eq. 6[4], this decrease in enzyme level should be mirrored by an exponential increase in body level of the induced agent. This hypothesis was verified by following the increase in plasma clonazepam level upon withdrawal of carbamazepine in four monkeys (7). The experimental data points and predicted concentrations were in excellent agreement ($0.905 < r < 0.964$).

4. Validation of this pharmacokinetic theory in humans was also realized (8). Seven healthy normal volunteers received (orally) clonazepam for 29 days and carbamazepine from Day 7 to 29. Least-squares fit of experimental data points to the corresponding model equation were adequate ($0.904 < r < 1.000$ in six subjects).

A priori, Eqs. 1 and 6 should also apply to autoinduction. This postulate was verified with published data from this laboratory on carbamazepine autoinduction in humans (9).

The proposed pharmacokinetic theory has broad implications. In biochemical pharmacology, it suggests a possibility of measuring enzyme turnover half-lives *in vivo* under experimental conditions that respect the integrity of the enzyme system(s). In clinical pharmacology, this theory provides a rational understanding of drug interactions caused by enzyme induction.

(1) A. H. Conney, *Pharmacol. Rev.*, **19**, 317 (1967).
(2) C. M. Berlin and R. T. Schimke, *Mol. Pharmacol.*, **1**, 149 (1965).
(3) G. E. Briggs and J. B. S. Haldane, *Biochem. J.*, **19**, 388 (1975).
(4) A. Rane, G. R. Wilkinson, and D. G. Shand, *J. Pharmacol. Exp. Ther.*, **200**, 420 (1977).
(5) P. H. Corbisier and R. H. Levy, *APhA Academy of Pharmaceutical Sciences Abstracts*, **7** (1), 163 (1977).
(6) *Ibid.*, **7** (2), 134 (1977).
(7) A. A. Lai and R. H. Levy, *J. Pharm. Sci.*, in press.
(8) A. A. Lai, R. H. Levy, and R. E. Cutler, *Clin. Pharmacol. Ther.*, **24**, 316 (1978).
(9) W. H. Pitlick, R. H. Levy, A. S. Troupin, and J. R. Green, *J. Pharm. Sci.*, **65**, 462 (1976).

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[2] When $\lambda \gg (\ln 2V/Q)$, the second term in Eq. 10 becomes negligible.

[3] In this case, S and k refer to the induced state and S' and k' refer to the non-induced (basal) state; thus, $S' < S$ and $k' > k$.

[4] Similarly, in this case, $Q' < Q$.