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Time-Dependent Kinetics I: Exponential Autoinduction of Carbamazepine in Monkeys

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Abstract □ The pharmacokinetics of carbamazepine were studied during a week-long infusion of the drug in 60% polyethylene glycol 400 solution in three rhesus monkeys. Serum concentrations approached steady state within 8–16 hr and then rapidly declined, within 72 hr, to a new asymptotic level approximately 46% of the maximum steady-state concentration. Serum concentrations remained at that level during the rest of the experimental period. The decline from the maximum value to the asymptotic steady state was exponential. It is postulated that the decline in the steady-state concentration is due to autoinduction by carbamazepine of its own metabolism.

Keyphrases □ Time-dependent pharmacokinetics—carbamazepine, 1-week infusion, monkeys □ Carbamazepine—time-dependent pharmacokinetics, 1-week infusion, monkeys □ Pharmacokinetics, time dependent—carbamazepine, 1-week infusion, monkeys □ Analgesics—carbamazepine, time-dependent pharmacokinetics, 1-week infusion, monkeys

Over the past 15 years, awareness of the various facets of dose dependency in drug disposition has increased. As a result, experimental designs of pharmacokinetic investigations often include studies at several dose levels. Examples of dose dependency in absorption, distribution, and elimination have been reported. However, the concept of *time dependency* in pharmacokinetics is still undefined.

BACKGROUND

Studies in this laboratory involving animals and humans clearly indicated that time dependency is a multifaceted phenomenon, at least as complex as dose dependency. Several types of time dependency exist, and this series of papers will provide examples. Carbamazepine is the drug of choice for the treatment of trigeminal neuralgia (1) and was recently approved for use as an anticonvulsant in adults (2). Single-dose intravenous and oral studies in monkeys indicated that the drug has a short biological half-life (1–2 hr) and that chronic oral administration during its efficacy testing in epileptic monkeys would be impractical (3, 4). Consequently, a continuous mode of administration such as constant-rate intravenous infusion in chronically catherized monkeys was considered.

Short-term infusion studies indicated that carbamazepine exhibits dose-dependent kinetics (5, 6). Infusion rates between 8.5 and 40 mg/hr yielded steady-state concentrations of carbamazepine between 2.0 and 5.8 μg/ml (6). However, the increase in steady-state concentration was more than proportional to the increase in infusion rate, and the time required to reach one-half of the steady-state level was not constant. A model with zero-order input and one capacity-limited elimination pathway was adequate to describe the pharmacokinetic behavior of the drug (6).

Table I—Data Obtained from Three Monkeys following Infusion of Carbamazepine at a Constant Rate during 1 Week

Monkey	R_0, mg/hr	Initial Steady-State Concentration, C_0*, μg/ml	Lag Time, θ, hr	Final Steady-State Concentration, C_∞*, μg/ml	Apparent Total Body Clearance		Induction Half-Life, hr
					Initial, liters/hr	Final, liters/hr	
1	17.3	4.10	16	2.04	4.2	8.5	5.8
2	16.0	4.32	12	1.84	3.7	8.6	11.6
3	9.0	2.86	16	1.29	3.1	6.9	7.6

The present investigation was undertaken to define infusion schedules and involved continuous infusion of the drug during 7 days. The steady-state levels of carbamazepine decreased during long-term constant rate infusion. Thus, carbamazepine appears to be the first example of a drug exhibiting simultaneously two types of nonlinearities, dose and time dependency. Furthermore, the long-term constant rate infusion approach used allowed a characterization of the kinetics of autoinduction. These findings provide an experimental basis for the development of nonlinear pharmacokinetic models involving time dependency.

EXPERIMENTAL

Materials—Carbamazepine[1] in polyethylene glycol 400–water (60:40) at 8 mg/ml was used for intravenous infusions.

Animals—Three healthy, male, chaired rhesus (*Macaca mulatta*) monkeys, 3.5–4.5 kg, with chronic jugular and femoral catheters were used. The patency of the catheters was assured by a slow continuous saline infusion into each catheter. The animals were maintained on monkey chow and fresh fruit.

Procedures—Carbamazepine was infused at a constant rate for 1 week. The intravenous infusion was accomplished by pumping the drug solution from a 100-ml calibrated reservoir[2] into the femoral vein catheter through an appropriate chamber attached to a calibrated peristaltic pump[3]. Infusion rates ranged between 9.0 and 17.3 mg/hr (Table I).

Samples of 1.5 ml of blood were drawn from the jugular catheter into a 5-ml plastic disposable syringe through a three-way stopcock attached to the catheter. Each sample was transferred to a nonheparinized tube, allowed to clot, and centrifuged at 2000 rpm for extraction immediately or frozen until assayed. Following the collection of each sample, the catheter was flushed with 1.5 ml of saline.

Twenty to 22 samples were collected over 1 week, the majority of the samples being taken in the first 48 hr. Twenty-four-hour urine collections were taken during the infusion studies. Serum and urine samples of carbamazepine were assayed using a GLC method presented previously (7).

RESULTS AND DISCUSSION

Serum concentration–time plots for Monkeys 1 and 2 are shown in Figs. 1 and 2, respectively. Serum concentrations approached an initial steady state, C_0*, within 8–16 hr and then fell off to a new asymptotic level, C_∞*, which was reached within 72 hr after the start of the infusion. There was no further decline from this final steady state during the rest of the experimental period. The serum concentrations observed within the first 12 hr were within 10% of the levels predicted from short-term infusion studies (6), as shown by the dotted lines in Figs. 1 and 2.

On the average, the final steady-state concentrations represented 46% (42–50%) of the maximum levels seen within the first 8–16 hr (Table I). This decrease corresponded to a twofold increase in apparent total body clearance (Table I). In all animals, the decline in steady-state concentrations from 12 hr onward was remarkable from two aspects: (*a*) the decline began somewhat abruptly, after a lag time (θ) of 12–16 hr, and (*b*) the decline in levels during a continuous infusion at a constant rate appeared to be an exponential process (Figs. 1 and 2). Semilogarithmic plots of the serum concentration data after the lag time, log ($C - C_\infty$*) *versus* ($t - \theta$), appeared linear (Fig. 3). An induction rate constant, K_I, and a corresponding half-life of induction, $T_{I\,1/2}$, can be measured to characterize the decreases in concentration at times larger than θ. The values of $T_{I\,1/2}$ obtained for these monkeys ranged between 5.8 and 11.6 hr. Serum concentrations at times larger than θ could then be fitted to the equation:

$$C = C_\infty^* + (C_0^* - C_\infty^*)\, e^{-K_I(t-\theta)} \qquad \text{(Eq. 1)}$$

A good agreement was observed between experimental data points and the fitted lines (continuous lines in Figs. 1 and 2).

No unchanged carbamazepine could be measured in the 24-hr urine samples. This finding was consistent with an earlier report that less than 1% of single intravenous and oral doses could be recovered as unchanged carbamazepine in urine (3).

Many drugs and chemicals affect the activity of drug-metabolizing enzymes in the liver microsomes. A large amount of evidence indicates that an increase in activity could be due to the increased synthesis of microsomal protein (8). In addition, a period of time follows treatment before the effect is apparent, and this time delay corresponds to known rates of protein synthesis (8). Carbamazepine has affected the half-lives of other drugs (9–12). A reduction in the half-life of doxycycline from 15 to 8 hr was reported in patients receiving carbamazepine (10). Carbamazepine also caused a decrease in the elimination half-life of phenytoin in patients (11). Likewise, a reduction in the half-lives of phenytoin and carbamazepine in monkeys pretreated with carbamazepine was reported (12). The effect of carbamazepine on the metabolism of several drugs is considered to be due to an induction of the drug-metabolizing enzyme systems in the liver. Other studies in this laboratory (excretion of *d*-

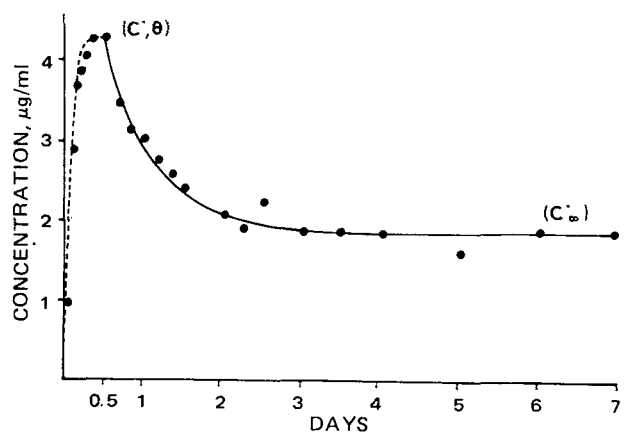

Figure 1—*Plot of serum carbamazepine concentrations* versus *time for Monkey 1 during 1 week on long-term infusion at a constant rate of* $R_0 = 17.3$ *mg/hr. The continuous line represents a fit to* $C = 2.04 + 2.06\, e^{-0.693/5.8(t-\theta)}$.

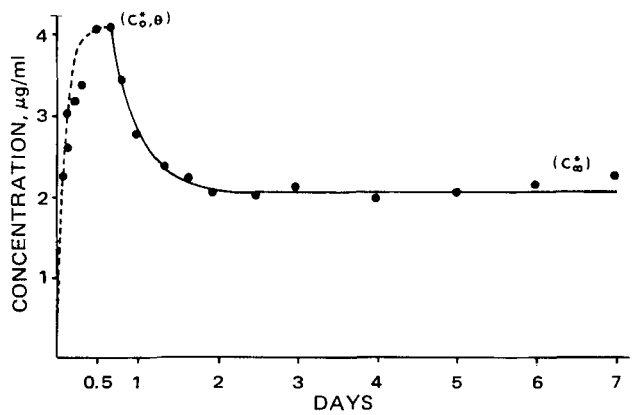

Figure 2—*Plot of serum carbamazepine concentration* versus *time for Monkey 2 during infusion for 1 week at a constant rate of* $R_0 = 16.0$ *mg/hr. The continuous line represents a fit to* $C = 1.84 + 2.48\, e^{-0.693/11.6(t-\theta)}$.

[1] Supplied by Ciba-Geigy Corp., Ardsley, N.Y.
[2] Soluset, Abbott Laboratories, North Chicago, Ill.
[3] Holter infusion pump, Extracorporeal Medical Specialties, King of Prussia, Pa.

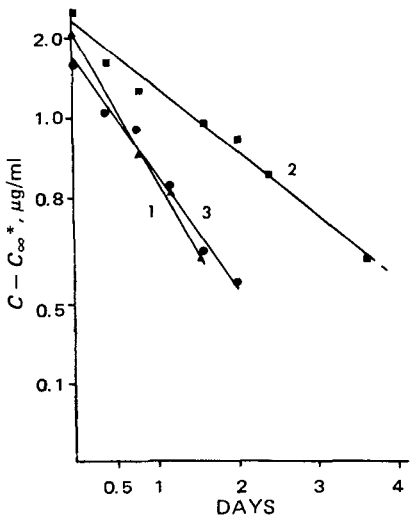

Figure 3—*Semilogarithmic plot of* (C − C_∞*) versus *time* (t − θ) *for Monkeys 1* (▲), *2* (■), *and 3* (●) *during 1 week of constant-rate infusion.*

glucaric acid) indicated that the observed autoinduction in steady-state plasma levels was probably due to enzyme induction.

Carbamazepine, in and of itself, is capable of stimulating its own metabolism in rhesus monkeys. Drug interaction studies with carbamazepine in other monkeys showed that the autoinduction phenomenon was consistently reproducible[4]. The possible role played by the solvent (polyethylene glycol 400) in the observed phenomenon was considered. Other anticonvulsants (ethosuximide, clonazepam, and dipropylacetic acid) were infused intravenously in rhesus monkeys with the same solvent for 1–2 weeks, and no index of autoinduction was observed[4]. In addition, Ronfeld and Benet (12) showed that the intravenous kinetics of phenytoin in rhesus monkeys were not altered after prolonged intravenous infusion of polyethylene glycol 400.

Several questions remain to be evaluated, particularly the relationship between the induction effect and the dosing regimen (dose or infusion rate and duration of infusion) of the inducing agent. It is not known whether the levels of carbamazepine achieved prior to induction (2.9–4.3 μg/ml) represent minimum or maximum inducing levels. However, it appears that the duration of infusion used in this study was long enough to permit an analysis of the time course of induction.

A significant feature of the present results is that the decrease in the steady-state concentration during autoinduction was exponential. In view of this relatively simple kinetic pattern, the phenomenon of autoinduction becomes quantifiable and, as such, predictable. Thus, it should be possible to design a pharmacokinetic model that will allow the calculation of dosage regimens that can maintain steady-state plasma concentrations of carbamazepine and overcome the phenomenon of autoinduction.

A one-compartment pharmacokinetic model with an exponentially increasing first-order elimination rate "constant" was proposed to explain the decreases in maximum and minimum serum levels of carbamazepine in human volunteers during a 3-week treatment (13). However, such a model would not be appropriate in the present study since short-term infusion studies (5, 6) indicated that the kinetics of carbamazepine in monkeys were dose dependent. A pharmacokinetic model involving simultaneous dose and time dependency is currently being investigated to account for the present results as well as additional chronic infusion data.

[4] Unpublished data.

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