um. The radioactivity was determined by a liquid scintillation technique.

The results (Fig. 1) indicated that 97% of the hydrocortisone had reacted within 45 min, whereas no appreciable reaction with prednisolone occurred.

We are currently attempting to adapt this separation procedure to a radioimmunoassay of prednisolone in plasma. The initial results are encouraging, and the Girard reagent T did not interfere with the radioimmunoassay of prednisolone. Details of this new radioimmunoassay procedure will be reported separately.

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Pharmacokinetic Model to Describe Self-Induced Decreases in Steady-State Concentrations of Carbamazepine

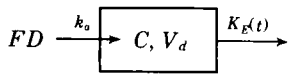
Keyphrases □ Carbamazepine—self-induced decreases in steady-state serum concentrations, pharmacokinetic model proposed □ Pharmacokinetics—model proposed, description of self-induced decreases in steady-state serum concentrations of carbamazepine

To the Editor:

It has been reported that carbamazepine reduces the serum concentrations and elimination half-lives of several drugs, including itself, in several species (1–9). A study was performed to examine the behavior of serum carbamazepine levels during chronic administration of 6 mg/kg/day for 22 days to six normal drug-free human volunteers.

During the 3 weeks of treatment, there were significant decreases in average, maximum, and minimum (C_{min}) steady-state serum concentrations compared to values predicted from single-dose studies in the same subjects (Table I). By the end of the 3rd week, the average steady-state concentration was 50% of the level predicted from single-dose studies. In addition, the elimination half-life at the end of the 3rd week had decreased from 33.9 ± 3.5 hr[1] (single-dose determination) to 19.8 ± 4.0 hr[1]. Similar results recently were reported by Eichelbaum *et al.* (9); they found biological half-lives of 35.6 ± 15.3 hr following single doses and 20.9 ± 5 hr after 15–21 days of chronic treatment (200 mg/day) in four patients.

[1] The single-dose value was obtained from a nonlinear least-squares fit of the data to $C = A(e^{-KEt} - e^{-kat})$ using a MBDX85 computer program. The terminal half-life was obtained by nonlinear least-squares fit of the 8–72-hr data points.



Scheme I

A literature review failed to produce a pharmacokinetic model that can be used to quantify and predict these self-induced decreases in steady-state concentrations. Several models were examined. The model proposed (Scheme I) is based on the observation that C_{min} appears to decrease at an exponential rate during multiple dosing with carbamazepine. The decrease in C_{min} is compatible with an exponential increase in the elimination rate constant (K_E) if one assumes that the drug is completely absorbed during the dosing interval. (This assumption is reasonable since the mean absorption half-life was 2.3 ± 1.1 hr and the dosing interval was 24 hr.)

In Scheme I, F is the fraction of dose D absorbed, k_a is a first-order absorption rate constant, and C is the concentration of drug in a single compartment of volume V_d. The term $K_E(t)$ represents an exponentially increasing elimination rate "constant," which is given by:

$$K_E(t) = K_E^{\infty} - (K_E^{\infty} - K_E^{0})e^{-K_I t} \qquad \text{(Eq. 1)}$$

where K_E^0 and K_E^∞ are the elimination rate constants at times zero and infinity, respectively, and K_I is a first-order rate constant. This model predicts that C_{min} decreases exponentially to an asymptotic minimum value.

Theoretical concentrations at any time t following multiple doses were approximated by:

$$C = \frac{FD}{V_d}\frac{k_a}{k_a - K_E(t)}\left[\left(\frac{1-e^{-nK_E(t)\tau}}{1-e^{-K_E(t)\tau}}\right)\times e^{-K_E(t)t} - \left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_a t}\right] \qquad \text{(Eq. 2)}$$

where n is the number of doses, and τ is the dosing interval.

Table I compares the experimentally observed mean serum concentrations with concentrations predicted using the proposed self-induction model as well as concentrations predicted using a one-compartment model with a *constant* elimination rate constant. Close agreement is observed between experimental values and predictions of the self-induction model, indicating that the proposed model is adequate to describe the pharmacokinetics of carbamazepine during chronic administration.

The phenomenon of self-induced decreases of steady-state levels during chronic dosing has significant clinical implications. The proposed pharmacokinetic model provides an adequate mathematical description of the rate of the process of self-induction. Also, this self-induction model allows the calculation of a dosage regimen that will maintain constant average concentrations at steady state even in the face of

Table I—Values of Observed Concentrations Compared to Values Predicted Using Single-Dose Data and Values Predicted Using the Self-Induction Model

Day	Hour	Concentration Predicted from Single-Dose Data, μg/ml	Observed Serum Concentration, μg/ml	Concentration Predicted Using Self-Induction Model, μg/ml
8	0	10.2	5.3	5.4
	2	13.4	8.9	9.3
	4	13.9	9.6	9.8
	6	13.5	9.0	9.6
	8	13.2	8.9	8.9
	12	12.5	7.8	8.3
	24	10.4	5.2	5.4
15	0	10.6	4.3	4.5
	2	13.6	7.8	8.2
	4	14.2	8.2	9.1
	6	13.6	7.6	8.2
	8	13.4	7.7	7.5
	12	13.0	6.5	6.5
	24	10.6	4.4	4.5
22	0	10.6	3.8	4.4
	2	13.6	7.1	8.0
	4	14.2	8.3	9.1
	6	13.6	8.0	8.6
	8	13.4	7.1	7.6
	12	13.0	6.3	6.5
	24	10.6	3.8	4.4
	48	6.4	1.8	1.9
	72	4.0	1.0	0.9

an increasing elimination rate constant, thus yielding more efficacious epilepsy therapy.

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Pharmacokinetic Analysis of Renal Handling of Sulfamethizole

Keyphrases □ Sulfamethizole—renal excretion mechanisms, pharmacokinetic analysis □ Excretion, renal—sulfamethizole, pharmacokinetic analysis □ Pharmacokinetic analysis—renal excretion mechanisms, sulfamethizole

To the Editor:

It is important to clarify the renal excretion mechanisms of drugs when considering their effectiveness and safety. Weiner and Mudge (1) carried out extensive physiological studies of renal tubular excretion mechanisms, but studies have not been made on the quantitative relationship between secretion and reabsorption of drugs in the nephron. Previously, we elucidated the renal handling of sulfonamides by means of inhibitory experiments (2, 3); but since the conditions are harsh, there is a limitation in the application of this method to humans.

The present study was undertaken to establish an analytical method for renal excretion mechanisms of drugs under more suitable conditions to enable clinical applications to humans. For this purpose, renal handling of sulfamethizole was analyzed using an analog computer to determine the alteration of plasma concentration and clearance ratio after intravenous administration of a single dose of sulfamethizole.

Generally, the excretion of a drug from the kidney into urine is expressed by:

$$UV = (GFR)P_f + S - A \qquad \text{(Eq. 1)}$$