method (pKa = 2.54) at the analytical wavelength, λ 316 nm (4). At the time of preparation of this manuscript, it was found[3] that the reported pKa value of methaqualone in the Schulman *et al.* (5) study was 2.59 ± 0.006 by absorptiometric and fluorometric pH titration. This result is additional evidence of the erratic pKa value reported by Chatten *et al.* (1).

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Application of Girard Reagent T to Radioimmunological Assay of Prednisolone in Plasma

Keyphrases □ Prednisolone—separation from hydrocortisone with Girard reagent T, applicability to radioimmunological determination □ Hydrocortisone—reaction with Girard reagent T, separation from prednisolone, plasma □ Girard reagent T—reaction with hydrocortisone, separation from prednisolone, plasma

To the Editor:

Due to the cross-reactivity between endogenous hydrocortisone and prednisolone, Sullivan *et al.* (1) suppressed the production of interfering endogenous hormone by pretreating the volunteers with dexamethasone in their recent bioavailability trial of this drug. In our study, we separated prednisolone from hydrocortisone by selectively forming the water-soluble derivative of the latter and extracting the prednisolone into the organic phase.

Lederer (2) reported that the rates of reaction of a number of steroid ketones with water-soluble Girard reagent T in an acetic acid–methanol mixture established the order of keto group reactivity to be Δ^4-3 ≫ 20 ≫ 11. It seems reasonable to expect that the reactivity of the $\Delta^{1,4}$-3 ketone function of prednisolone is much less than that of the Δ^4-3 ketone group of hydrocortisone on the basis of resonance and steric considerations. Thus, a water-soluble hydrazone derivative of hydrocortisone can be selectively formed in the presence of prednisolone.

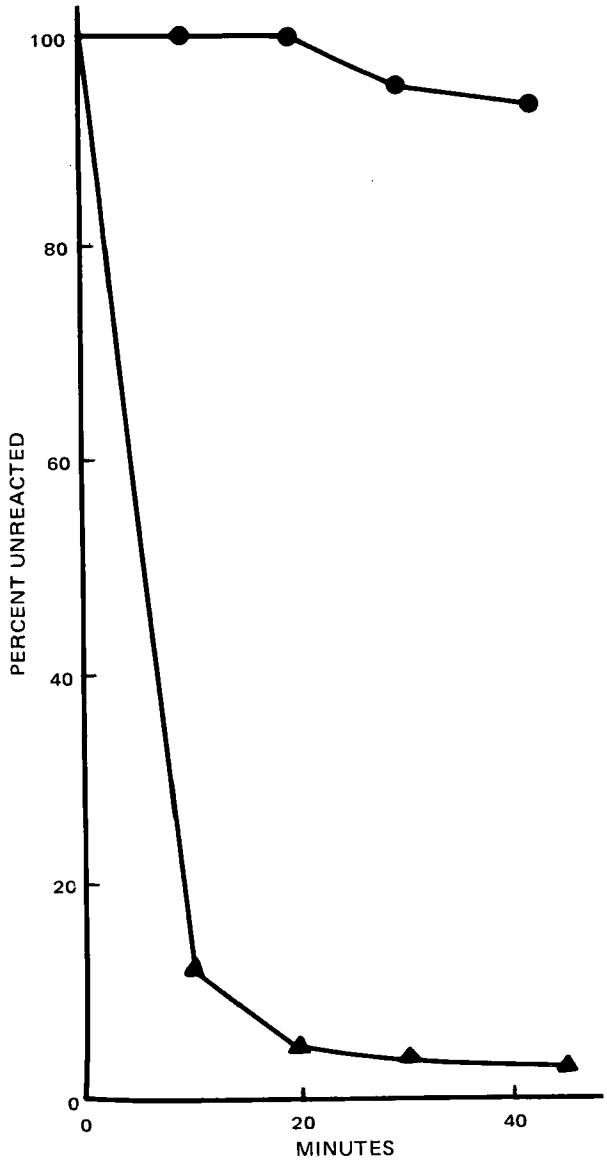

Figure 1—*Separation of prednisolone and hydrocortisone in plasma using Girard reagent T. Key:* ●, *prednisolone; and* ▲, *hydrocortisone.*

In our experiment, 1.0 ml of plasma was spiked with either 100,000 dpm of prednisolone (6,7-^{3}H)[1] plus 5 ng of cold carrier or 50,000 dpm of hydrocortisone (1,2-^{3}H)[2] plus 10 ng of cold carrier. Following the extraction of the drug into 5 ml of methylene chloride–ether (40:60), the dried residue was reacted with 50 μl of 10% Girard reagent T [dissolved in acetic acid–methanol (1:10)]. The reaction was stopped at 10, 20, 30, and 45 min by the addition of 0.5 ml of pH 8 phosphate buffer. The aqueous phase was extracted with 5 ml of methylene chloride–ether (40:60), the organic phase was transferred to a scintillation vial, and the solvent was evaporated under vacu-

[1] Specific activity = 40 Ci/mmole.
[2] Specific activity = 35 Ci/mmole.

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

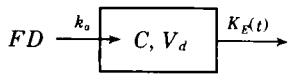
Keyphrases □ Carbamazepine—self-induced decreases in steady-state serum concentrations, pharmacokinetic model proposed □ Pharmacokinetics—model proposed, description of self-induced decreases in steady-state serum concentrations of carbamazepine

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