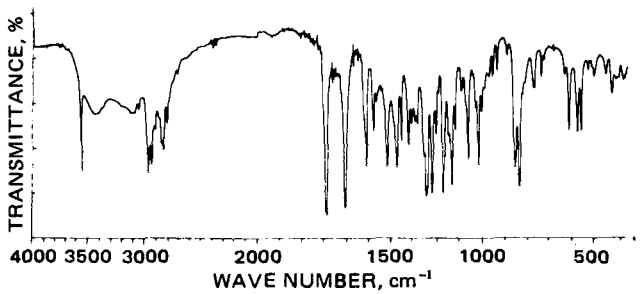

Figure 1—*Spectrum of moperone base; grinding with potassium bromide without any solvent.*

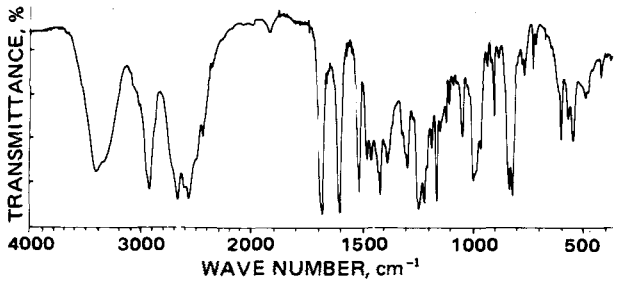

Figure 2—*Spectrum of moperone hydrochloride; grinding with potassium bromide without any solvent.*

In the case of amine hydrochloride, the exchange of chlorine ions with bromine ions was reported (3, 4). However, this explanation is unsatisfactory for the free base form. The presence of very intense absorption bands between 2650 and 2500 cm^{-1}, indicating nitrogen protonation, was confirmed (Figs. 1–3). In the case of moperone, the hydrobromide reextracted from the potassium bromide pellet by a minimum volume of methanol shows a final melting temperature of 184°, determined by thermomicroscopy, even though melting temperatures of the hydrobromide, hydrochloride, and free base forms are 186, 222, and 123°, respectively. It was reported (5) that amine salts having a protonated nitrogen atom of the NH_3^+, NH_2^+, or NH^+ type possess characteristic frequencies of 4000–2000 cm^{-1}.

The hydrobromide form of moperone (reextracted from potassium bromide pellets) was confirmed using X-ray diffraction. The spectra present the characteristic moperone hydrobromide pattern, including intense bands corresponding to *d* values of 0.64, 5.29, 5.16, 4.89, 4.78, 4.25, 3.68, and 3.61 Å. Identical results were obtained with pharmaceutical organic raw materials such as bupivacaine, cinnarizine, diethylpropion, diisopromine, fenfluramine, fluanisone, haloperidol, homatropine, and moperone.

The hydrobromide formation may be attributed to atmospheric carbon dioxide combined with the entropy of the system since the potassium bromide effect persists when sodium redistilled methanol or pyridine and potassium bromide solutions (pH 10) are used. Thus, it is important not to attribute the spectral consequences of this potassium bromide effect to the existence of a new polymorphic form.

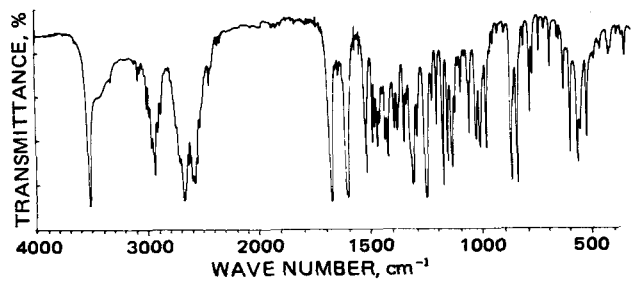

Figure 3—*Spectrum of moperone base or hydrochloride; grinding with potassium bromide and solvent.*

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First-Pass Clearance of Lidocaine in Healthy Volunteers and Epileptic Patients: Influence of Effective Liver Volume

Keyphrases □ Lidocaine—first-pass clearance in healthy volunteers and epileptic patients compared □ Bioavailability—lidocaine, compared in healthy volunteers and epileptic patients, influence of effective liver volume □ Hepatic retention—effect on first-pass clearance of lidocaine, healthy volunteers and epileptic patients compared

To the Editor:

Recent reports (1, 2) compared the absolute oral bioavailability of lidocaine in epileptic patients receiving chronic anticonvulsant drug therapy to that in normal healthy volunteers not receiving enzyme-inducing drugs. The authors of these reports concluded that the greater than twofold reduction in absolute availability observed in the epileptic patients was the result of increased hepatic first-pass metabolism caused by the chronic administration of anticonvulsant drugs.

The present study considers the possible impact of increased hepatic retention, rather than increased metabolic activity, on reduced bioavailability using the first-pass perfusion model presented in Scheme I. The model was used to simulate the effect of increased hepatoportal retention of lidocaine that could result from the induction of nonenzyme-related protein synthesis in the eliminating organ. The product of the liver volume (V_H) and liver retention (R_H) is the effective liver volume (3). Therefore, by definition, an increase in liver mass or hepatic tissue binding is reflected as an increase in hepatic organ clear-

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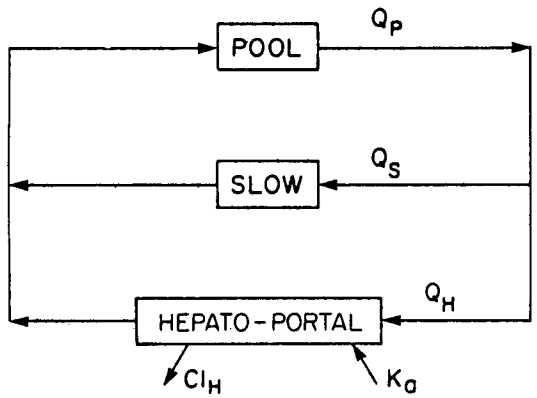

Scheme I—First-pass perfusion model. The perfusion model contains three compartments: 1, the pool, which includes the serum and highly perfused noneliminating tissues where V_P is the pool volume; 2, more slowly perfused noneliminating tissues where V_SR_S is the effective volume of this more slowly equilibrating pool; and 3, the hepatoportal system, which is responsible for drug elimination and where V_HR_H is the effective liver volume. Blood flow to the more slowly perfused organs and the hepatoportal system are described as Q_S and Q_H, respectively, whereas the hepatic clearance is described as Cl_H.

ance (Cl_H) as a result of an increase in the effective liver volume. Classic clearance concepts (4) dictate that changes in hepatic organ clearance (Cl_H) and hepatic blood flow (Q_H) result in changes in the first-pass extraction (E) and total body clearances (Cl_B) according to:

$$E = \frac{Cl_H}{Q_H + Cl_H} \quad \text{(Eq. 1)}$$

$$Cl_B = \frac{Q_H Cl_H}{Q_H + Cl_H} \quad \text{(Eq. 2)}$$

Hepatic organ clearance is generally assumed to mean metabolic clearance, although, in reality, it includes both metabolic activity and tissue retention in the liver due to tissue binding (3).

The experimental data was obtained from a previous report (1) in which six epileptic patients receiving chronic anticonvulsant therapy with known enzyme-inducing agents (*i.e.*, phenobarbital, primidone, carbamazepine, and phenytoin) and six healthy volunteers were studied. Each person was administered 86 mg of lidocaine base equivalents intravenously as the hydrochloride salt and ingested 608 mg of lidocaine base equivalents orally as the monohydrate salt on two separate occasions. Blood samples were withdrawn over 240 min to assess the pharmacokinetics of lidocaine in serum. Serum concentrations were determined by enzyme immunoassay (1).

The following differential equations describe the model presented in Scheme I and were used to simulate serum concentration–time data for oral and intravenous doses simultaneously using the nonlinear least-squares regression program NONLIN (5):

$$\frac{dC_P}{dt} = [(Q_S C_S/R_S) + (Q_H C_H/R_H) - Q_P C_P]/V_P \quad \text{(Eq. 3)}$$

$$\frac{dC_S}{dt} = [Q_S C_P - (Q_S C_S/R_S)]/V_S \quad \text{(Eq. 4)}$$

For the intravenous dose:

$$\frac{dC_H}{dt} = [Q_H C_P - (Q_H C_H/R_H) - (Cl_H C_H/R_H)]/V_H \quad \text{(Eq. 5)}$$

For the oral dose:

$$\frac{dC_H}{dt} = [k_a D e^{-kat} + Q_H C_P - (Q_H C_H/R_H) - (Cl_H C_H/R_H)]/V_H \quad \text{(Eq. 6)}$$

where C_P, C_S, and C_H are the concentrations of lidocaine in the sampled compartment that contains the serum and the highly perfused tissues, more slowly perfused tissues, and hepatoportal system, respectively; V_P, V_S, and V_H are the physiological volumes of these compartments; Q_P, Q_S, and Q_H are the serum flow rate for these compartments; R_S and R_H are the retention factors for drug in the more slowly perfused tissues and the hepatoportal tissues, respectively; Cl_H is the hepatic clearance rate; k_a is the apparent absorption rate constant; and D is the oral dose.

The parameters used in the simulations are presented in Table I. Both oral and intravenous data were simulated to determine the impact of increased effective linear volume on the pharmacokinetics of both administration routes.

The results of the simultations, together with the experimental data for the normal subjects and epileptic patients, are presented in Fig. 1. The differences between normal subjects and patients receiving enzyme-inducing agents can be adequately described by a perfusion model that allows only for a change in the effective liver volume rather than for changes in the enzyme activity *per se*.

Perucca and coworkers (1, 2) attributed reduced oral bioavailability of lidocaine in epileptic patients ingesting

Table I—Pharmacokinetic Parameters Used in the Simulation of Lidocaine Serum Concentration–Time Data for Normal Healthy Volunteers and Epileptic Patients

Parameter	Normal Healthy Controls	Epileptic Patients
k_a, min^{-1}	0.145	0.145
V_P, liters	35	35
V_SR_S, liters	40	40
V_HR_H, liters	50	150
Q_S, liters/min	2.4	2.4
Q_H, liters/min	1.3	1.3
Cl_H, liters/min	2.3	6.2
Cl_B, liters/min	0.83	1.07
E	0.64	0.83

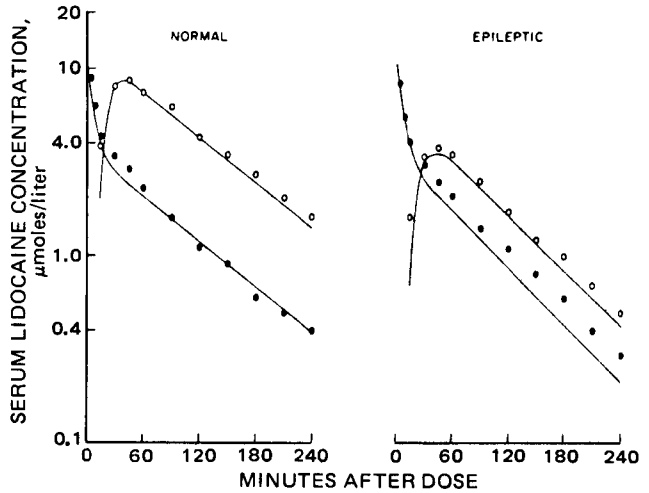

Figure 1—*Simulated and observed serum concentrations of lidocaine following intravenous (●) and oral (○) doses to epileptic patients receiving chronic anticonvulsant therapy and normal, healthy volunteers. The solid lines were simulated according to the model in Scheme I, assuming that the effective liver volume V_HR_H was the only difference between the two study groups. (See Table I for parameters used in the simulation.)*

enzyme-inducing agents to a simple increase in hepatic first-pass metabolism. Although the existence of increased first-pass clearance was supported by the present analysis, the data suggest that an alternative mechanism, increased effective linear volume, may be responsible. Due to the increased retention of lidocaine in the liver as a result of increased effective liver volume, the first-pass clearance of lidocaine was much more extensive in epileptic patients than in normal volunteers.

Although the possibility exists for a reduction in the extent of lidocaine absorption in the epileptic patient, no evidence for a similar interaction could be found in the literature. In addition, it is highly unlikely that all of the anticonvulsant drugs used in this study should have the same effect on absorption. However, there is evidence (7–9) for the increase in effective liver volume observed in the present study. An increase in liver mass during anticonvulsant therapy, as well as an increase in binding affinity by the newly synthesized protein, has been postulated as possible mechanisms.

In conclusion, changes in the pharmacokinetics of drugs due to the chronic administration of enzyme-inducing agents has been attributed solely to increases in the intrinsic metabolic activity (6–9). Concomitant changes in blood flow are sometimes postulated as complementary mechanisms for increased clearance (9–11). However, one mechanism that has generally been overlooked is the effect of enzyme-inducing agents on the effective volume of the eliminating organ, *e.g.*, the liver and/or intestinal mucosa, by increasing tissue mass or tissue binding (10–12).

The results of the present analysis indicate that first-pass clearance may be a complex interaction of several pharmacokinetic parameters including blood flow, metabolic activity, and effective tissue volume. The complexity of this interaction may help to explain the apparent discrepancies between enzyme induction observed *in vitro* and *in vivo*.

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Solubility and Partitioning V: Dependence of Solubility on Melting Point

Keyphrases □ Solubility—dependence on melting point, crystalline compounds □ Crystalline compounds—polycyclic aromatic hydrocarbons, dependence of solubility on melting point

To the Editor:

It is well known that the solubility (in any solvent) of a crystalline solute is at least partially dependent on certain properties of the crystal. The reduction in solubility that is attributable to solute crystallinity is given by:

$$\log \frac{X^C}{X^{SCL}} = \frac{-\Delta S_f (T_m - T)}{2.303RT} + \frac{\Delta C_p (T_m - T)}{2.303RT} - \frac{\Delta C_p}{2.303R} \ln \left(\frac{T_m}{T}\right) \quad \text{(Eq. 1)}$$

where X^C and X^{SCL} are the mole fractional solubilities of the crystalline solute and of the supercooled liquid, respectively; T_m and T are the melting point and temperature of interest, respectively (both in °K); ΔS_f is the entropy of fusion of the crystal; and ΔC_p is the difference in heat capacity between the crystal and the supercooled liquid.

The supercooled liquid, SCL, is the result of melting the crystal at the temperature of interest, which is assumed to be below the melting point. It is the equivalent to the "oil" form of the substance. In most cases, it is not possible to produce the oil or molten form below the melting point. For these cases, the supercooled liquid represents a hypothetical state.

To estimate the solubility of crystalline compounds, it is necessary to estimate the crystal–liquid solubility ratio, X^C/X^{SCL}. This estimation is normally facilitated by simplifying Eq. 1 to remove the ΔC_p terms. Two alternative approximations for ΔC_p are commonly used: $\Delta C_p = 0$ and $\Delta C_p = \Delta S_f$. These approximations lead to the following simplifications.

If $\Delta C_p = 0$:

$$\log \frac{X^C}{X^{SCL}} = -\frac{\Delta S_f (T_m - T)}{2.303RT} \quad \text{(Eq. 2)}$$

If $\Delta C_p = \Delta S_f$:

$$\log \frac{X^C}{X^{SCL}} = -\frac{\Delta S_f}{2.303R} \ln \left(\frac{T_m}{T}\right) \quad \text{(Eq. 3)}$$

Equation 2 was used by Yalkowsky and coworkers (1–4), whereas Eq. 3 was used by Martin *et al.* (5) and was recommended by Hildebrand *et al.* (6).

To verify one or the other of these approximations, it is necessary to find a set of crystalline solutes and a solvent for which X^{SCL} is known. The crystalline polycyclic aromatic hydrocarbons (pah) in benzene are such a system. Since the solutes and solvent have no permanent dipoles, the major cohesive interactions will be the result of London dispersion forces. Dispersion forces are primarily dependent on polarizability, which is proportional to volume for hydrocarbons. Thus, the cohesive energy density of the solutes and the solvent is very similar, and the solutions are very nearly ideal. Because the components of an ideal solution are completely miscible (if they are liquids), it can be assumed that $X^{SCL} = 1.0$ for the polycyclic aromatic hydrocarbons in benzene.

It has been shown that the entropy of fusion of confor-

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