Hepatic Tissue Binding and the Oral First-Pass Effect

Keyphrases □ Oral bioavailability—influence of hepatic tissue binding on first-pass effect □ Lidocaine—oral availability in healthy subjects and epileptic patients compared □ Hepatic tissue binding—effect on oral availability of lidocaine, healthy subjects and epileptic patients compared

To the Editor:

The development in recent years of physiological pharmacokinetic models has provided valuable quantitative insights into factors determining drug disposition. This is particularly so for the process of elimination by either a single (1–3) or a series of multiple organs (4, 5). A seminal contribution was that of Rowland and colleagues (1) who conceptualized the quantitative interrelationship between organ clearance and certain determinants:

$$CL = Q\left[\frac{k_m K_P V_E}{Q + k_m K_P V_E}\right] \qquad \text{(Eq. 1)}$$

where Q is the organ blood flow, k_m is the first-order rate constant for drug elimination, K_P is the apparent partition coefficient of total drug between the eliminating organ and the emergent venous blood, and V_E is the actual tissue volume of the eliminating organ. Subsequent refinement of what has become known as the "venous equilibration" or "well-stirred" model of elimination (3) led to the concept of intrinsic clearance of either total (CL_{int}^{tot}) or unbound (CL_{int}^{u}) drug, and the definition of organ clearance in these terms and the other physiological determinants. Namely, organ blood flow and the unbound fraction of drug in the blood (f_B):

$$CL = Q\left[\frac{CL_{int}^{tot}}{Q + CL_{int}^{tot}}\right] = Q\left[\frac{f_B CL_{int}^{u}}{Q + f_B CL_{int}^{u}}\right] \qquad \text{(Eq. 2)}$$

For a drug that is metabolized under linear conditions, free intrinsic clearance is equivalent to the ratio of the net maximal rate of metabolism from liver water, *i.e.*, nonproteinaceous fluid of the liver (V_{max}) to the Michaelis–Menten constant (K_m) for the involved enzyme(s) (6). It is readily apparent, therefore, that organ clearance, *i.e.*, irreversible drug removal, is independent of the extent of tissue binding in the organ, as reflected by the unbound fraction in the tissue. Nevertheless, some confusion over this matter appears to exist (7) presumably because of the apparent involvement of tissue uptake in Eq. 1. This misconception arises because of the failure to recognize the equivalence of the clearance terms $k_m K_P V_E$ (Eq. 1) and $f_B CL_{int}^{u}$ (Eq. 2), and the inverse relationship between the first-order rate constant (k_m) and effective volume of distribution ($K_P V_E$) when clearance is constant. Such equivalence is readily apparent if K_P is expressed according to its physiological determinants, *i.e.*, the ratio of the unbound fractions of drug present in the blood and the liver (f_B/f_L), and CL_{int}^{u} is equated in the conventional fashion to the product of the rate constant (k_m) and the volume of distribution of unbound drug (V_E/f_L).

The conclusion that tissue binding could affect drug clearance by an organ was based on an analysis (7) of data obtained following oral and intravenous administration of lidocaine to normal volunteers and patients who were receiving chronic anticonvulsant therapy with known enzyme-inducing agents (8). In essence, a simple three-compartmental physiological model was postulated to include rapidly and slowly equilibrating noneliminating tissue pools and the hepatoportal system. By assigning parameter values to tissue volumes, partition coefficients between serum and the tissue (referred to as retention factors in Ref. 7), tissue flow rates, and total intrinsic clearance, the study in the normal subjects was simulated with good agreement between the experimental data and the model. Parameter adjustment then permitted a reasonably good simulation of the different pharmacokinetic findings obtained in the epileptic patients, *i.e.*, a significantly reduced area under the serum concentration–time profile following oral but not intravenous administration with essentially no change in the elimination half-lives. It was indicated in the text and in the legend of Fig. 1 of Ref. 7 that the only difference between the two simulations was an increase in the effective liver volume ($V_H R_H$, equivalent to $V_E K_p$ of Eq. 1). However, examination of the parameters provided in Table I of Ref. 7 indicates that the successful simulation of the data from the epileptic patients required modification of *both* the effective liver volume *and* the total intrinsic clearance (referred to as CL_H in Ref.

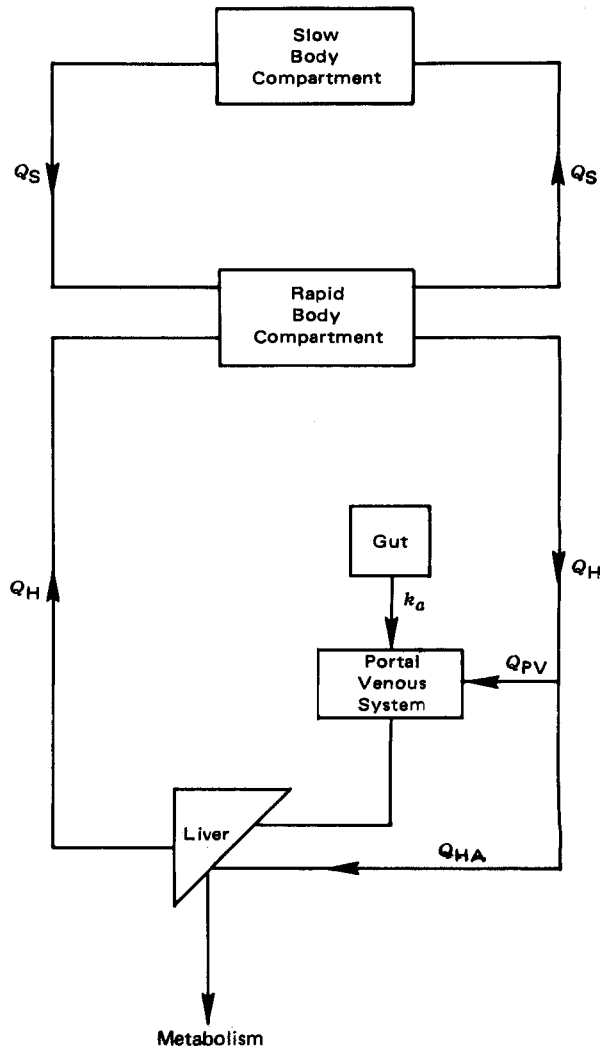

Figure 1—*Physiological model for evaluating the first-pass effect when the body has the characteristics of a two-compartmental system.*

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Table I—Model Parameters for Lidocaine

Volume, L	
V_B	5.0
V_L	1.5
V_{PV}	1.0
V_T^R	11.47
V_T^S	23.0
Flow rate, L/h	
Q_{HA}	18.0
Q_{PV}	72.0
Q_S	198.0
Unbound fraction	
f_B	0.40
f_L	0.65
f_T^R	0.176
f_T^S	0.176
Free intrinsic clearance, L/h	390
Absorption rate constant, h^{-1}	1.75

7). It is, therefore, impossible to conclude that the changes in the pharmacokinetics of lidocaine produced by enzyme-inducing agents was caused solely by an increase in the effective volume of the liver. An additional problem with the simulations is the parameter values chosen for the effective liver volumes: 50 and 150 L for the normal and epileptic subjects, respectively; the physiological basis and appropriateness of these values were not indicated.

To clarify the findings with lidocaine in normal and epileptic subjects, and to specifically examine the role of tissue binding in organ clearance and elimination, a number of simulations were performed based on the physiological model shown in Fig. 1 and described by the following mass balance equations.

Rapidly equilibrating compartment:

$$\frac{dA_T^R}{dt} = (Q_{PV} + Q_{HA})\left(C_L\frac{f_L}{f_B} - C_B\right) + Q_T^S\left(C_T\frac{f_T^S}{f_B} - C_B\right) \quad \text{(Eq. 3)}$$

Slowly equilibrating compartment:

$$\frac{dA_T^S}{dt} = Q_T^S\left(C_B - C_T\frac{f_T^S}{f_B}\right) \quad \text{(Eq. 4)}$$

Liver:

$$\frac{dA_L}{dt} = Q_{PV}C_{PV} + Q_{HA}C_B - (Q_{HA} + Q_{PV})C_L\frac{f_L}{f_B} - CL_{int}^u C_L f_L \quad \text{(Eq. 5)}$$

Metabolism:

$$\frac{dM}{dt} = -CL_{int}^u C_L f_L \quad \text{(Eq. 6)}$$

Portal vein:

$$\frac{dA_{PV}}{dt} = k_a G + Q_{PV}C_B - Q_{PV}C_{PV} \quad \text{(Eq. 7)}$$

Gut:

$$\frac{dG}{dt} = -kaD \quad \text{(Eq. 8)}$$

where C_B, C_T, C_L, and C_{PV} refer to the total drug concentrations in the arterial blood, slowly equilibrating tissue, liver, and portal vein, respectively; Q_T^S, Q_{PV}, and Q_{HA} are the blood flows to the slowly equilibrating tissue, portal vein, and hepatic artery; f_B, f_T^R, f_T^S, and f_L are the unbound fractions of drug in the blood, the rapidly equilibrating tissue, the slowly equilibrating tissue, and the liver; CL_{int}^u is the free intrinsic clearance; D is the oral dose; and k_a is the first-order rate constant for oral absorption.

Furthermore, the effective volumes of the various "organs" may be defined assuming equilibration of the emergent and tissue concentrations of unbound drug.

Rapidly equilibrating compartment:

$$V_R = V_B + V_T^R\frac{f_B}{f_T^R} \quad \text{(Eq. 9)}$$

Slowly equilibrating compartment:

$$V_S = V_T^S\frac{f_B}{f_T^S} \quad \text{(Eq. 10)}$$

Liver:

$$V_L = V_T^L\frac{f_B}{f_L} \quad \text{(Eq. 11)}$$

where V_B, V_T^R, V_T^S, and V_T^L correspond to the actual physiological volumes of the blood, the other rapidly equilibrating tissues, the slowly equilibrating tissues, and the liver, respectively.

The present model is essentially the same as that used by Colburn (7) except that the hepatoportal system is separated into its component organs and the apparent partition coefficient of the drug between the blood and tissue is identified by its physiological determinants, namely the ratio of the unbound fractions of drug in the blood and the tissue. Accordingly, Eq. 5 which describes the mass balance relationship in the liver is mathematically equivalent to Eq. 5 of Ref. 7.

Parameter values for the model (Table I) were selected on the basis of standard values of blood volume, hepatic blood flow, liver weight, and portal venous system volume for a 70-kg man. Other values were based on the known disposition characteristics of lidocaine, for example, the unbound fraction in the blood was taken to be 0.4 (9). The liver/emergent venous plasma partition coefficient of lidocaine at steady state has been experimentally determined to be 0.61 ± 0.16 in the rhesus monkey (10). Based on a blood–plasma concentration ratio in the monkey of 0.8 and an unbound fraction in the plasma of 0.4 (10), this partition ratio provided an estimate of the unbound fraction of lidocaine in the liver of 0.65. To investigate the effect of altering such binding and, therefore, changing the effective volume of the liver, values of f_L ranging from 0.002 to 1.0 were also used. The values of V_T^R and f_T^R and V_T^S and f_T^S were arbitrarily selected to provide the appropriate effective tissue volumes according to preliminary conventional compartmental analysis based on the first-pass model described by Gibaldi and Feldman (11). This analysis also provided an estimate of the blood flow to the slowly equilibrating compartment. The estimate of free intrinsic clearance was based on the mean value reported by Perucca and Richens (8) in the control subjects after taking into account the extent of binding in the blood. Finally, to compare the simulations based on blood concentrations with the experimental serum concentration, the theoretical data was corrected by the blood–serum concentration of lidocaine using a value of 0.88 (8).

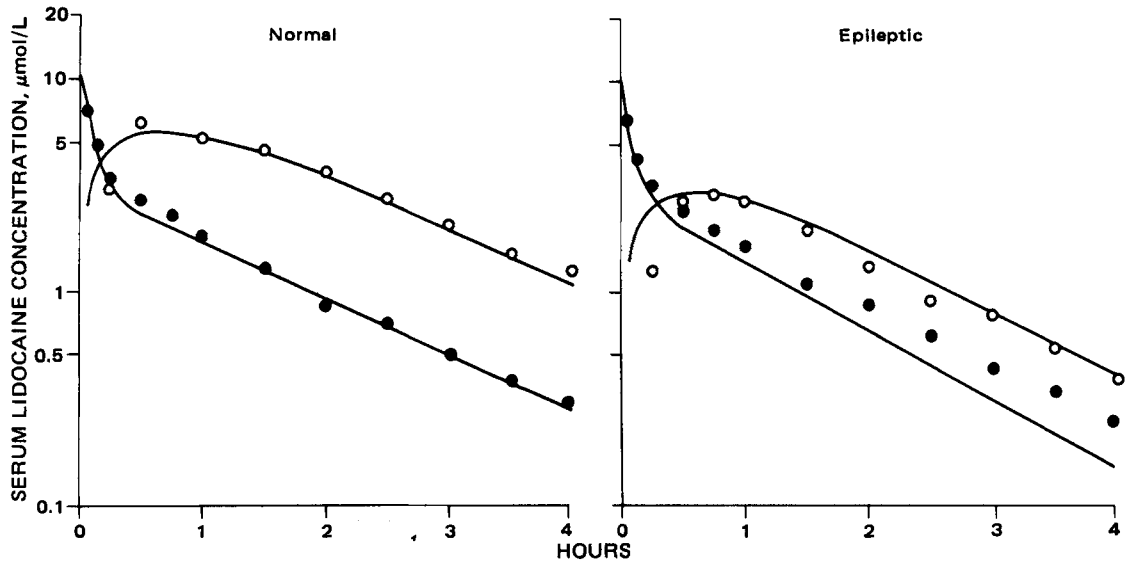

Figure 2—*Simulated and mean observed serum concentrations of lidocaine in normal subjects and epileptic patients following intravenous (●) and oral (○) doses of lidocaine. The solid lines represent the theoretical curves according to the model in Fig. 1 and parameter values in Table I; in the simulation of the epileptic patients only the free intrinsic clearance value was increased.*

Excellent agreement was obtained between the simulation using the parameter values in Table I and the experimental data from the normal subjects (Fig. 2). To test the hypothesis that the altered pharmacokinetics of lidocaine in the epileptic patients was solely due to an increase in hepatic drug-metabolizing ability, as suggested by Perucca and Richens (8), the value of free intrinsic clearance was increased from 390 to 930/h. Again, excellent agreement was obtained with the experimental observations (Fig. 2).

The effect of altering hepatic tissue binding on the oral disposition of lidocaine was examined by altering the unbound fraction over a 500-fold range (0.002–1.0) equivalent to changing the effective liver volume from 0.6 to 300 L. As shown in Fig. 3, this had essentially no effect on the serum concentration–time profile other than a small reduction in the peak serum level and a modest prolongation of the elimination half-life at very high levels of hepatic binding ($f_L < 0.01$). At such extreme values, about 20–70% of drug in the body during the terminal elimination phase would be present in the liver. Importantly, the changes in hepatic tissue binding had no effect on the total area under the oral serum concentration–time curve. Additional simulations indicated that these effects were independent of the value of the free intrinsic clearance, *i.e.*, they applied equally to low- and high-extraction drugs.

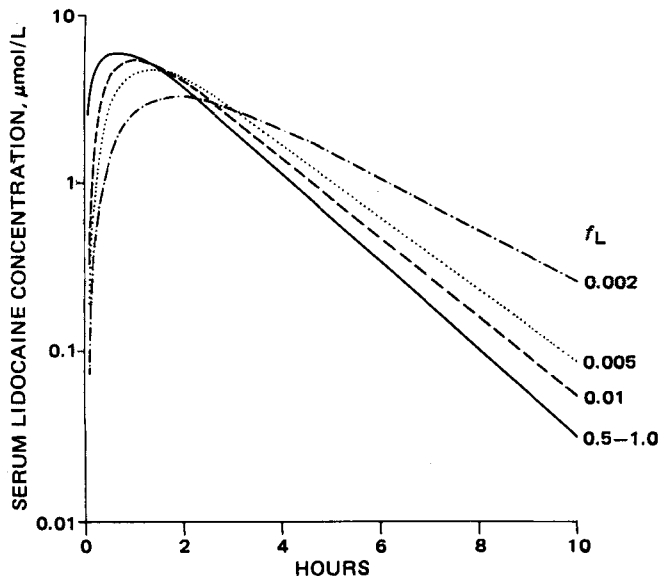

Figure 3—*The effects of the fraction of lidocaine not bound to liver tissue (f_L) on the serum concentrations of lidocaine following oral administration.*

The major experimental finding concerning the effect of chronic anticonvulsant therapy on the disposition of lidocaine was a reduction in the areas under the serum concentration–time curve to about 40% of that determined in subjects not receiving such medication. The elimination half-life and disposition profile following intravenous administration were, however, largely unaffected. It was concluded that these differences were consistent with enzyme induction leading to a two- to threefold increase in the hepatic drug metabolizing activity of a drug that is well extracted by the liver and, therefore, undergoes a large first-pass effect (8). The present analysis based on physiological modeling completely supports this conclusion using parameters consistent with the known disposition of lidocaine. Moreover, the simulations indicate that changes in hepatic tissue binding leading to alterations in the effective volume of the liver have no effect on oral clearance. This is not unexpected, since the total area under the curve following oral administration is equal to the ratio of the absorbed dose to the total intrinsic clearance (2). The major effects of increasing liver binding is to modestly reduce the peak serum concentration and prolong the elimination half-life, as would be predicted from the increased total volume of distribution of the drug.

Considerable insights have been obtained in recent years concerning the quantitative disposition of drugs and the factors controlling important processes such as elimination. In particular, the oral first-pass effect is well understood, especially under linear conditions. While hepatic

tissue binding contributes to the initial uptake and storage of drug in the liver, except in unusual situations, this is a reversible process, and such binding does not affect the irreversible removal of drug by the clearance processes. Accordingly, such a mechanism does not need to be invoked to explain the increased first-pass effect of drugs, including lidocaine, produced by the administration of enzyme-inducing agents.

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Aspirin Prodrug Studies: Lack of Proper Literature Citation

I read with great interest the recent article by Hussain *et al.*, *J. Pharm. Sci.*, **72**, 1093 (1983), which contradicts the observations of Amidon *et al.*, *J. Pharm. Sci.*, **70**, 1299 (1981), concerning the question of aspirin phenylalanine ethyl ester as an aspirin prodrug.

Although the former article unequivocally demonstrates the inadequacies of the latter, it appears that both senior authors have been remiss in acknowledging the important contributions of other investigators in the development of aspirin prodrugs.

In particular, the aspirin triglyceride works of Paris *et al.*, *J. Med. Chem.*, **22**, 683 (1979) and *Agents and Actions*, **10**, 240 (1980) are never cited. More importantly, the only published article which describes the detection of aspirin in the plasma after *in vivo* administration of a prodrug of aspirin is conspicuously absent, Bodor *et al.*, *J. Pharm. Sci.*, **70**, 743 (1981).

The lack of proper literature citation by these authors is a poor reflection of the care taken by them in the preparation of their manuscripts, and is also a reflection on the quality of the reviewers who would allow such an obvious lack of citation to occur.

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