Models of Hepatic Drug Elimination: A Response

Keyphrases □ Hepatic drug clearance—sinusoidal perfusion model, venous equilibrium model

To the Editor:

Although the distributed sinusoidal perfusion model of hepatic elimination described by Bass (1) appears more physiologically realistic than the two previous models, the statement that these latter models have been refuted experimentally should be challenged. First, the data on which this statement is based arise from only two studies (2, 3) and are not as conclusive as implied (1). The study design used in one of these studies (2) has already been acknowledged as not very useful for discriminating among the models in an earlier publication (4). In the other study (3) hepatic venous outflow concentrations of galactose were examined in the perfused rat liver under the influence of two perfusate flow rates (11 ml/min for 50 min, followed by 7 ml/min for 40 min, followed by 11 ml/min for 40 min). The sinusoidal models predict a lowering of the outflow substrate concentration at the lower flow rate, while the venous equilibrium model predicts no change in the outflow substrate concentration. A significant drop in outflow concentration was reported (3), but this was largely determined by averaging the data from the two periods of higher flow even though in about half the 10 experiments the outflow concentration during the second period was considerably greater than the outflow concentration during the first period.

One of the reviewers of this report has highlighted this fact by showing that a paired t test of outflow concentration during the two 11-ml/min flow periods, which were separated by 40 min of perfusion at 7 ml/min (or a constant flow of 11 ml/min in the three control studies), yields a statistically significant difference at the $p < 0.05$ level ($t = 2.19$ $DF = 12$). Similarly, when inflow concentration from these two time periods with a flow at 11 ml/min are tested, a statistically significant difference $p < 0.05$ ($t = 2.24$, $DF = 12$) is observed. One assumption necessary to ensure the legitimacy of all of the calculations performed by Bass is that the liver preparation is physiologically stable over the course of the experiment. Specifically, if a liver is infused with substrate at a constant rate, inflow and outflow concentrations should depend only on hepatic blood flow rate (*i.e.* V_{max} and K_m should not vary as a function of time).

Comparing the first two flow periods only (11 ml/min and 7 ml/min), during which the preparation is more reliable, the outflow of galactose concentrations actually increased in three experiments, decreased by no more than that of control livers (about 10%) in two livers, and decreased more substantially in the other five. Thus, the data could be viewed as inconclusive. Bass has also used the data from the earlier study (3) to support the distributed sinusoidal model (4) which predicts an increase in the logarithmic average of perfusate inflow and outflow concentrations of substrate with decreasing flow. The logarithmic average concentration, however, increased in only 5 of the 10 experiments, the mean change being 0.0009 mM ($SD = 0.0267$), a change of barely 1%: again not conclusive.

The other point that should be made is that the published data on lidocaine (5) supporting the venous equilibrium model have never been refuted by further experimentation with that drug. The studies with galactose cannot be assumed to automatically hold for all other substrates because the experiments were carried out under Michaelis–Menten conditions, galactose is an endogenous substance, and the zone of the liver in which a substance is eliminated (6) may dictate which model applies. For example, a substance, such as galactose, that is eliminated in the periportal region may be expected to follow the distributed sinusoidal model, whereas the venous equilibrium model may be appropriate for drugs that are eliminated in the centrilobular region where the enzymes for drug biotransformation are predominant (6). Therefore, in view of the functional hepatocellular heterogeneity it is naive to assume that all observed phenomena can be explained in terms of a single model as suggested (1). Models will, however, have served their function if they provide inspiration for further experimentation, as suggested previously (7), that ultimately results in more refined and physiologically meaningful models.

(1) L. Bass, *J. Pharm. Sci.*, **72**, 1229 (1983).
(2) S. Keiding, S. Johansen, K. Winkler, K. Tønnesen, and N. Tygstrup, *Am. J. Physiol.*, **230**, 1302 (1976).
(3) S. Keiding and E. Chiarantini, *J. Pharmacol. Exp. Ther.*, **205**, 465 (1978).
(4) L. Bass and P. J. Robinson, *J. Theor. Biol.*, **81**, 761 (1979).
(5) K. S. Pang and M. Rowland, *J. Pharmacokinet. Biopharm.*, **5**, 655 (1977).
(6) K. Jungermann and N. Katz, *Hepatology*, **2**, 385 (1982).
(7) D. J. Morgan and K. Raymond, *J. Pharm. Sci.*, **71**, 600 (1982).

Denis J. Morgan
Victorian College of Pharmacy
Parkville
Victoria, Australia, 3052

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Hepatic Extraction of Free Fatty Acids in Pregnant and Nonpregnant Female Rats

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To the Editor:

Plasma protein binding can have important effects on the metabolic and excretory clearance of drugs (1, 2). Free fatty acids, whose concentrations in plasma can vary appreciably due to stress, diet, and other physiological variables (3), can competitively inhibit the plasma protein binding of many drugs (4, 5). Wiegand and Levy (6) have pointed out previously that extensive hepatic extraction of a protein binding inhibitor could cause an increase in the steady-state plasma concentration of unbound drug, with little or no effect on the concentration of total (free plus bound) drug, if the plasma protein binding of the drug

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