Evidence Favoring the Venous Equilibrium Model for Hepatic Clearance of (S)-(−)-Propranolol

Keyphrases □ Propranolol—hepatic clearance, venous equilibrium model □ Hepatic clearance—propranolol, venous equilibrium model

To the Editor:

Drug clearance is an important pharmacokinetic parameter since it most closely reflects the ability of the body to rid itself of drug. Because the liver is a major site of drug elimination, there is considerable interest in understanding the processes by which drugs are cleared as they pass through this organ. Two physical models for hepatic drug clearance have been proposed. The venous equilibrium or "well-stirred" model assumes that the liver can be viewed as a single homogeneous compartment with the free or unbound drug concentration in hepatic venous blood in equilibrium with that in the liver (1). The sinusoidal model assumes that the liver is composed of a number of parallel tubes with drug-metabolizing enzymes evenly distributed throughout (2). In this model, drug concentration declines continuously as blood traverses the sinusoid. Although the determinants of drug clearance are the same in both models (liver blood flow, unbound fraction of drug in blood, and intrinsic clearance of unbound drug), the equations relating these variables to hepatic clearance differ. For the venous equilibrium model:

$$CL = Q \cdot f_u \cdot CL_{u,int}/(Q + f_u \cdot CL_{u,int}) \quad \text{(Eq. 1)}$$

while for the sinusoidal model:

$$CL = Q(1 - e^{-f_u \cdot CL_{u,int}/Q}) \quad \text{(Eq. 2)}$$

where Q is the liver blood flow, f_u is the fraction of unbound drug in blood, $CL_{u,int}$ is the intrinsic clearance of unbound drug, and CL is the liver clearance.

Despite the difference between these equations, both predict quantitatively similar values for drug clearance under most conditions of varying blood flow, free fraction, or intrinsic clearance. However, an extensive theoretical analysis of the models has suggested that major differences exist in predictions of area under the concentration–time curve (AUC) and systemic availability (F) when highly extracted drugs are administered orally (3). In the venous equilibrium model:

$$F = Q/(Q + f_u \cdot CL_{u,int}) \quad \text{(Eq. 3)}$$

and:

$$\text{AUC} = \text{Dose}/f_u \cdot CL_{u,int} \quad \text{(Eq. 4)}$$

while in the sinusoidal model:

$$F = e^{-f_u \cdot CL_{u,int}/Q} \quad \text{(Eq. 5)}$$

and:

$$\text{AUC} = \text{Dose}(e^{-f_u CL_{u,int}/Q})/Q(1 - e^{-f_u CL_{u,int}/Q}) \quad \text{(Eq. 6)}$$

It is readily appreciated from these equations that changes in blood flow or drug binding will result in approximately linear changes in F and AUC for a highly extracted drug according to the venous equilibrium model, while the sinusoidal model predicts exponential changes.

The venous equilibrium model appears to be much more commonly employed in pharmacokinetic analysis today. However, there is little physiological or experimental evidence to suggest that this model is preferable. Using the isolated perfused rat liver preparation, Pang and Rowland (4) found that the clearance of highly extracted lidocaine was best described by the "well-stirred" model. The hepatic elimination of galactose, however, has been observed to be more consistent with the predictions of the sinusoidal model (5). Both of these investigations were conducted under conditions of perturbed blood flow. Such studies could also be carried out by varying the degree of protein binding (3). Jones *et al.* (6) have recently reported that a sevenfold change in the free fraction of propranolol does not alter effluent unbound propranolol concentration in the perfused rat liver, a finding consistent with venous equilibrium theory. The discovery over the past several years that many highly extracted basic drugs are highly bound to α_1-acid glycoprotein (7) makes this approach feasible not only *in situ* but also in the intact animal, since the concentration of α_1-acid glycoprotein and degree of protein binding may change dramatically and rapidly in a number of conditions and disease states (8–10).

The recently published data of Terao and Shen (11) provides an excellent opportunity to evaluate the relative merits of the proposed models based on *in vivo* observations. These investigators administered oral and intravenous (S)-(−)-propranolol to rats 1 and 7 d following implantation of an indwelling jugular venous catheter. The free fraction of (S)-(−)-propranolol decreased from an average of 0.169 1 d following catheter insertion to 0.074 7 d later, presumably due to a catheter-stimulated increase in α_1-acid glycoprotein concentration. Bioavailability and AUC were measured following the administration of oral drug on both occasions and are listed in Table I. F was found to increase from 4.1 to 7.8%, while AUC increased from 3.45 to 6.95 μg·min/mL as protein binding increased.

The predicted effect of such a change in binding on these parameters was calculated for both models using Eqs. 3–6. These predictions assume complete absorption of (S)-(−)-propranolol, that liver blood flow and intrinsic clearance of unbound drug are the same on both study days and that

Table I—Observed and Predicted Changes in F and AUC Secondary to Increased Protein Binding

	$f_u = 0.169$	$f_u = 0.074$	Ratio[b]
Observed F (%)[a]	4.1	7.8	1.90
Predicted			
Venous equilibrium model	—	8.9	2.17
Sinusoidal model	—	24.6	6.00
Observed AUC (μg·min/mL)[a]	3.45	6.95	2.01
Predicted			
Venous equilibrium model	—	7.88	2.28
Sinusoidal model	—	26.32	7.63

[a] Data from Terao and Shen (11). [b] Ratio of value at $f_u = 0.074$ to observed value at $f_u = 0.169$.

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(S)-(−)-propranolol is entirely cleared by the liver. The value of $CL_{u,int}$ for each model was estimated from Eqs. 1 and 2 using the (S)-(−)-propranolol clearance of 6.61 mL/min/100 g observed following intravenous administration 1 d after catheter insertion. Q was calculated using this value for clearance and an extraction ratio of 0.959. Table I lists the predictions and compares the ratio of predicted or observed values at the time of increased binding to the original observation. As expected, significant differences between the models were observed with the venous equilibrium equations predicting 2.17- and 2.28-fold increases in F and AUC, respectively, given the observed binding change, while the sinusoidal model predicted 6.00- and 7.63-fold increases in these parameters. Clearly, the predictions of the venous equilibrium model more closely approximate the values observed by Terao and Shen (11). In fact, there is remarkably good agreement with only 14.1 and 13.4% error in the predictions of F and AUC, respectively, using this model.

Although this data is limited to observations in one species with a single substrate, it does provide *in vivo* evidence in support of the venous equilibrium model for hepatic clearance. This is important information since there are many clinical situations in which liver blood flow, protein binding, or intrinsic drug clearance may be altered. Knowledge of the appropriate physical model for hepatic clearance allows one to predict with reasonable accuracy the effect of changes in these factors on important pharmacokinetic parameters such as F and AUC. This is particularly crucial when highly extracted compounds are administered orally. Prospective studies examining this issue further with other highly extracted drugs are needed in order to confirm that the venous equilibrium model is indeed the preferred physical model for hepatic drug clearance.

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Method for Determination of First-Pass Metabolism in Human Skin

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To the Editor:

The technological advances in drug-delivery systems have allowed increased utilization of transdermal formulations for therapeutic purposes. This route of administration is most suitable for potent drugs possessing short biological half-lives, extensive first-pass metabolism after oral administration, and narrow therapeutic indices. By controlling the rate of delivery and absorption through the skin, it is possible to maintain therapeutic drug concentrations in the blood and/or at the site of action. The systemic blood concentrations of such compounds after transdermal administration in humans is very low and often below the sensitivity levels of specific assay procedures. Nitroglycerin, which undergoes extensive first-pass metabolism when given orally, is one of the most widely used drugs in transdermal systems. To circumvent the assay sensitivity problem and allow for a comparison of dosage forms, Karim (1) has proposed, and effectively implemented, blood sampling from the ipsilateral antecubital forearm veins after application of the topical formulation on the volar surface of the wrist. The purpose of this communication is to describe a similar procedure that can also estimate the percutaneous first-pass metabolism of topically applied compounds, even when extensive biotransformation takes place in the skin.

Drug and/or drug and metabolite (*i.e.*, total) concentrations in samples from the contralateral antecubital forearm will be low and represent the systemic blood concentrations (C_c). The ipsilateral samples will contain higher blood concentrations (C_i), and represent the concentration of the drug absorbed plus C_c at any given time. After correction for C_c, the ipsilateral concentrations will directly reflect the flux of the drug (C_j) through the skin; *i.e.*,

$$C_j = C_i - C_c \qquad \text{(Eq. 1)}$$

where $C_i = C_{p,j} + C_{m,j} + C_{p,c} + C_{m,c}$, $C_c = C_{p,c} + C_{m,c}$, and $C_j = C_{p,j} + C_{m,j}$. In this case C_p is the concentration of the unchanged drug and C_m is the total concentration of metabolites.

In the absence of any metabolism and/or degradation of the drug during the percutaneous absorption process, C_j will consist of the intact drug only, *i.e.*, $C_j = C_{p,j}$. If during the absorption processes the drug undergoes metabolism, C_j will consist of the concentrations of the drug ($C_{p,j}$) and metabolite(s) ($C_{m,j}$) in the ipsilateral samples at any time. In such a situation the magnitude of the first-pass metabolism can be estimated by calculating the fractions of unchanged drug and metabolite(s). Biotransformation and/or binding in the vein from the absorption site (the skin) up to the point of blood sampling would be accounted for but not differentiated from metabolism in the skin. The same is true if degradation processes other than biotransformation were involved.

When the rate of absorption through the skin is constant, and C_j reaches steady-state level, the fraction metabolized in the skin (f_s) can be estimated by:

$$f_s = \frac{C_{m,j}}{C_{p,j} + C_{m,j}} \qquad \text{(Eq. 2)}$$

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