Hepatic Elimination—Dispersion Model

To the Editor:

The liver is the main organ in the body for the biotransformation of endogenous substances and foreign chemicals (e.g., drugs). The rate at which the liver handles these substances is of importance, as this rate determines the resultant amount of such substances in the body and, hence, the magnitude of any consequent effect. Amongst the main determinants of hepatic elimination of a substance are the flow rate of blood to the liver, the binding of the substance to components within blood, and the activity of the related liver enzymes.[1] Stress, diet, disease, drugs, and various physiological variables can affect these and other determinants. Predicting quantitatively the likely outcome on hepatic elimination, therefore, requires the development of a meaningful model that incorporates these determinants. Three models of hepatic elimination have been widely used: the "well-stirred" or "venous equilibration" model,[1] the "parallel-tube" or "sinusoidal perfusion" model,[2] and the "distributed" model[3,4] (Fig. 1). Various experimental data have been obtained which support one or other of these models.[5-7] Vigorous discussion by proponents of each model have been forthcoming.[8-11] We now present a new unifying model of hepatic elimination, the *dispersion model* (Fig. 1). We show that the dispersion model of the liver is consistent with hepatic physiology and that all existing models of hepatic elimination are specific forms of this more general model.

The dispersion model proposed here is analogous to that proposed by chemical engineers to describe nonideal flow in a packed-bed reactor.[12] The model is characterized by two main parameters: the *efficiency number* (R_N) and the *axial dispersion number* (D_N). The efficiency number is a measure of the efficiency with which a solute is irreversibly removed from the blood passing through the liver. This parameter is dependent on the binding of solute with components within blood, the permeability of the sinusoidal wall to solute, hepatocellular enzymatic activity, solute concentration, and other variables. The axial dispersion number is a measure of the dispersion or spread in residence times of solute molecules moving through the liver: the higher the value of D_N, the greater the degree of axial dispersion. In packed beds, mixing or dispersion is caused by both "splitting" of the fluid streams as they flow around the bed particles and by variations in solute velocity across the bed. Both diffusional and convectional forces are involved. The branching of the sinusoids and interconnections, together with variations in the velocity and path lengths traveled by elements of blood, cause a similar type of dispersion in the liver. Axial diffusion of solute down individual sinusoids is a relatively small component of overall dispersion within the liver.[13,14]

Consider now the liver being perfused with a constant concentration of solute. An axial dispersion model expresses the transport of solute molecules in the liver in terms of bulk (convective) flow, axial dispersion (mixing of blood), and disappearance by elimination. Considering the liver to be a cylinder, at steady state, for a first-order reaction, the following rate equation for an axial dispersion model holds:

$$D_{ax}\frac{d^2C}{dx^2} - v\frac{dC}{dx} - kC = 0 \qquad (1)$$

Axial Dispersion — Convective Flow — Elimination

where D_{ax} is the axial mixing or dispersion coefficient, v is the mean velocity of blood in the liver, C is the concentration of solute at distance x in the liver (of length L), and k is the first-order rate constant for irreversible removal of solute. Equation 1 can be restated in dimensionless terms, $\boldsymbol{C} = C/C_{in}$ (where C_{in} is the input concentration), $z = x/L$, $D_N = D_{ax}/vL$, and $R_N = k \cdot L/v$:

$$\frac{d^2\boldsymbol{C}}{dz^2} - \frac{1}{D_N}\cdot\frac{d\boldsymbol{C}}{dz} - \frac{R_N}{D_N}\cdot\boldsymbol{C} = 0 \qquad (2)$$

where z is the fraction of the distance from the inlet to exit of the liver and $\boldsymbol{C}$ is the concentration of solute at point z, normalized to the entering solute concentration. In the absence of a permeability limitation, at distance x along the liver:

$$\text{Rate of elimination} = CL'_{int}\cdot C_u = f_u\cdot CL'_{int}\cdot C \qquad (3)$$

where CL'_{int} is the intrinsic hepatocellular clearance of solute per unit volume of liver, C_u is the unbound concentration of solute at distance x, and f_u is the fraction of solute unbound (i.e., C_u/C). Under such conditions, the efficiency number can be reexpressed in terms of the liver "cross-sectional area" (A), hepatic volume ($A \cdot L$), hepatic blood flow Q ($v \cdot A$), f_u, and CL_{int}, the intrinsic clearance of the liver. Thus:

$$R_N = \frac{f_u\cdot CL'_{int}\cdot L}{v} = \frac{f_u\cdot CL'_{int}\cdot L\cdot A}{v\cdot A} = \frac{f_u\cdot CL_{int}}{Q} \qquad (4)$$

The boundary conditions appropriate for an eliminated solute in the liver are the Dankwerts conditions,[15] which are:

$$\text{at}\quad z = 0, \qquad \boldsymbol{C} - D_N\frac{d\boldsymbol{C}}{dz} = 1 \qquad (5)$$

$$\text{at}\quad z = 1, \qquad \frac{d\boldsymbol{C}}{dz} = 0 \qquad (6)$$

Refinements of these conditions to yield continuous-distance profiles with dispersion prior to the site of elimination[16] or with dispersion only after the site of elimination[17] yield the same complete solution. The appropriateness of application of these boundary conditions to hepatic elimination is discussed elsewhere. The complete solution is:[16]

$$F = \frac{4a}{(1+a)^2\cdot\exp[(a-1)/2D_N] - (1-a)^2\cdot\epsilon\cdot\exp[-(a+1)/2D_N]} \qquad (7)$$

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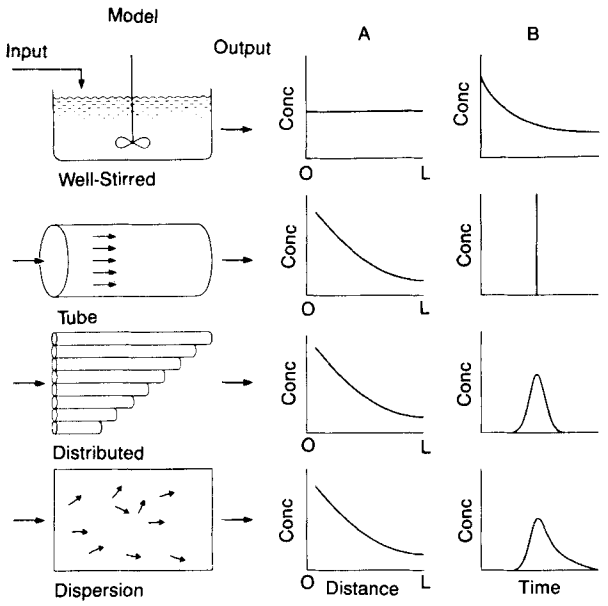

Figure 1—*Models of hepatic elimination. The diagrammatic representation of the dispersion model is adapted from a proposed zonal sinusoidal configuration in the liver presented by Gumucio (ref. 19). The other models represent a well-mixed (stirred) solution in a beaker (the well-stirred or venous equilibration model), the plug flow of an impulse of solute down a tube (the tube or sinuosidal perfusion model), and a normal distribution of blood flow and enzyme activity across the liver (the distributed model). Column A is concentration–distance profiles within the liver; column B is output concentration–time profiles.*

where F is the ratio of output to input concentrations of solute, i.e., the bioavailability of substance across the liver, and $a = (1 + 4R_N \cdot D_N)^{1/2}$.

Now, as $D_N \rightarrow \infty$ (i.e., when there is extensive axial dispersion), the higher-order terms of the series expression for the exponents can be neglected, and hence eq. 7 reduces to:

$$F = \frac{1}{1 + R_N} \tag{8}$$

which is the expression for the "well-stirred" or "venous equilibration" model.[1] If $D_N \rightarrow 0$ (i.e., axial dispersion is negligible), eq. 7 reduces to:

$$F = \exp(-R_N) \tag{9}$$

Equation 9 is that obtained using the "parallel-tube" or "sinusoidal perfusion" model[1,2] of hepatic elimination.

The more recent hepatic elimination model, the distributed model,[3] was introduced to improve predictions of the parallel-tube model. In the distributed model, a normal distribution of blood velocities and enzyme activity within the liver is assumed, and the differences in the predictions of the tube and distributed models are determined by the coefficient of variation of this normal distribution.[4,12] If axial dispersion of a solute within the liver is small (D_N is small) then dispersion approximates to a normal (Gaussian) distribution, and eq. 7 reduces to:[12]

$$F = \exp(-R_N + R_N^2 \cdot D_N) \tag{10}$$

This equation is equivalent to the form of the distributed model given by Bass et al.,[3] with $D_N = \epsilon^2/2$ (where ϵ is defined in the distributed model as the coefficient of variation of blood flows within the liver).

It is of interest that the "parallel-tube" and "well-stirred" models are the two asymptotic solutions of the dispersion model. The difference between these two solutions only becomes apparent at large values of R_N, i.e., rapid rate of solute extraction. If R_N is small such that extraction of solute across the liver is low ($0.6 < F < 1$), eq. 7 can be approximated to eq. 11 by expanding the exponents and neglecting higher-order terms:

$$F = \exp(-R_N) = \frac{1}{\exp(R_N)} = \frac{1}{1 + R_N + \frac{R_N^2}{2!} + \frac{R_N^3}{3!} \cdots} \simeq \frac{1}{1 + R_N} \tag{11}$$

Accordingly, F is most dependent on D_N for large values of R_N.

We now consider the relationship of the dispersion and other models with the known physiology of the liver. Figure 1 shows an idealized representation of each model and corresponding concentration versus distance–time profiles. The parallel-tube and well-stirred models[1] represent an ideal flow behavior of fluid within the liver and are inconsistent with the observed behavior of solutes within the liver. Nonideal flow behavior is represented by the distributed and dispersion models. However, the basis of these two models is fundamentally different. The distributed model developed by Forker and Luxon[4] is based on a precise and ideal representation of flow within individual sinusoids and extralobular vasculature, of morphological arrangement, and of enzymatic distribution. Elegant simulations using this model have revealed that the shape of the solute disappearance curve is insensitive to intralobular heterogeneities.[10] The model correctly predicts that the concentration down the liver decreases with distance traveled by blood and that the concentration–time profile of a substance after an impulse injection into the liver will be of a bell shape. The skewness of the profile is highly dependent on the form of the distribution model used. The relatively complex model of Forker and Luxon[4,10] gives a skewed-to-right profile, whereas a single assumption of a normal distribution in blood flow–enzyme activity[3] will lead to an approximately symmetric profile.[12] As the distributed model is attempting to simulate the precise physiology of the liver, it is characterized by certain deficiencies and complex mathematics.

The dispersion model, in contrast, ignores the detailed events occurring within the liver and seeks to provide a global representation of the outcome of hepatic elimination after injection of a solute into the liver. In this model, the dispersion number is a measure of the dispersion or nonideal flow behavior of solute within the liver as indicated by the spread (variance) of the solute outflow concentration versus time profile following bolus input. In chemical engineering, the dispersion number (or its reciprocal, the Peclet number) is often estimated by using the method of moments.[12,18] For a noneliminated solute, the basic differential equation for the dispersion model is:[12]

$$\frac{\partial C}{\partial T} = D_N \cdot \frac{\partial^2 C}{\partial z^2} - \frac{\partial C}{\partial z} \tag{12}$$

where T is dimensionless time ($t \cdot v/L$). The variance for this model with boundary conditions given in eqs. 5 and 6 is:[12,18]

$$\sigma^2 = \mathrm{VRT} - \mathrm{MRT}^2 = 2D_N - 2D_N^2(1 - e^{-1/D_N}) \tag{13}$$

where σ^2 is the normalized variance, and MRT and VRT are the first and second moments of the output concentration–time curve, respectively. The other parameter, the efficiency number R_N, is also a global "average" and can be determined for a given solute from F, D_N, and eq. 7.

Several pieces of information point to a high degree of dispersion of solute within the liver. Figure 2 shows the cumulative probability distribution of blood velocities in hepatic sinusoids. It is apparent that the distribution is not normal (Gaussian) as would have been expected if there was only moderate dispersion, but skewed and can better be represented as a logarithmic normal distribution. Further evidence for a high degree of dispersion is the pronounced skewed output

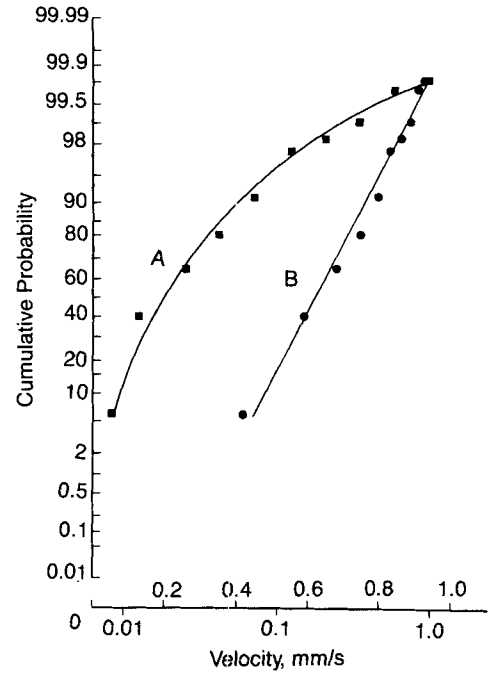

Figure 2—*The normal (A) and log-normal (B) plots of cumulative probability distribution of erythrocyte velocities in rat hepatic sinusoids. Data taken from Koo et al. (ref. 20) and represents the measurement of 515 sinusoids. The upper abscissa is a linear scale and the lower abscissa is a logarithmic scale of velocities.*

concentration–time profile for boluses of labeled erythrocytes and albumin injected into the portal vein[13] (Fig. 3). Evaluation of these profiles by the method of moments yields a dispersion number of ~0.2. It appears likely that the value of D_N is, however, highly dependent on the experimental conditions and solutes employed, which may account, in part, for differences in the ability of the well-stirred and parallel-tube models to explain existing hepatic clearance data for drug substances.[22] For instance, according to the definition for D_N ($D_{ax} \cdot A/Q \cdot L$), dispersion reduces with increasing blood flow. Simulations show that the change in bioavailability with flow is less with

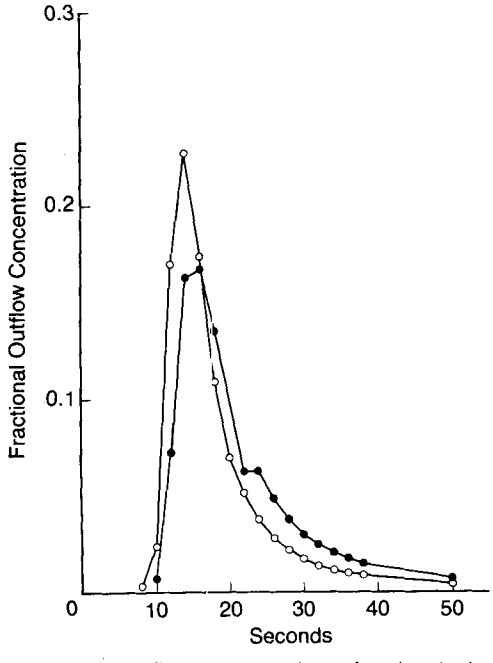

Figure 3—*Fractional outflow concentrations after the single pass of an impulse (bolus) of ^{51}Cr-labeled red blood cells (○) and ^{125}I-labeled albumin (●) into the portal vein of an isolated perfused rat liver system [modified from Ahmad (ref. 21)].*

the dispersion model than would be anticipated using the tube and distributed models and is in greater agreement with experimental findings and the predictions of the well-stirred model.

The hepatic dispersion model presented here is based on the assumption that the dispersion number is reflected solely by the variation in the residence times of erythrocytes in the liver. This assumption does not hold when there is slow efflux of the solute back into the blood from hepatocytes. However, significant redistribution implies a low efficiency number (R_N) and according to eq. 11, F for these solutes is relatively insensitive to the model used. As the slow efflux of solute from the cell is likely to decrease the concentration–distance gradient along the liver, the predictions for F should be intermediate between those of the "well-stirred" model and the dispersion model based on a dispersion number corresponding to the residence time distribution of erythrocytes. Although the hepatic dispersion model presented here is more general than other models of hepatic elimination previously considered, it is still rather simple, being characterized by only two parameters, R_N and D_N. Still, it appears to be suitable to describe the steady-state behavior of solutes in the liver. However, at some stage additional known complexities, such as the efflux of solute from cell[23] and heterogeneous enzyme distribution[24] will need to be incorporated into any model that attempts to describe quantitatively transient hepatic elimination.

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MICHAEL S. ROBERTS*
MALCOLM ROWLAND‡x

* School of Pharmacy
University of Tasmania
Hobart, Australia
‡ Department of Pharmacy
University of Manchester
Manchester M13 9PL, U.K.

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