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Hepatic Drug Clearance Model: Comparison among the Distributed, Parallel-Tube and Well-Stirred Models

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The potential influence of the transverse heterogeneity in the sinusoidal enzyme contents and the capillary transit times on the elimination from the liver sinusoids was evaluated by using distributed models. Moreover, the predictions of the undistributed model (the parallel tube model), the venous equilibration model (the well-stirred model), the new distributed models presented in this study and the distributed model by Bass *et al.* (*J. Theor. Biol.*, **72**, 161 (1978)) for the hepatic drug clearance were compared. Data on lidocaine kinetics reported by Pang and Rowland (*J. Pharmacokinet. Biopharm.*, **5**, 655 (1977)) were employed. The steady state output concentration of lidocaine in the blood leaving the liver was predicted better by the well-stirred and distributed models than by the parallel tube model. Because both the parallel tube and well-stirred models ignore the anatomic and metabolic heterogeneities in the liver lobule, they may be refuted experimentally and theoretically, as reported by Goresky *et al.* (*J. Clin. Invest.*, **52**, 991 (1973)). It is considered that the distributed model taking account of the transverse heterogeneity in the sinusoidal enzyme contents and the capillary transit time, based on anatomical evidence, can well accommodate the experimental data on lidocaine.

Keywords—hepatic drug clearance; distributed model; undistributed model; well-stirred model; parallel tube model; sinusoidal enzyme heterogeneity; capillary transit time

Two models for hepatic drug clearance incorporating the physiological variables of hepatic blood flow, drug binding and the activity of drug-metabolizing enzymes have been developed in recent years. Rowland *et al.*[1] assumed that the liver is a single well-stirred compartment (the venous equilibration model or well-stirred model), and that the concentration of the unbound drug in the emergent blood is in equilibrium with unbound drug within the liver. Winkler *et al.*[2] assumed that the liver is composed of a number of identical and parallel tubes (the undistributed model or parallel-tube model), along which the drug concentration decreases progressively in the direction of the blood flow, due to its elimination by enzymes in the hepatocytes. Theoretical analysis of the two models for hepatic clearance has revealed that the most powerful discriminator between the two models is the effect of the blood flow on either the emergent drug concentration or the availability of a highly extracted compound.[3] Pang and Rowland[4] have examined the effect of changes in the blood flow rate on the hepatic clearance of lidocaine (extraction ratio, $E=0.99$) in the perfused rat liver. The concentrations of lidocaine and its metabolite in the emergent venous blood were better predicted by the well-stirred model than by the parallel tube model. However, these models ignore the anatomic and metabolic heterogeneities in the liver lobule. Thus, the following features seem important.

1) The distribution of the sinusoidal transit times is ignored in the well-stirred and parallel tube models. Goresky *et al.*[5] carried out multiple indicator dilution studies of the hepatic circulation in the dog using labeled red blood cells, albumin and other substances. They concluded that the outflow patterns of these substances could best be explained in terms of a distribution of transit times.

2) The intracellular concentration gradient in the lobule is ignored in the well-stirred model. Goresky *et al.*[5] reported the presence of a lengthwise concentration gradient from the portal triad to the central vein in both the sinusoids and the hepatic cells when a process of intracellular sequestration takes place.

3) The difference in enzyme contents among capillaries is ignored in both the well-stirred and parallel tube models.

Bass *et al.*[6,7] extended the parallel tube model to hepatic elimination with functionally identical sinusoids by introducing statistical distributions of the enzyme contents per sinusoid and of the blood flow per sinusoid.

In this paper, we present distributed models based on the concept of transverse heterogeneity in the sinusoidal enzyme contents and the capillary transit time. The purpose of the present article is to derive equations for the various models that relate the determinants of the hepatic drug clearance (the hepatic blood flow and the hepatocellular enzymatic activity) with various pharmacokinetic parameters and to elucidate the similarities and differences in the behavior of the models when these determinants of the drug clearance change.

Theoretical

Models and experimental techniques for measuring the kinetics of hepatic transport based on the distributed model in the whole liver have evolved over many years, from the analysis of sigle-pass, multiple-indicator dilution curves by Goresky *et al.*[5] to the analyses of disappearance curves using a recirculation method by Forker and Luxon.[8] Bass *et al.*[6,7] extended the parallel tube model by introducing statistical distributions of enzyme contents per sinusoid and blood flow per sinusoid. The transverse heterogeneity is exemplified by arteriovenous shunts of the extracting system. In this study we investigated the effect of the distribution of enzyme contents among capillaries on the hepatic drug clearance of lidocaine. Moreover, our proposed model was compared with the well-stirred and parallel tube models, which were reported by Rowland *et al.*[1] and Winkler *et al.*[2] and the distributed model of Bass *et al.*[6,7] respectively.

Based on a single-pass steady-state liver system, the steady state hepatic extraction ratio (E_H) was expressed as follows:

$$E_H = \frac{C_{in} - C_{out}}{C_{in}} \tag{1}$$

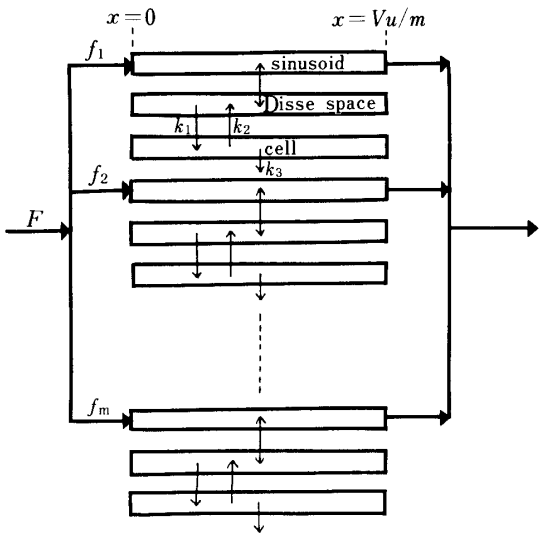

Fig. 1. Compartmental Model for a Typical Sinusoidal Array

so that

$$C_{out}=C_{in}\cdot(1-E_H) \tag{2}$$

where C_{in} and C_{out} are the influent and effluent concentration of the drug in the blood respectively. Consider m identical sinusoids grouped in n classes according to the n values of f_i, the plasma flow per sinusoid. The flow distribution scheme assigns a fraction, α_i, of the m sinusoids to each flow class as shown in Fig. 1. The corresponding extraction ratio (E_H) obtained from Forker and Luxon's model[8] is

$$E_H=1-\sum_{i=1}^{n}\frac{\alpha_i\cdot m\cdot f_i}{F}\cdot\exp\left(-\frac{\frac{Vu}{m}\cdot\gamma\cdot k_1\cdot\frac{Vu}{m}\cdot\theta\cdot k_3}{f_i\cdot\frac{Vu}{m}\cdot\theta\cdot(k_2+k_3)}\right) \tag{3}$$

$$\alpha_i=\frac{\exp\left(-\frac{1}{2}\cdot\frac{2\cdot i-1-n}{n\cdot\sigma}\right)^2}{\sum_{i=1}^{n}\exp\left(-\frac{1}{2}\cdot\frac{2\cdot i-1-n}{n\cdot\sigma}\right)^2} \tag{4}$$

$$\frac{\alpha_i\cdot m\cdot f_i}{F}=\frac{\alpha_i\cdot(2\cdot i-1)}{n} \tag{5}$$

$$m\cdot f_i=\frac{(2\cdot i-1)\cdot F}{n} \tag{6}$$

where Vu, γ, θ, k_1, k_2, k_3, σ and F are the aggregate volume of all m sinusoids, the ratios of the Disse volume and the intracellular volume to Vu, the influx, efflux, and sequestration rate constants, the coefficient of variation and the total hepatic blood flow, respectively.

It is assumed that there is no diffusional barrier between the drug in blood and the enzyme within the hepatocyte: that is, the rate of distribution is perfusion-limited. This assumption appears to hold.[9,10] Then,

$$k_1\cdot\gamma=k_2\cdot\theta>>k_3\cdot\theta \tag{7}$$

so that

$$E_H=1-\sum_{i=1}^{n}\frac{\alpha_i\cdot m\cdot f_i}{F}\cdot\exp\left(-\frac{Vu}{m\cdot f_i}\cdot\theta\cdot k_3\right) \tag{8}$$

Next, let us consider the frequent distribution of enzyme contents per sinusoid. When a sinusoid with the capillary transit time, $Vu/(m\cdot f_i)$, in the i-th class has the fractional metabolic intrinsic clearance of $x\cdot\beta_i$, that of the whole liver can be expressed as follows:

$$\sum_{i=1}^{n}x\cdot\beta_i\cdot\alpha_i\cdot m=\theta\cdot Vu\cdot k_3 \tag{9}$$

where x and β_i are a proportional constant and a distribution function of the metabolic intrinsic clearance contents ($\sum_{i=1}^{n}\beta_i=1$) per sinusoid, respectively. Thus,

$$x\cdot\beta_i=\frac{\theta\cdot Vu\cdot k_3}{m\cdot\sum_{i=1}^{n}(\beta_i\cdot\alpha_i)}\cdot\beta_i \tag{10}$$

Substituting Eq. 9 into Eq. 8 gives

$$E_H = 1 - \sum_{i=1}^{n} \frac{\alpha_i \cdot m \cdot f_i}{F} \exp\left(- \frac{\theta \cdot Vu \cdot k_3 \cdot \beta_i}{m \cdot f_i \sum_{i=1}^{n} (\beta_i \cdot \alpha_i)} \right) \tag{11}$$

Substituting Eq. 11 into Eq. 2 gives

$$C_{out} = C_{in} \cdot \sum_{i=1}^{n} \frac{\alpha_i \cdot m \cdot f_i}{F} \exp\left(- \frac{Vu \cdot k_3}{m \cdot f_i \cdot \sum_{i=1}^{n} (\beta_i \cdot \alpha_i)} \right) \tag{12}$$

We will now consider various models according to distribution function of the metabolic intrinsic clearance enzyme contents per sinusoid.

[1] Model I

As shown in Fig. 2(a), each sinusoid has the same enzyme content or metabolic intrinsic clearance.[8] Thus,

$$\beta_i = \frac{1}{n} \tag{13}$$

Rearranging Eq. 11 gives

$$E_H = 1 - \sum_{i=1}^{n} \frac{\alpha_i \cdot m \cdot f_i}{F} \exp\left(\frac{-\theta \cdot Vu \cdot k_3}{m \cdot f_i} \right) \tag{14}$$

[2] Model II

As shown in Fig. 2(b), when the sinusoidal flow (f_i) is slow, the enzyme content or the intrinsic clearance per sinusoid is high, and a linear relationship can be assumed between the two parameters.

$$\beta_i = \frac{2 \cdot (n - i)}{n \cdot (n - 1)} \tag{15}$$

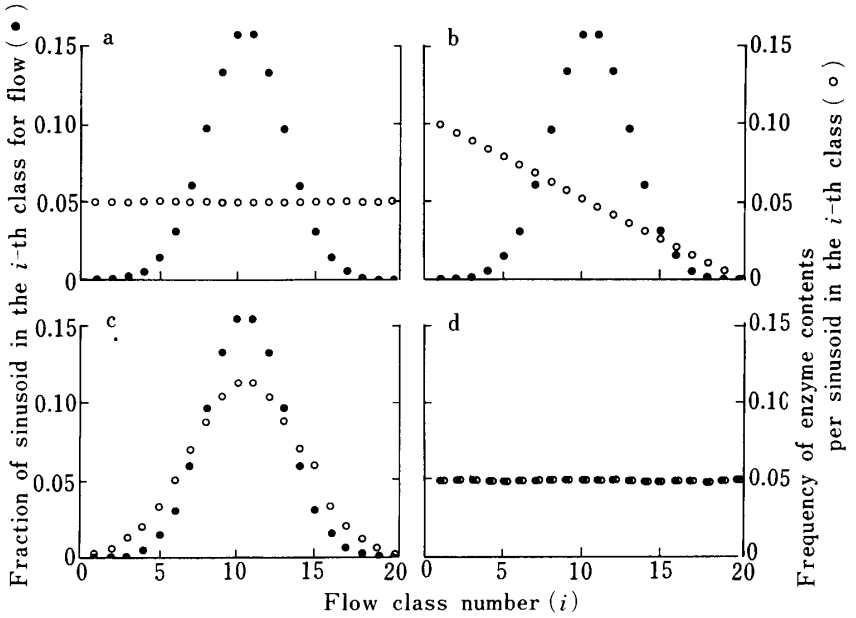

Fig. 2. Transverse Distribution of Sinusoidal Flows and Enzyme Contents

a, model I; b, model II; c, model III; d, model IV. Key: ●, fraction of the sinusoids in the i-th flow class; ○, frequency of the enzyme content (or the metabolic intrinsic clearance) per unit sinusoid in the i-th class.

Rearranging Eq. 11 gives

$$E_H=1-\sum_{i=1}^{n}\frac{\alpha_i\cdot m\cdot f_i}{F}\cdot\exp\left(\frac{-\theta\cdot Vu\cdot k_3\cdot 2\cdot(n-i)/n/(n-1)}{m\cdot f_i\cdot\sum_{i=1}^{n}2\cdot(n-i)/n/(n-1)\cdot\alpha_i}\right) \tag{16}$$

[3] Model III

As shown in Fig. 2(c), when the density in the distribution of sinusoidal flow (f_i) is high, the enzyme content or the metabolic intrinsic clearance per sinusoid is also high. β_i was assumed to be the same function of normal probability density as α_i and a coefficient of variation equal to 0.30 was assumed.

$$\beta_i=\frac{\exp\left(-\frac{1}{2}\cdot\frac{2\cdot i-1-n}{n\cdot\sigma'}\right)^2}{\sum_{i=1}^{n}\exp\left(-\frac{1}{2}\cdot\frac{2\cdot i-1-n}{n\cdot\sigma'}\right)^2} \tag{17}$$

By substituting Eq. 17 into Eq. 11, E_H can be calculated.

[4] Model IV

The hepatic extraction ratio (E_H) according to the well-stirred model is given by the following equation.[3)]

$$E_H=\frac{\theta\cdot Vu\cdot k_3}{F+\theta\cdot Vu\cdot k_3} \tag{18}$$

[5] Model V (Fig. 2(d))

The E_H according to the parallel tube model is given by the following equation.[2)]

$$E_H=1-\exp\left(-\frac{\theta\cdot Vu\cdot k_3}{F}\right) \tag{19}$$

This is a special case of Model I ($n=1$).

[6] Model VI

Model VI is the Bass-type model.[6,7)]Normal probability density functions as the distribution function in both the sinusoidal enzyme content and the capillary transit time were assumed in this model. The sum of clearances in the sinusoids with the capillary transit time in the i-th class and with the enzyme activity (or the metabolic clearance) in the j-th class was expressed as follows (this equation is similar to Eqs. 5 and 6).

$$(\alpha_i\cdot m)\cdot g_j=\frac{(2\cdot j-1)\cdot E_j}{n} \tag{20}$$

where g_j and E_j are the enzyme activity (or the metabolic intrinsic clearance) per sinusoid in the j-th class and the sum of the enzyme activities (or the metabolic intrinsic clearances) in the sinusoids with the transit time in the i-th class. Then,

$$\sum_{i=1}^{n}E_i=k_3\cdot Vu\cdot\theta \tag{21}$$

so that

$$\sum_{i=1}^{n}\alpha_i\cdot m\cdot g_j=\sum_{i=1}^{n}\frac{2\cdot j-1}{n}\cdot E_i \tag{22}$$

$$m\cdot g_j=\frac{2\cdot j-1}{n}\cdot k_3\cdot Vu\cdot\theta \tag{23}$$

$$g_j=\frac{2\cdot j-1}{m\cdot n}k_3\cdot Vu\cdot\theta \tag{24}$$

and E_H is given by

$$E_H=1-\sum_{i=1}^{n}\left\{\sum_{j=1}^{n}\left(\frac{\alpha_i\cdot m\cdot\varepsilon_j\cdot f_i}{F}\right)\cdot\exp\left(-\frac{g_j}{f_i}\right)\right\}\cdot k_3 \tag{25}$$

The normal probability density function was used as the distribution function (ε_j) of the enzyme activity (or the metabolic intrinsic clearance).

$$\varepsilon_j=\frac{\exp\left\{-\frac{1}{2}\cdot\left(\frac{2\cdot i-1-n}{n\cdot\sigma''}\right)\right\}^2}{\sum_{i=1}^{n}\exp\left\{-\frac{1}{2}\cdot\left(\frac{2\cdot i-1-n}{n\cdot\sigma''}\right)\right\}^2} \tag{26}$$

After dividing this range into 20 equally spaced enzyme activities (or clearances), the fraction of the sinusoids with a particular enzyme activity (or metabolic intrinsic clearance) was calculated from the function using a coefficient of variation (σ'') equal to 0.25 or 0.4. In our experience, takin $n=20$ will define the distribution of enzyme activities with sufficient precision to estimate the availability (1-E) and the output drug concentration (C_{out}).

Results

Figure 3 illustrates the relationship between the sequestration rate constant ($\theta\cdot k_3$) and the availability ($A=1\text{-}E_H$) calculated by using equations 11, 14, 16, 18 and 19 based on the various models described in Theoretical. For simulation, the values of 7.65,[11] 0.0749 ml/g liver[6] and 1 ml/min/g liver were used for θ, Vu and F, respectively. The procedure for assigning the distribution of sinusoidal blood flows assumed a range of flows from zero to twice the mean value. After dividing this range into 20 equally spaced flow classes, the fraction of sinusoids receiving a particular flow was calculated from the function of normal density using a coefficient of variation equal to 0.25.

A large difference was observed in the simulation curves with A ranging from 0 to 0.5 among these models, while no remarkable difference in the simulation curves for A ranging from 0.5 to 1.0 was observed. The simulation curves based on the distributed model, *i.e.*, models I, II, III and VI, lay midway between those of the well-stirred model (model IV) and the parallel tube model (model V).

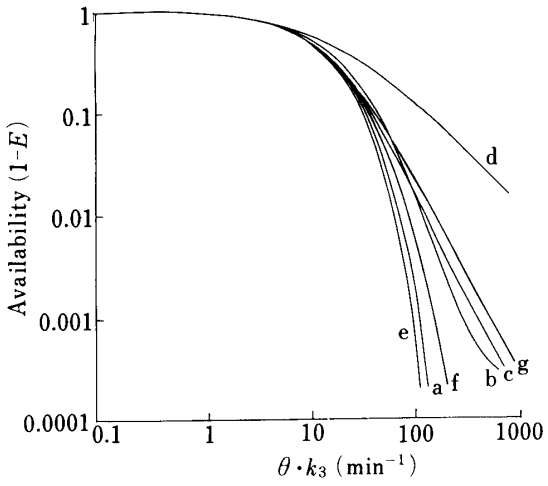

Fig. 3. Relationship between the Availability ($A=1-E$) and the Enzyme Activity ($\theta\cdot k_3$) in Six Models

a, model I; b, model II; c, model III; d, model IV; e, model V; f, model VI ($\sigma''=0.20$); g, model VI ($\sigma''=0.40$).

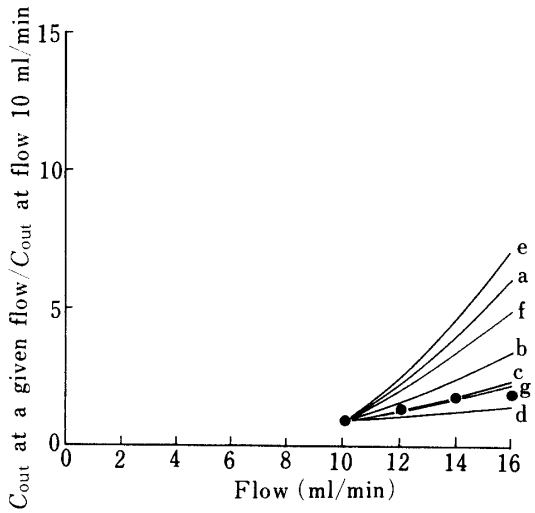

Fig. 4. Plots of the Predicted and Observed Lidocaine Concentrations in the Effluent Blood (C_{out}) Obtained by Using Five Models When the Hepatic Blood Flow was Changed from the Control Flow Rate (10) to 12, 14 and 16 ml/min per Liver

The lines represent predictions by models I, a; II, b; III, c; IV, d; V, e; VI ($\sigma'=0.25$), f; VI ($\sigma''=0.40$), g and the points represent observations reported by Pang and Rowland.[4]

Discrimination among models was examined in the case of lidocaine under linear conditions by varying the hepatic blood flow. Pang and Rowland[4] reported the effect of the hepatic blood flow on C_{out} of lidocaine using model IV and V. In this study we compared our proposed distributed models (models I, II and III) with the well-stirred, parallel tube and the Bass-type models. By changing the values of C_{in} and C_{out} for lidocaine at a control flow rate (10 ml/min), the E_H was calculated to be 0.9945 by means of Eq. 1. By appropriate substitution of E_H and the blood flow rate into Eq. 11, the values of the metabolic intrinsic clearance ($Vu \cdot \theta \cdot k_3$) were calculated using models I, II, III, IV, V and VI. Assuming that the value of $Vu \cdot \theta \cdot k_3$ is constant, the C_{out} of lidocaine at the steady state was predicted for each new flow rate (12, 14 and 16 ml/min) by using Eq. 12. The predicted values calculated by using models I, II, III, IV, V and VI were then compared with the reported data. As shown in Fig. 4, it is clear that the prediction by using models I, II, III, IV and VI gives a better fitting to the observed data than that by using model V.

Discussion

With respect to the hepatic elimination of galactose, the well-stirred and the parallel tube models have already been experimentally refuted, the former at $p=0.01$[12] and the latter at $p=0.002$[13,14] statistical significance. Moreover, Goresky[5] demonstrated the presence of a lengthwise concentration gradient of galactose from the portal triad to the central vein, in both the sinusoids and the hepatic cells when a process of irreversible intracellular sequestration takes place. Heterogeneity of the transit times of indicators was observed in the hepatic vein as dilution curves following an arterial bolus injection (see, for example, reference 5). These findings appear to be grounds for refuting the two models. As shown in Fig. 4, the simulation curve calculated by using model I, where a heterogenous distribution of the sinusoidal transit times is assumed, was closer to the observed curve than that calculated by using the parallel tube model. However, we could not completely account for the observed behavior of lidocaine in terms of the transverse heterogeneity of the transit times alone. Thus, we developed a new model incorporating the heterogenous distribution of enzyme contents among the sinusoids. Model II shows a linear relationship between the the sinusoidal flow rate and the enzyme content (or the metabolic intrinsic clearance) per sinusoid. Namely, a sinusoidal unit with a larger transit time (or slower sinusoidal flow) has a higher content of available intracellular enzyme for substrates. As shown in Fig. 4, the simulation curve calculated by using Eq. 12 for model II was closer to the observed data than that obtained by using model I. The following logic may explain this finding. If all the sinusoids

have an identical volume (Vu/m) and capillary velocity (w), a highly perfused sinusoid (capillary with a small transit time) may have a wide capillary diameter, a short capillary length and a relatively small capillary surface. Assuming that the enzyme content (or the metabolic intrinsic clearance) per unit sinusoidal area is identical among capillaries, a sinusoid with smaller transit time may have lower enzyme activities. Koo *et al.*[15] observed microscopically a hepatic microcirculation in the transilluminated liver of the rat. The portal and hepatic venous microvessels were classified into four groups according to their branching hierarchy, and the hepatic sinusoids into branching, direct and interconnecting types according to their topographic arrangements. The diameters of the three types of sinusoids did not significantly differ, but the velocity of the erythrocytes in the direct sinusoid was significantly faster than that in the branching sinusoid while that in the interconnecting sinusoid fluctuated widely. Consequently, a sinusoid with a slower flow (a larger transit time) may have a more ramified network and higher enzyme content. These considerations may partly explain the results shown in Fig. 4. In model III, a sinusoid in a fraction with a higher distribution of capillary transit times has a greater enzyme content. Furthermore, model VI, which is similar to the distributed model presented by Bass *et al.*,[6,7] assumed a normal probability density function in the distributions of both the sinusoidal enzyme contents and the capillary transit times. Bacause experimental evidence for the transverse heterogeneity in the sinusoidal enzyme contents has not yet been obtained, we cannot determine which model (model III and VI; $\sigma'' = 0.40$) correctly reflects the situation *in vivo*.

In any case, the distributed model with transverse heterogeneity of the sinusoidal enzyme contents and capillary transit times, based on anatomical evidence, seems to account quite well for the experimental data for lidocaine. Although the well-stirred model unexpectedly showed the same phenomena as the distributed model, this model seems to be inconsistent with experimental findings on the microcirculation of the liver. Moreover, the distributed model proposed in this study seems to be more appropriate for defining the zonal heterogenous distribution of enzymes and carrier proteins[16] than the well-stirred model.

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