Models of Hepatic Drug Elimination

Keyphrases □ Hepatic drug clearance—saturation kinetics, sinusoidal perfusion model, venous equilibrium model □ Heterogeneity of organ extraction—intrahepatic shunts

To the Editor:

In a recent communication (1) Morgan and Raymond identify observable quantities which would help to discriminate between two models of drug uptake by the intact liver: the venous equilibration model (2) and the undistributed sinusoidal perfusion model (3, 4). Several comments are necessary in light of recent results.

In the case of hepatic elimination of galactose, the two models have already been refuted experimentally: the first at 0.01 (5) and the second at 0.002 (6, 7) levels of statistical significance. To be so decisive, these experiments involved substrate concentrations across the entire Michaelis–Menten range, whereas Morgan and Raymond (1) confine their considerations to the limiting forms of the models at substrate concentrations so low that the hepatic uptake kinetics become linear (first order).

The quantitative results which refute the undistributed sinusoidal perfusion model give strong support to the distributed sinusoidal perfusion model (7, 8) not discussed by Morgan and Raymond (1). Michaelis–Menten uptake by a single perfused sinusoid is treated the same in the undistributed (4) and distributed (8) models, but the distributed model drops the biologically incredible assumption that all sinusoids extract equally: it incorporates and quantifies functional heterogeneity of sinusoids and its effect on organ uptake.

Envisage an intact liver with hepatic blood flow rate F and, for some enzyme–substrate combination, the Michaelis constants, V_{max} and K_m (intrinsic hepatic clearance V_{max}/K_m), resulting in a steady uptake rate:

$$V = F(C_i - C_o) \qquad \text{(Eq. 1)}$$

when the substrate concentration is C_i at the inlet and C_o at the outlet of the liver. For N sinusoids acting in parallel, the undistributed model asserts that the corresponding quantities for each sinusoid are:

$$f = F/N = \bar{f},\ v_{max} = V_{max}/N = \bar{v}_{max},\ v = V/N = \bar{v} \qquad \text{(Eq. 2)}$$

By contrast, the distributed model works with statistical dispersions of v_{max} and f (about their means $\bar{v}_{max}$ and $\bar{f}$) over the assembly of sinusoids comprising a liver. It is, in fact, the dispersion of the ratio v_{max}/f that controls deviations from the undistributed model in the context of uptake (7).

Now, let an arbitrary distribution of v_{max}/f over the sinusoids of an intact liver have the variance σ^2. A remarkable feature of Michaelis–Menten kinetics [and of more general saturation kinetics (7, 9)] is that when it is put in the hepatic setting, the rate of uptake by an undistributed liver, $V(\sigma^2 = 0)$, is always greater than the rate of uptake by a distributed liver, $V(\sigma^2)$, which has the same values of the macroscopic parameters F, V_{max}, K_m. The rate $V(\sigma^2 = 0)$ is thus an *upper limit* of the rate $V(\sigma^2)$; it is remarkably close in some cases (7, 10). There is also a lower limit of $V(\sigma^2)$ valid for any shape of the v_{max}/f distribution (7). For Michaelis–Menten kinetics:

$$V(\sigma^2 = 0) \geqq V(\sigma^2) \geqq V(\sigma^2 = 0) - 2F\sigma^2/(27K_m) \qquad \text{(Eq. 3)}$$

This exact result will suffice to indicate how functional heterogeneity of the intact liver can be studied in terms of the distributed model. A clinically interesting problem of this kind is the quantification of intrahepatic shunts (8), since such shunts are kinetically equivalent to a fraction of sinusoids with $v_{max} = 0, f \neq 0$.

The study by Keiding and Chiarantini (5) went beyond merely refuting the venous equilibration model: it set a calculable upper limit on the possible values of σ^2 in the rat liver (10). An altogether different attempt at discriminating between the venous equilibration model and the undistributed perfusion model has been made by Pang and Gillette using the hepatic conversion of a substrate into a metabolite, which is in turn conjugated in liver cells (11). When suitably interpreted, the results of the experiment neither refute nor confirm the sinusoidal perfusion model, but rather give information about functional heterogeneity of the liver along the blood flow [zones of liver function (12 and references therein)].

The aforementioned comments emphasize the fruitfulness of the controversy touched upon recently (1), which is surely a sufficient consolation for the refutation of both the contending models.

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