Scand. J. clin. Lab. Invest., Vol 36, 1976.

EDITORIAL

Hepatic Elimination Kinetics: The Influence of Hepatic Blood Flow on Clearance Determinations

The capacity of the liver to eliminate various substances from the blood stream is important clinically. Using various test substances we may obtain a quantitative measure of certain of the liver's life- and health-sustaining processes. Furthermore, the elimination of several drugs depends on liver function, and the correct dosage presumes information on their hepatic elimination kinetics and on the degree of modification induced therein by liver damage.

Apart from non-steady-state processes—as, for example, distribution in the various parts of the body—the disappearance rate from the blood of substances eliminated by the liver is determined by the rate-limiting step in the hepatic elimination process. This can, for instance, be the hepatocyte-membrane transport, the intracellular transport, the enzymatic conversion, or the excretion into the bile. In making the theoretical models of the kinetics of the liver, it is usually either assumed that the rate-limiting process is irreversible or the model (and the experimental setup) is designed to describe the net forward reaction only.

With few exceptions compartmental analysis has been used. The concentration at which the elimination takes place is taken to be that measured in arterial or peripheral venous blood. This corresponds roughly to the concentration in the inflow to the liver (c_i). This model would be correct if the hepatocytes were distributed in such a way that all cells are exposed to the substrate at the inflow concentration (a 'sieve model'). The removal process is mostly assumed to follow a first-order reaction; that is, the elimination rate (v) is proportional to the concentration (c_i). Accordingly, v/c_i is independent of the elimination rate and can be used to describe the elimination kinetics as

$$\text{'systemic clearance'} = v/c_i \,. \qquad [1]$$

In agreement with this concept, Krarup & Larsen (8) found a ratio of v/c_i (called plasma clearance) that is independent of the infusion rate of indocyanine green during steady state.

'Systemic clearance' can be used in clinical pharmacology to predict drug dosage, since the elimination of several drugs follows first-order kinetics at therapeutic concentrations. In quantitative evaluation of liver function, how-

ever, 'systemic clearance' is of limited value, because for most drugs it depends not only on hepatic elimination capacity but also on hepatic blood flow. The flow dependence of the 'systemic clearance' of indocyanine green has been demonstrated in the cat (8) and in man (5).

In an attempt to account for the flow dependence of 'systemic clearance', Rowland et al. in 1973 (9) developed a perfusion model of hepatic removal processes that has been extensively used in pharmacology (see, for example Refs. 4, 10). The model assumes that the hepatic and the systemic compartments are connected by the hepatic blood flow (F) and that the removal reaction from the hepatic compartment is a first-order reaction. The concentration in the hepatic compartment equals the outflow concentration (c_o), as if all hepatocytes were floating freely in a substrate solution (a 'jar model'). The elimination kinetics is in this model described by

$$\text{'intrinsic clearance'} = v/c_o, \qquad [2]$$

when recalculated from Ref. 10.

In this model 'instrinsic clearance' is independent of hepatic blood flow, and it is assumed to reflect the inherent ability of the liver to remove the substrate. However, the model does not take into consideration the effect of the decreasing concentration along the sinusoid from c_i to c_o. This phenomenon implies that 'intrinsic clearance' may be flow-dependent, as discussed below.

Most hepatic processes are enzymatic reactions which often are described in vitro by Michaëlis-Menten kinetics—that is, saturation kinetics. This relation is described by the maximal elimination rate, Vmax, and the half saturation concentration, *K*m—that is, the concentration at which the elimination rate is half of Vmax. A sinusoidal perfusion model that assumes the decreasing concentration profile along the sinusoidal tubes to be created by an irreversible Michaëlis-Menten removal process at each location of the sinusoid has been developed (3, 11) and experimentally supported (7). From the model three basic equations arise that in principle express the same relations:

$$v = Vmax \cdot \hat{c}/(Km + \hat{c});\ \hat{c} = (c_i - c_o)/\ln(c_i/c_o), \qquad [3]$$

$$v = F \cdot c_i \cdot (1 - e^{-(Vmax - v)/KmF}), \qquad [4]$$

$$v = F \cdot c_o \cdot (e^{(Vmax - v)/FKm} - 1). \qquad [5]$$

Fig. 1 graphs these three relations for various values of Vmax/*K*m and F. The straight lines give the amount offered to the liver by the flow, $F \cdot c_i$. Equation 3 is the Michaëlis-Menten relation, where the concentration $\hat{c}$, being the logarithmic average of the inflow and outflow concentrations, lies between c_i and c_o. It follows from the model used that, for a given v, $\hat{c}$ (Equation 3) is independent of F (see Fig. 1).

Vmax is independent of the liver blood flow, as shown, for example, for the galactose elimination in man (5), and independent of *K*m and of the sampling site for concentration measurements (*cf.* Fig. 1). It gives an estimate of the

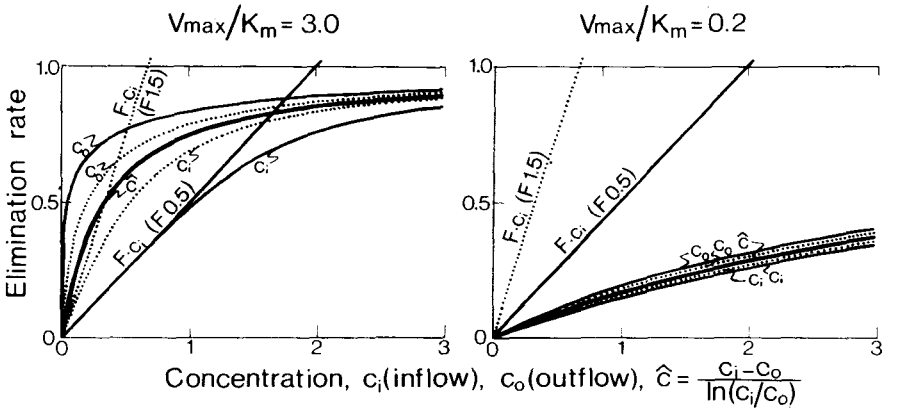

Fig. 1. Relation of hepatic elimination rate (v) to the concentrations c_i (inflow), c_o (outflow), and $\hat{c}$ ($=(c_i-c_o)/\ln(c_i/c_o)$) at a hepatic blood flow rate of 1.5 $l \cdot min^{-1} \cdot kg^{-1}$ (·····) and 0.5 $l \cdot min^{-1} \cdot kg^{-1}$ (———). The curves are estimated from the equations of the sinusoidal perfusion model (Equations 3, 4, and 5) for Vmax=1.0 $mmol \cdot min^{-1} \cdot kg^{-1}$ and *K*m= 0.33 $mmol \cdot l^{-1}$ (left side) and *K*m=5 $mmol \cdot l^{-1}$ (right side). The straight lines give the amount of substrate presented to the liver by the blood stream, $F \cdot c_i$. The Figure shows the flow independence of the relation of v to $\hat{c}$ and the flow independence of 'true clearance' (=the slope $v/\hat{c}$ at concentrations approximating zero), the flow dependence at a high ratio of Vmax/*K*m of 'systemic clearance' ($=v/c_i$ at low concentrations) and of 'intrinsic clearance' ($=v/c_o$ at low concentrations), and the flow independence at a low ratio of Vmax/*K*m of both 'systemic clearance' and 'intrinsic clearance'.

capacity of the removal process and may be used in quantitative evaluation of 'liver function'. By Equation 3, 4, or 5, direct estimation of Vmax by at least two sets of three of the four variables v, F, c_i, and c_o (they are interconnected by the Fick relation $v=F(c_i-c_o)$) may be difficult in practice, since it requires samples of blood from the hepatic veins. Vmax may be approximated by the elimination rate at high concentrations. This, however, may be impossible if, for example, the concentrations necessary are toxic. In this case clearance measurements may be useful in quantitative measurements of 'liver function', provided that certain conditions are fulfilled (12, 14).

Obviously, a blood-flow-independent definition of clearance is not possible according to the saturation kinetics model (Equations 3, 4, and 5), but it still is useful to discuss a clearance concept in the approximate first-order regime—that is, at low concentrations, for example for $\hat{c} \ll K$m (13). A flow-independent clearance can then be defined from Equation 3,

$$\text{'true clearance'} = v/\hat{c} = \text{Vmax}/K\text{m}. \qquad [3a]$$

This clearance corresponds to the slope of the relation between v and $\hat{c}$ at concentrations approximating zero (Fig. 1).

Krarup & Larsen (8) have demonstrated that for the elimination of indocyanine green in the intact cat the hepatic 'true clearance' is unchanged during both a 50% reduction and a 50% increase in the hepatic plasma flow rate. These authors arrived at the same clearance expression as the above-mentioned

'true clearance' from a first-order compartmental model in which the concentration is taken to be a space average concentration of the sinusoid ($\bar{c}$). This is consistent with the fact that $\bar{c}$ approximates $\hat{c}$ at low concentrations (14), so that the clearance calculated as $v/\bar{c}$ is about the same as that obtained by $v/\hat{c}$. It should be stressed, however, that the relation between v and $\bar{c}$ does not follow the Michaëlis-Menten relation. This is visualized by noting the curvilinear relationship between $1/v$ and $1/\bar{c}$ (11), in contrast to the linear relationship between $1/v$ and $1/\hat{c}$ (7).

The 'systemic clearance' (v/c_i) can be interpreted and the degree of flow dependence quantitated for $v \ll Vmax$ since, then, by Equation 4,

$$\text{'systemic clearance'} = v/c_i = F \cdot (1 - e^{-Vmax/KmF}). \qquad [4a]$$

For this relation, which holds at low relative uptake rates (at low plasma concentrations), two limiting cases can be defined. First, for a $Vmax/Km$ small in relation to F, Equation 4a reduces to

$$\text{'enzyme-limited systemic clearance'} = v/c_i = Vmax/Km. \qquad [4b]$$

Thus 'systemic clearance' of substrates with a low $Vmax/Km$ may be used as an estimate of 'true clearance' (see Equation 3a). For example, at $Vmax/Km = 0.06$ the 'systemic clearance' equals $0.9 \cdot Vmax/Km$. With lower values the approximation improves even further, and 'systemic clearance' for such substances thus is as good an estimate of liver function as a direct measurement of Vmax, provided that Km is not changed by liver diseases. For example, the 'systemic clearance' of phenazone (antipyrine), which has a low ratio of $Vmax/KmF$ (about 0.05 in the perfused pig liver (1)), may be used as a quantitative measurement of hepatic microsomal function (2). In monkeys, phenobarbital doubles the 'systemic clearance' of phenazone and increases hepatic blood flow by 50% (4). It can be estimated that enzyme induction almost exclusively is responsible for the increased clearance, whereas the increment in F accounted for less than 10% of the increase.

Second, for a $Vmax/Km$ large in relation to F, Equation 4a reduces to

$$\text{'flow-limited systemic clearance'} = v/c_i = F. \qquad [4c]$$

At $Vmax/KmF = 2.3$, 'systemic clearance' equals $0.9 \cdot F$ and may be used as an estimate of hepatic blood flow (*cf.* Fig. 1). Equation 4c applies to, for example, the hepatic clearance of ethanol ($Vmax/KmF$ of about 4 (6)) and of galactose ($Vmax/KmF$ of about 2 (7)).

For substrate with a $Vmax/KmF$ of between 0.06 and 2.3 the 'systemic clearance' depends both on $Vmax/Km$ and on F. For indocyanine green $Vmax/KmF$ is about 0.3 when calculated from Ref. 8, and the 10% to 20% changes in 'systemic clearance' following 50% changes in F are consistent with the changes that can be predicted from Equation 4a.

Similarly, 'systemic clearance' of propranolol in monkeys depends on both flow and enzyme activity (4); recalculation of the data from Ref. 4 in accordance with this gives an estimate of Vmax/*K*mF about unity. Also bromosulfophthalein has a ratio of Vmax/*K*mF about unity, and reduction of bromosulfophthalein 'systemic clearance' or increase of 'bromosulfophthalein retention' therefore can be ascribed either to reduced hepatic blood flow or to reduced hepatic elimination capacity.

'Intrinsic clearance' can also be evaluated in the light of the sinusoidal perfusion model. According to Equation 5 we have for $v \ll Vmax$ that

$$\text{'intrinsic clearance'} = v/c_o = F \cdot (e^{Vmax/F\,Km} - 1). \qquad [5a]$$

Hence 'intrinsic clearance' depends on the flow as well as the enzymatic parameters, and the alleged property of flow independence has to be questioned.

Several authors use the extraction ratio $(c_i - c_o)/c_i$ as a characteristic parameter of the hepatic elimination of substrates. The sinusoidal perfusion model describes the extraction ratio as

$$(c_i - c_o)/c_i = 1 - e^{-Vmax/KmF}. \qquad [6]$$

It therefore depends on both Vmax/*K*m and F in the conditions of study most often encountered (that is, when $0.06 < Vmax/KmF < 2.3$). In conclusion, assessment of the ratio Vmax/*K*m should be preferred to characterize hepatic function. This means the determination of 'systemic clearance' at a low concentration ($v \ll Vmax$) of a substance having a small Vmax/*K*m ratio relative to F as phenazone (antipyrine). If possible, however, Vmax measurements should be preferred.

Susanne Keiding
Division of Hepatology
Medical Dept. A
Rigshospitalet 2151
Copenhagen, Denmark

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