Organ Perfusion Studies: A Rebuttal

Keyphrases □ Organ perfusion—pharmacokinetics, sampling □ Pharmacokinetics—organ perfusion, effect of sampling

To the Editor:

Colburn *et al.* (1) discussed the influence of sampling in organ perfusion studies. In this respect we want to make the following critical remarks. These authors defined the elimination rate constant K as Q/V_R, in which Q represents the perfusion flow rate and V_R represents the reservoir volume. According to this equation, however, K is *not* the elimination rate constant.

It is explicitly stated by Rowland *et al.* in their Table I (2), that the rate constant k_{12} of the compartmental model corresponds to $\dot{V}_B/V_R$ of the perfusion model. In Colburn's terminology $\dot{V}_B = Q$. Since Colburn states that $K = Q/V_R$, it is erroneous to call K an elimination rate constant; it simply is the transport rate constant from the reservoir to the eliminating perfused organ in terms of the perfusion model. Similarly, the rate constant k_{12} of the compartmental model represents the transport rate constant from the central to the peripheral compartment in the compartmental model. The elimination rate constant itself, k_e, contrary to the opinion of Colburn *et al.*, is independent of the perfusion flow rate, since it reflects the intrinsic ability of the organ to eliminate drug. As we have pointed out (3), the drug decrease in the reservoir will be more rapid under the influence of sampling than without sampling. Consequently, a pharmacokinetic analysis based on the uncorrected time course of drug concentration in the reservoir will result in overestimation of the parameter k_e.

Colburn *et al.* stated that clearance will be unaffected by sampling from the reservoir. We do not agree with their statement. They define clearance as:

$$CL_o = Q\left(\frac{C_{in} - C_o}{C_{in}}\right) \qquad \text{(Eq. 1)}$$

where C_{in} and C_o represent the inflow and outflow concentrations of the eliminating organ. This expression, however, defines *instantaneous* clearance (2), which is time- and concentration-dependent. A more relevant measure of clearance is the *mean* clearance, which essentially is a steady-state concept. The mean clearance equals:

$$CL = \frac{Q \cdot k_e}{Q/(K_p \cdot V_o) + k_e} \qquad \text{(Eq. 2)}$$

where V_o is the physical organ volume and K_p is the apparent partition coefficient of drug between the eliminating organ and the emergent perfusion fluid (2). This leaves K_p and k_e as two independent parameters to be estimated from the concentration *versus* time curve as measured in the reservoir.

As discussed above, the parameter k_e will be overestimated due to sampling. Similarly, the estimate of the parameter K_p is biased, in a complicated way, by sampling (3). It follows that sampling from the reservoir definitely influences the estimate of clearance. The extent to which clearance is biased by neglecting corrections for sampling is dependent on the numerical values of Q, K_p, k_e, and of course the sample volumes.

In conclusion it can be stated that the instantaneous clearance is the wrong parameter to look at and that the mean clearance estimated from concentration *versus* time curves in the reservoir will certainly depend on sampling from this reservoir.

(1) W. A. Colburn, R. K. Brazzell, and I. Bekersky, *J. Pharm. Sci.*, **72**, 970 (1983).

(2) M. Rowland, L. Z. Benet, and G. G. Graham, *J. Pharmacokinet. Biopharm.*, **1**, 123 (1973).

(3) C. J. Timmer and H. P. Wijnand, *J. Pharmacokinet. Biopharm.*, **5**, 335 (1977).

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Estimation of Mean Residence Time from Data Obtained when Multiple-Dosing Steady State Has Been Reached

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To the Editor:

When the plasma concentration (C) *versus* time (t) profile of a drug, on single dosing, can be described, irrespective of dosing route, as an exponential series:

$$C = \sum_{i=1}^{n} A_i \cdot \exp(-k_i t) \qquad \text{(Eq. 1)}$$

then the concentration *versus* time profile on multiple dosing to steady state, at a constant interval, Υ, can be described (1) as:

$$C_{ss} = \sum_{i=1}^{n} \frac{A_i}{1 - \exp(-k_i \Upsilon)} \cdot \exp(-k_i t) \qquad \text{(Eq. 2)}$$

where C_{ss} represents the plasma concentration at multiple-dosing steady state and, in this case, t is time after the last dose administered. Equation 2 is valid on the assumptions that the dose remains constant, the dosing interval is constant, and clearance is constant. It has been demonstrated (see Ref. 1) that under these conditions:

$$\int_0^\infty C dt = \int_0^\Upsilon C_{ss} dt \qquad \text{(Eq. 3)}$$

When the time course of drug concentration is regarded as a statistical distribution curve (2) the mean residence time (MRT) of the drug, on single dosing, can be defined (3) as:

$$\text{MRT} = \int_0^\infty tCdt \Big/ \int_0^\infty Cdt = \left(\sum_{i=1}^{n} A_i/k_i^2\right) \Big/ \left(\sum_{i=1}^{n} A_i/k_i\right) \qquad \text{(Eq. 4)}$$

In addition to using the analytical integrals of Eq. 1, as shown in Eq. 4, the MRT has been calculated using integrals estimated by the trapezoidal rule (4).

On the basis of Eq. 2, the first moment curve at steady state would be:

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