The reproducibility of the chemical assay (on a day to day basis) is superior to the enzyme assay, as seen by comparing the standard deviations and coefficients of variance from the data obtained from five consecutive test periods. The need for rigid controls of temperature and timing and the low reproducibility of the enzyme assay dictate that a standard working curve be generated each time numerous samples are run. The chemical assay offers a significant improvement in reproducibility and requires only an initial standard curve. The chemical assay described in this paper offers an easy, inexpensive, and reproducible method of determining glycerol in aqueous samples.

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Clearance Constants in Physiologically Based Pharmacokinetic Models

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Abstract □ The intrinsic clearance of an organ is usually approximated by the apparent clearance from that organ in the development of a physiologically based pharmacokinetic model. In this study, the exact relationship between the two clearances was derived and analyzed. When the extraction ratio of the drug was small (<0.05), the approximation was reasonable. However, when the extraction ratio was high (>0.2), serious errors could be made by using the approximation. These errors could be as much as 50% reduction in the estimated extraction ratio and as much as an order-of-magnitude difference in the intrinsic clearance.

Keyphrases □ Pharmacokinetics—drug clearance through an organ, estimation □ Drug clearance—estimation of clearance through an organ, pharmacokinetics □ Antineoplastic agents—estimation of clearance through an organ, pharmacokinetics

In a typical linear physiologically based pharmacokinetic model (1), the drug concentration in an organ such as the kidney is governed by the differential equation:

$$V\frac{dC}{dt} = Q\left(C_p - \frac{C}{R}\right) - K\frac{C}{R} \qquad \text{(Eq. 1)}$$

where C and C_p are the drug concentrations in the organ and plasma (or blood), respectively; V is the physiological volume of the organ; Q is the plasma (or blood) flow rate through the organ; R is the equilibrium partition coefficient for drug distribution between the organ tissue and its venous plasma, and the constant K is a clearance term for drug elimination from the organ.

The development of a physiological model for predicting drug concentration–time histories requires the estimation of V, Q, R, and K. The parameters V and Q are the physiological volumes and blood flow rates through the organs for the subject to be simulated; R can be estimated from animal experiments and calculated according to a recently developed method (2). The clearance K is usually assumed to be equal to K_{app}, the apparent drug clearance from the organ. For example, if the organ is the kidney, K is usually calculated from:

$$K = K_{app} \equiv \text{total urinary excretion} \Big/ \int_0^\infty C_p\,dt \qquad \text{(Eq. 2)}$$

Several questions can be posed regarding K and its significance. What is its physical meaning? Is it equal to the apparent drug clearance from the organ? Can it be greater than Q, the plasma flow rate through the organ? How can K be estimated from experimental data? These questions will be discussed in the present paper.

THEORETICAL

Without loss of generality, the typical organ to be studied will be the kidney. The total cumulative urinary excretion, U, is then given as:

$$\frac{dU}{dt} = K\frac{C}{R} \qquad \text{(Eq. 3)}$$

or:

$$U = \frac{K}{R}\int_0^T C\,dt \qquad \text{(Eq. 4)}$$

where T is the urine collection time interval. Chen and Gross (2) showed recently that the drug concentration in the organ is related to the plasma drug level by:

$$C = \frac{QRC_p}{Q + K - \beta VR} \qquad \text{(Eq. 5)}$$

during the terminal elimination phase after intravenous bolus injection and that:

$$C = \frac{QRC_p}{Q + K} \qquad \text{(Eq. 6)}$$

at steady state after a constant-rate infusion. The parameter β is the apparent elimination rate constant for the terminal phase after intravenous injection. Therefore, Eq. 4 may be approximated as:

$$U = \frac{QK}{Q + K}\int_0^T C_p\,dt \qquad \text{(Eq. 7)}$$

for all modes of drug administration if $K + Q \gg \beta VR$ and if the tissue

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to plasma concentration ratio can be approximated by Eq. 6 during the entire study period.

Comparison of Eq. 7 with the definition of apparent clearance, K_{app}, given by Eq. 2 yields:

$$K_{app} = \frac{QK}{Q+K} \quad \text{(Eq. 8)}$$

and:

$$K = \frac{QK_{app}}{Q-K_{app}} \quad \text{(Eq. 9)}$$

These equations apply to all organs except the lung where all the venous blood from all organs converges. A similar derivation for the lung gives:

$$(K_{app})_{lung} = K_{lung}(Q_{plasma} + K_{plasma})/Q_{plasma} \quad \text{(Eq. 10)}$$

and:

$$K_{lung} = \frac{(Q_{plasma})(K_{app})_{lung}}{Q_{plasma} + K_{plasma}} \quad \text{(Eq. 11)}$$

The reason for the difference is based on the definition of K_{app}; K_{app} is defined as the blood (or plasma) volume from which drug is completely removed in a unit time. For the other organs, the blood flows from the pooled plasma compartment into each individual organ. For the lung, the blood exits from the lung compartment into the plasma pool.

RESULTS AND DISCUSSION

Equation 8 shows that, as Q increases and approaches infinity, K_{app} approaches K. It is clear, then, that K is the true capacity of the organ to eliminate the drug. In other words, K is the intrinsic clearance, a concept developed for hepatic drug clearance (3). In fact, Eq. 8 reduces to the equation for hepatic clearance but is more general and applicable to all drug-eliminating organs except the lung.

In view of Eq. 8, which can be rewritten as:

$$K_{app} = K\left(1 - \frac{K}{Q+K}\right) = Q\left(1 - \frac{Q}{Q+K}\right) \quad \text{(Eq. 12)}$$

the apparent clearance K_{app} is always smaller than K or Q. However, there will be no upper limit for the intrinsic clearance K. Once the value of K_{app} is obtained from experiment using Eq. 2, K can be calculated from Eq. 9 by using the blood flow rate Q through that particular organ.

The alternative to this approach is to rearrange Eq. 12 to yield:

$$K = \frac{K_{app}}{1-E} \quad \text{(Eq. 13)}$$

where:

$$E = \frac{K}{Q+K} = \frac{K_{app}}{Q} \quad \text{(Eq. 14)}$$

is the steady-state extraction ratio, defined as the amount of drug eliminated divided by the amount of drug entering the organ at steady state. The approximation of K by K_{app} is valid only when the extraction ratio E is very small ($E < 0.05$). Most anticancer drugs have small E values, and this approximation is reasonable. However, when E is high and closer to unity, serious error of as much as an order-of-magnitude difference in K and as much as 50% in the estimated E may result from the approximation of K by K_{app}. Therefore, for drugs that have high hepatic extraction ratios such as doxorubicin ($E = 0.6$) (1), fluorodeoxyuridine ($E = 0.95 \sim 0.98$) (4), and fluorouracil [$E = 0.9$ in one study (5) and $E = 0.2$–0.5 in another (4)], Eq. 9 or 13 always should be used to calculate the intrinsic clearance.

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COMMUNICATIONS

New Calculation Method for Mean Apparent Drug Volume of Distribution and Application to Rational Dosage Regimens

Keyphrases □ Drug distribution volume—calculations, arithmetic mean method, harmonic mean method □ Dosage regimens—design, calculation of drug distribution volume, arithmetic mean method, harmonic mean method

To the Editor:

One important purpose of clinical pharmacokinetic studies is to obtain mean pharmacokinetic data to be used as an initial guide for drug therapy. The apparent volume of distribution (V_d) of a drug is a useful pharmacokinetic parameter in the one-compartment open-model system, which is often adequate clinically for the characterization of drug disposition kinetics (1–5). For example, the product of the mean V_d ($\overline{V}_d$) obtained from several subjects and the desired plasma level ($\overline{C}_p$) of the drug could be equal theoretically to the *mean* priming dose recommended for the same type of patient.

The mean V_d of test subjects has been calculated almost exclusively to date by the arithmetic mean method. In this method, the individual V_d values (V_{d1}, V_{d2}, ..., V_{dn}) estimated by various standard or approximate (3) methods are added and the sum is divided by the total number of test subjects (n). The purposes of this communication are to propose a new method for calculating the mean V_d and to point out the potential shortcoming of the conventional arithmetic mean method in predicting rational dosage regimens.

If the test subjects are representative of the mean patient population, one should expect that the recommended mean dose ($\overline{V}_d\overline{C}_p$) when applied to the original test subjects should *ideally* result in an arithmetic mean plasma level of all the test subjects *exactly* equal to the originally targeted $\overline{C}_p$ value. In other words:

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