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Short Communication

Determination of absolute drug bioavailability without intravenous administration by renal clearance perturbation using urinary excretion data

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Lalka and Feldman (1974) have derived a model-independent equation by which it is possible to calculate the absolute bioavailability of a large class of drugs, those whose renal clearance is perturbable, without the administration of an intravenous dose. The perturbation of the renal clearance can be achieved by co-administration of the drug with a urinary acidifying or alkalinizing agent. The equation of Lalka and Feldman (1974) is given below:

$$F = \frac{\Delta Cl_R}{D}\left[\frac{(AUC)(AUC')}{AUC' - AUC}\right] \quad (1)$$

In Eqn. 1, F is absolute bioavailability, ΔCl_R is the difference between the renal clearance values of the drug under different conditions, i.e. with and without clearance perturbation, D is the dose of drug, (AUC) and (AUC') are areas under the blood level curves between times 0 and infinity (∞) under the different conditions. The usefulness of Eqn. 1 has been demonstrated by Poust et al. (1977) and Lalka et al. (1978). However, Eqn. 1 requires several blood samples in order to determine the values of (AUC) and (AUC'). This may cause discomfort to the subject in clinical trials.

In this communication two equations are derived from which one can calculate F from urinary excretion data provided a fraction of drug is excreted intact in urine, thus avoiding the discomfort of several blood samplings. The details of the derivations of the equations are as follows:

(1) The urinary excretion rate of a drug, dU/dt, is related to its renal clearance, Cl_R, and its blood concentration, C, by the following equation (Gibaldi and Perrier, 1975).

$$\frac{dU}{dt} = Cl_R \times C \quad (2)$$

Upon integration between times 0 and ∞ Eqn. 2 becomes

$$U_0^{\infty} = Cl_R \int_0^{\infty} C \cdot dt \tag{3}$$

Where U_0^{∞} is the cumulative amount of intact drug excreted in urine between times 0 and ∞ and the integral $\int_0^{\infty} C \cdot dt$ represents the area under the blood level curve (AUC) between times 0 and ∞. Therefore, Eqn. 3 can be written as Eqn. 4

$$U_0^{\infty} = Cl_R \cdot (AUC) \tag{4}$$

Solving for AUC, Eqn. 5 is obtained

$$(AUC) = \frac{U_0'^{\infty}}{Cl_R} \tag{5}$$

Similarly under the perturbed condition

$$(AUC') = \frac{U_0'^{\infty}}{Cl_R'} \tag{6}$$

Substitution for (AUC) and (AUC') from Eqns. 5 and 6 into Eqn. 1 gives

$$F = \frac{\Delta Cl_R}{D}\left[\frac{U_0^{\infty} U_0'^{\infty}}{Cl_R U_0'^{\infty} - Cl_R' U_0^{\infty}}\right] \tag{7}$$

To calculate F by Eqn. 7 requires only two blood samples for determination of Cl_R and Cl_R'. The value of U_0^{∞}s can be calculated from urinary excretion studies using the rapid methods given by Niebergall et al. (1975) or Newburger et al. (1979).

(2) For a drug which confers upon the body one-compartment open model, the relation between U_0^{∞} and F is given by Eqn. 8 (Gibaldi and Perrier, 1975)

$$U_0^{\infty} = \frac{k_e FD}{K} \tag{8}$$

Where k_e is a first-order urinary excretion rate constant of the intact drug and K is its overall first-order elimination rate constant. The latter constant is the sum of urinary excretion rate constant and non-renal elimination rate constant(s), k_{NR}, i.e.

$$K = k_e + k_{NR} \tag{9}$$

It is assumed that the urinary acidifying and/or alkalinizing agents would alter K and k_e to K' and k_e', respectively, but do not change k_{NR}.
Therefore:

$$K' = k_e' + k_{NR} \tag{10}$$

From Eqns. 9 and 10 Eqn. 11 can be obtained

$$k_e' - k_e = K' - K \tag{11}$$

Rearrangement of Eqn. 8 yields:

$$k_e = \frac{KU_0^\infty}{FD} \tag{12}$$

and similarly

$$k_e' = \frac{K'U_0'^\infty}{FD} \tag{13}$$

Substitution for k_e and k_e' from Eqns. 12 and 13 into Eqn. 11 gives:

$$\frac{K'U_0'^\infty}{FD} - \frac{KU_0^\infty}{FD} = K' - K \tag{14}$$

Solving for F results in Eqn. 15:

$$F = \frac{K'U_0'^\infty - KU_0^\infty}{D(K' - K)} \tag{15}$$

Eqn. 15 requires no blood sampling. The K values can be calculated from the slopes of the terminal linear part of the semi-logarithmic plots of urinary excretion rate vs time and U_0^∞ values can be determined using the rapid methods mentioned above.

For drugs with the two-compartment open model, with the elimination occurring only from the central compartment and provided intercompartment transfer constants are independent of perturbation of the renal excretion, the equation obtained from a similar derivation would be similar to Eqn. 15 in which K_{10}s (the elimination rate constant from the central compartment) replace Ks. In this case U_0^∞s are calculated by the method of Niebergall et al. (1975) and K_{10}s are obtained from urinary excretion plots using a similar method described by Gibaldi and Perrier (1975).

Therefore, in the cases where several blood samplings are not feasible, Eqn. 7 or 15 may be used for the calculation of the value of F.

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