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Rapid Communication

Determination of absolute drug bioavailability without intravenous administration

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The classic method of determining absolute drug bioavailability, the fraction of an extravascularly administered dose reaching the general circulation, requires data obtained from both extravascular and intravenous administration (Gibaldi and Perrier, 1982). Some drugs, however, for a number of reasons e.g., insolubility and instability, cannot be used by intravenous injection. Methods of determining the absolute bioavailability without intravenous administration for drugs with perturbable renal clearance and/or excretion rate constant involving blood level and urinary excretion data (Lalka and Feldman, 1974) and urinary excretion data alone (Barzegar-Jalali, 1980) were given. These methods involve two separate experiments with varied or perturbed renal clearance and assume that the absolute bioavailability in the two treatments remains unchanged. Therefore, application of these methods requires the administration of the same dosage form of a drug from the same route of administration in the two treatments.

In this communication a method based on the same principle is presented which does not impose restriction on the type of dosage form administered as well as the extravascular route chosen. The method gives the bioavailabilities of the drug in the two treatments regardless of whether these are equal or not. The application of the method is demonstrated using some experimental data. Also, the principle of renal clearance perturbation is extended to a single treatment and the equation derived requires data collected only from a single experiment and is applicable for drugs with long elimination half-lives. Details of the derivation of the equations are as follows:

Method involving two treatments:

(A) The relationships of the fraction, F, of an extravascular dose, D, reaching the general circulation with total plasma clearance of drug, Cl, and its first order elimination rate constant from the central compartment, K, are given by Eqns 1 and 2 (Gibaldi and Perrier, 1982):

$$FD = \mathrm{Cl}(\mathrm{AUC}) \tag{1}$$

$$FD = \frac{KU_0^{\infty}}{k_r} \tag{2}$$

(AUC) is the area under plasma level of drug vs time curve between times 0 and ∞, U_0^{∞} is the amount of drug excreted unchanged in urine during the same period, and k_r is the first-order urinary excretion rate constant of drug. It is obvious that:

$$\mathrm{Cl} = \mathrm{Cl}_r + \mathrm{Cl}_{nr} \tag{3}$$

$$K = k_r + k_{nr} \tag{4}$$

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where Cl_r, Cl_{nr}, k_r and k_{nr} are renal clearance, nonrenal clearance, renal excretion rate constant and nonrenal excretion rate constant, respectively. If only the renal components of drug elimination parameters are varied or perturbed between treatments and the parameters in the two treatments are shown with subscripts x and y, then it can be shown from Eqns 3 and 4 that:

$$Cl_x - Cl_y = Cl_{r_x} - Cl_{r_y} \tag{5}$$

$$K_x - K_y = k_{r_x} - k_{r_y} \tag{6}$$

Substitution for Cls and k_rs from Eqns 1 and 2 into Eqns 5 and 6 results in:

$$\left(\frac{FD}{AUC}\right)_x - \left(\frac{FD}{AUC}\right)_y = Cl_{r_x} - Cl_{r_y} \tag{7}$$

$$\left(\frac{KU_0^\infty}{FD}\right)_x - \left(\frac{KU_0^\infty}{FD}\right)_y = K_x - K_y \tag{8}$$

Solving Eqn 7 for F_x and substitution of the resulting equation into Eqn 8 will yield:

$$\left[(K_x - K_y)\left(\frac{D}{AUC}\right)_y\right]F_y^2 + \left[(Cl_{r_x} - Cl_{r_y})(K_x - K_y) - \left(\frac{KU_0^\infty}{AUC}\right)_x + \left(\frac{KU_0^\infty}{AUC}\right)_y\right]F_y + \left(\frac{KU_0^\infty}{D}\right)_y (Cl_{r_x} - Cl_{r_y}) = 0 \tag{9}$$

Recognizing that $U_0^\infty/(AUC) = Cl_r$, Eqn 9 is written as:

$$\left[(K_x - K_y)\left(\frac{D}{AUC}\right)_y\right]F_y^2 + \left(2K_yCl_{r_y} - K_yCl_{r_x} - K_xCl_{r_y}\right)F_y + \left(\frac{KU_0^\infty}{D}\right)_y (Cl_{r_x} - Cl_{r_y}) = 0 \tag{10}$$

The quadratic equation 10 has two roots as follows:

$$F_y = \left[\frac{Cl_r(AUC)}{D}\right]_y = \left(\frac{U_0^\infty}{D}\right)_y \tag{11}$$

$$F_y = \left[\frac{K(AUC)}{D}\right]_y \left(\frac{Cl_{r_x} - Cl_{r_y}}{K_x - K_y}\right) = \left(\frac{KU_0^\infty}{Cl_rD}\right)_y \left(\frac{Cl_{r_x} - Cl_{r_y}}{K_x - K_y}\right) \tag{12}$$

Eqn 11 is valid only when drug is eliminated exclusively by renal clearance. Therefore, Eqn 12 is the acceptable root. Similarly, F_x is given by:

$$F_x = \left[\frac{K(AUC)}{D}\right]_x \left(\frac{Cl_{r_x} - Cl_{r_y}}{K_x - K_y}\right) = \left(\frac{KU_0^\infty}{Cl_rD}\right)_x \left(\frac{Cl_{r_x} - Cl_{r_y}}{K_x - K_y}\right) \tag{13}$$

Comparison of Eqns 12 and 13 with the classic equation $F = K(AUC)V_1/D$ reveals that the volume of distribution, V_1, in both treatments is equal and is given by $V_1 = (Cl_{r_x} - Cl_{r_y})/(K_x - K_y)$. In other words Eqns 12 and 13 give the exact values of Fs only if V_1 remains unchanged between the treatments. The same assumption has also been made in determination of absolute bioavailability by the clearance method involving intravenous administration (Kwan et al., 1976).

(B) If it is assumed that V_1 remains unchanged in the same subject between the treatments, then Eqns 12 and 13 are derived using the simple method given below: Eqn 5 can be written as Eqn 14

$$K_xV_1 - K_yV_1 = Cl_{r_x} - Cl_{r_y} \tag{14}$$

from which

$$V_1 = \frac{Cl_{r_x} - Cl_{r_y}}{K_x - K_y} \tag{15}$$

Substitution of V_1 from Eqn 15 into the corresponding classic equation $F = K(\mathrm{AUC})V_1/D$ will result in Eqns 12 and 13.

Method involving single treatment:

For drugs with long elimination half-life single-treatment data instead of two-treatment data can also be used. A drug is coadministered with a renal clearance perturbing agent (a urinary acidifying or alkalinizing agent) and blood and urine levels of the drug are determined up to some time during the elimination phase and then the renal clearance of the drug is perturbed using an agent with the opposite effect on renal clearance. It is obvious that Eqn 15 for this case is:

$$V_1 = \frac{\mathrm{Cl_r} - \mathrm{Cl'_r}}{K - K'} \tag{16}$$

$\mathrm{Cl_r}$s and Ks are the renal clearances and the elimination rate constants from the central compartment upon administration of the perturbing agents. The change in the elimination constant due to renal clearance perturbation can easily be detected from the change in the slope of semilogarithmic plot of blood levels vs time during the elimination phase. Substitution of V_1 from Eqn 16 into the equation $F = K(\mathrm{AUC})V_1/D$ yields Eqn 17

$$F = \frac{K(\mathrm{AUC})(\mathrm{Cl_r} - \mathrm{Cl'_r})}{D(K - K')} \tag{17}$$

where (AUC) is the area under the blood level vs time curve between times 0 and ∞ upon coadministration with the first renal clearance perturbing agent.

Eqns 12 and 13 were applied to the simulations 2 and 4 given in a paper of Till et al. (1974) and the calculated F for both simulations was 0.6 (the exact value was 0.6) using the information given in Tables 2 and 5 of that paper. Eqns 12 and 13 were also applied to some indomethacin data (Kwan et al., 1976) and the results which were in good agreement with the reported values are given in Table 1.

TABLE 1

Percent of administered dose absorbed from indomethacin dosage forms calculated by Eqns 12 and 13 and the clearance method involving intravenous administration

Subject	Dosage form	Model with hypothetical organ		Model with enterohepatic circulation	
102	capsule	82.5 [a]	(80.5) [b]	101.8 [a]	(107.2) [b]
	suppository	51.0	(49.8)	62.0	(65.2)
104	capsule	109.7	(119.5)	132.1	(135.6)
	suppository	67.4	(70.0)	80.0	(78.5)
105	capsule	129.2	(129.7)	138.7	(155.3)
	suppository	97.0	(97.4)	104.2	(116.9)

[a] Ks for the model with hypothetical organ and the model with enterohepatic circulation were taken from Tables 4 and 12, respectively, $\mathrm{Cl_r}$s and U_0^∞s were taken from Table 10 of the paper by Kwan et al. (1976).

[b] The numbers in parentheses are percentages of the administered doses adsorbed calculated from the clearance method involving intravenous administration and reported in Tables 10 and 13 of that paper.

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