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# Bioavailability determination for drugs exhibiting variable renal excretion rate constant between treatments

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**Abstract**

A method of bioavailability calculation for drugs exhibiting a variable renal excretion rate constant between treatments is presented. The method is a model-dependent equation and its advantages over the previous model-dependent and model-independent clearance methods are discussed using some simulated and experimental data.

*Keywords:* Bioavailability; Renal excretion rate constant; Renal clearance

The commonly used methods for assessing the extent of bioavailability, the fraction of an extravascularly administered dose of a drug that reaches the systemic circulation, are the comparison of the total areas under the plasma level of drug vs time curves or total drug amounts excreted unchanged in the urine of the single extravascular and intravenous doses.

In applying these methods it is assumed that all elimination parameters of drug, i.e., renal and nonrenal clearances as well as the corresponding elimination rate constants, do not vary between extravascular and intravenous administrations. However, the renal elimination parameters, e.g., renal clearance and urinary excretion rate constant of some drugs may depend on urine flow and pH and these properties may vary within and between treatments. In fact, studies indicated that the renal clearance of some drugs varied between treatments in the same subject (Kwan et al., 1976; Ekstrand et al., 1978; Ehrnebo et al., 1979). In these cases the elimination parameters should be taken into account in the bioavailability calculation.

Three model-independent equations (Kwan and Till, 1973; Ekstrand et al., 1978; Øie and Jung, 1979) and one model-dependent equation (Kwan et al., 1976) have been given for bioavailability calculation when the renal clearance of drug varies between treatments. The model-independent equations are:

$$F_x = f_{u_x}\left(\frac{Cl_{p_{iv}} - Cl_{r_{iv}} + Cl_{r_x}}{Cl_{r_x}}\right) \quad (1)$$

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$$F_x = \frac{(AUC_x)_0^\infty \cdot D_{iv}}{(AUC_{iv})_0^\infty \cdot D_x}(1 - f_{u_{iv}}) + f_{u_x} \quad (2)$$

$$F_x = \frac{[D_{iv} - (U_0^\infty)_{iv}]\dfrac{(AUC_x)_0^\infty}{(AUC_{iv})_0^\infty} + (U_0^\infty)_x}{D_x} \quad (3)$$

where $F_x$ is the bioavailability of extravascularly administered dosage form, $f_u$ denotes the fraction of dose excreted ultimately in urine, $Cl_p$ and $Cl_r$ are the total plasma and renal clearances of drug, respectively, $(AUC)_0^\infty$ represents the area under the plasma level curve between times zero and infinity, $D$ is the dose of drug, $U_0^\infty$ denotes total drug amount excreted in urine between times zero and infinity and the subscripts x and iv refer to extravascular and intravenous administrations. These equations can be converted to each other if one makes the appropriate substitutions. Recognizing $U_0^\infty/D = f_u$, Eq. 2 can be obtained from Eq. 3 and substitution of $U_0^\infty/Cl_r$ for $(AUC)_0^\infty$, $U_0^\infty/D$ for $f_u$ and $Cl_{p_{iv}}$ for $(Cl_r/f_u)_{iv}$ in Eq. 2 gives Eq. 1. Therefore, Eq. 1–3 should produce an equal value for $F_x$.

Eq. 3 was proposed as a method of calculation of the bioavailability when the renal clearance of drug varied within a treatment (Øie and Jung, 1979), however, Eq. 2 can be of use for this purpose as well. Eq. 1 can also be employed for the same purpose provided that the average renal clearance from time zero to time infinity is used instead of the renal clearance over a short period of time.

The model-dependent equation for the calculation of bioavailability when the renal clearance of drug varies between treatments in the same subject (Kwan et al., 1976) is:

$$F_x = f_{u_x}\left[\frac{(KV_1)_{iv} - Cl_{r_{iv}} + Cl_{r_x}}{Cl_{r_x}}\right] \quad (4)$$

in which $K$ is a first-order elimination rate constant of drug from the central compartment, $V_1$ denotes the apparent volume of distribution of drug in the central compartment and the other symbols were defined previously.

All the methods outlined above employ the concept of clearance and implicit in their application is that the apparent volume of drug distribution in the body should remain unchanged between the treatments. However, clearance is the product of the rate constant (elimination or excretion) and the apparent volume of distribution. Therefore, if either the apparent volume of distribution alone or the apparent volume of distribution and the rate constant vary between the treatments, the clearance-based methods do not give the exact value of the bioavailability as will be shown in this report. Also, the model-independent methods did not give accurate results when the kinetics of drug were complex (Kwan et al., 1976). In order to omit the effect of the volume of distribution, one may use a method based on the elimination rate constant for the bioavailability calculation which is unlike the clearance-based methods independent of the distribution volume as well as being applicable to the complex kinetics and can be derived as follows:

The fraction of the administered dose excreted unchanged in the urine from time zero to time infinity, $f_{u_x}$, for linear models following the extravascular administration is given by Eq. 5 (Gibaldi and Perrier, 1982):

$$f_{u_x} = \frac{F_x k_{r_x}}{K_x} \quad (5)$$

where $k_{r_x}$ and $K_x$ are first-order rate constants for urinary excretion and elimination from the central compartment, and $F_x$ denotes the bioavailability. The corresponding equation for intravenous administration is:

$$f_{u_{iv}} = \frac{F_{iv} k_{r_{iv}}}{K_{iv}} \quad (6)$$

It is obvious that:

$$K_x = k_{r_x} + k_{nr_x} \quad (7)$$

$$K_{iv} = k_{r_{iv}} + k_{nr_{iv}} \quad (8)$$

where $k_{nr_x}$ and $k_{nr_{iv}}$ represent the nonrenal elimination rate constants for the two treatments. If it is assumed that the nonrenal elimination rate constant does not vary between the treatments which is usually the case, then:

$$K_x - K_{iv} = k_{r_x} - k_{r_{iv}} \quad (9)$$

Substitution for $k_{r_x}$ and $k_{r_{iv}}$ from Eq. 5 and 6 into Eq. 9 and subsequent solution for $F_x$ will give:

$$F_x = \frac{(Kf_u)_x}{(Kf_u/F)_{iv} + K_x - K_{iv}} \quad (10)$$

The values of $K$ can be obtained from the compartmental analysis of the plasma level data (Wagner, 1975; Gibaldi and Perrier, 1982) and the $f_u$ can be calculated by means of either the relationship $f_u = Cl_r(AUC)_0^\infty/D$ or the rapid methods (Niebergall et al., 1975; Barzegar-Jalali, 1981).

If $K_x = K_{iv}$ then Eq 10 simplifies to Eq. 11:

$$F_x = F_{iv}\frac{f_{u_x}}{f_{u_{iv}}} \quad (11)$$

Usually $F_{iv} = 1$, therefore Eq. 11 becomes Eq. 12:

$$F_x = \frac{f_{u_x}}{f_{u_{iv}}} \quad (12)$$

However, when the difference existing in the values of $K$ is not taken into account and the bioavailability is calculated from Eq. 11, then the extent of error, $\%E$, associated with the latter relative to that calculated from Eq. 10 is given by:

$$\%E = 100\left(\frac{K_x - K_{iv}}{K_x}\right)\left(\frac{F_{iv} - f_{u_{iv}}}{f_{u_{iv}}}\right) \quad (13)$$

For example, if $[(K_x - K_{iv})/K_x] = 0.2$, $F_{iv} = 1$ and $f_{u_{iv}} = 0.1$, there will be 180% error in $F_x$ calculated from Eq. 11. Conversely, if $[(K_x - K_{iv})/K_x] = 0.1$, $F_{iv} = 1$ and $f_{u_{iv}} = 0.9$, the error will be 1.1%. Generally, according to Eq. 13 the lower the $f_{u_{iv}}$ and the higher the difference between the values of $K$ relative to $K_x$, the greater is the error.

Eq. 10 was applied to a simulated data (Till et al., 1974) in which in addition to the renal excretion rate constant, the volume of distribution had been varied between the treatments and $F_x$ value obtained was 0.60 (the exact value was 0.60) whereas Eq. 1–4 resulted in an $F_x$ value of 0.55.

Eq. 10 is applicable to any drug with a linear kinetic model regardless of the complexity of the model provided that the absorption and disposition of drug are first-order processes. An example of such drugs is indomethacin whose kinetic models are more complex than the conventional ones (Kwan et al., 1976). The results of the application of Eq. 1–4 and 10–12 to some indomethacin data are given in Table 1. There was an excellent agreement between the results obtained from Eq. 10 and 4 indicating the applicability and suitability of Eq. 10. Because of this agreement and the fact that Eq. 10 is independent of the distribution volume, it was concluded that there was no appreciable intrasubject variation in the distribution volume between the treatments. The model-independent Eq. 1–3 underestimated the bioavailability in comparison with the model-dependent Eq. 4 and 10, indicating the importance of modeling in the bioavailability studies. Eq. 11, although model-dependent, underestimated the bioavailability because it did not take into account the difference in the renal excretion rate constants. The extent of the underestimation became even greater when the model-independent form of Eq. 11, i.e., Eq. 12, was used.

Table 1
Extent of bioavailability of indomethacin from capsules and suppositories calculated using Eq. 1–4 and 10–12 [a]

| Subject | Dosage form | Eq. 1–3 | Model with hypothetical organ | | | Model with enterohepatic circulation | | | Eq. 12 |
|---|---|---|---|---|---|---|---|---|---|
| | | | Eq. 4 | Eq. 10 | Eq. 11 | Eq. 4 | Eq. 10 | Eq. 11 | |
| 102 | capsule | 0.756 | 0.805 | 0.788 | 0.503 | 1.072 | 1.080 | 0.652 | 0.479 |
| | suppository | 0.470 | 0.498 | 0.494 | 0.419 | 0.652 | 0.645 | 0.543 | 0.399 |
| 104 | capsule | 0.960 | 1.195 | 1.210 | 0.865 | 1.356 | 1.341 | 0.970 | 0.708 |
| | suppository | 0.572 | 0.700 | 0.698 | 0.685 | 0.785 | 0.783 | 0.768 | 0.561 |
| 105 | capsule | 0.969 | 1.297 | 1.299 | 1.122 | 1.553 | 1.549 | 1.334 | 0.846 |
| | suppository | 0.724 | 0.974 | 0.976 | 0.781 | 1.169 | 1.177 | 0.929 | 0.589 |

[a] The necessary data for calculations were taken from Kwan et al. (1976).

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