Estimating Reduced Availability Due to First Pass Elimination from Relative Total Clearance and Renal Clearance

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Summary. A simple formula is presented for estimating the systemic availability of an orally administered drug from the relative total clearance (oral clearance) when renal clearance forms an important part of total clearance.

Hepatic plasma flow is used in the equation and is represented by an average value taken from the literature. The formula is applied to data for cimetidine discussed in the literature. A further application is demonstrated for a drug under development for which an intravenous formulation was not available.

It is possible to estimate the upper and lower limit of availability if some information on the amount of drug absorbed is available.

Key words: cimetidine; bioavailability estimate, oral clearance, first-pass effect, renal clearance

In many publications about pharmacokinetics the authors present at least characteristics describing the concentration-time curve, such as peak-concentration, time to reach peak-concentration and area under the concentration-time curve. The characteristics of the concentration-time profile depend on dose, however, and cannot be subjected to direct physiological or pharmacokinetic interpretation. In contrast, pharmacokinetic characteristics, such as clearance, volumes of distribution and mean residence time and half-life can be discussed in relation to physiology. They may also be dose-dependent in special cases. In the following, only first order pharmacokinetics is considered.

In the early and sometimes even the late stages of the development of a drug an intravenous formulation may not be available, so after oral administration total clearance and volumes of distribution can only be computed in a relative manner. It would be desirable to be able to estimate at least roughly the systemic availability of an oral formulation, particularly since relative total clearance (oral clearance or apparent oral clearance) as the quotient of dose and area under the curve may yield a 'meaningless' large number.

Gibaldi et al. (1971) proposed evaluation of the availabililty of a drug after oral administration by means of the relative total clearance and hepatic flow rate. Somogyi et al. (1982) evaluated the same relationship by regression analysis of the reciprocal of bioavailability versus the relative total clearance in order more precisely to predict bioavailability from relative total clearance values. These methods are applicable if absorption is complete and the elimination of the drug by organs other than the liver is negligible.

In the present paper, an estimate of systemic availability after oral administration is deduced for drugs which exhibit important renal excretion.

Theoretical Analysis

In order correctly to determine total clearance from oral administration data, it is necessary to know the fraction f of the administered dose available to the central circulation. Since f can frequently not be specified, relative total clearance (oral clearance) is the only value which can be calculated:

$$CL/f = D/AUC_{oral} \quad (1)$$

Assuming approximately complete absorption of the drug, and with hepatic clearance as the major mechanism of elimination, the systemic availability

of drug is estimated from the following formula (Gibaldi et al. 1971):

$$f = \frac{Q}{Q + D/AUC_{oral}} \quad (2)$$

where Q represents the hepatic plasma flow rate, and AUC refers to plasma concentration. For the sake of simplicity, possible redistribution of drug from the erythrocytes during the passage through the liver is not considered.

In the case of important renal elimination of the drug, which occurs in parallel with the hepatic elimination, a similar formula to that resulting in Equation (2) can be applied:

$$(CL_H + CL_R)/f = D/AUC_{oral} \quad (3)$$

$$CL_H = (1-f) * Q \quad (4)$$

where CL_H is the hepatic and CL_R is the renal clearance, which together constitute total clearance. Substituting Eq. (3) into (4) and rearrangement yields an estimate for systemic availability very similar to Eq. (2):

$$f = \frac{Q + CL_R}{Q + D/AUC_{oral}} = \frac{Q + A_e/AUC_{oral}}{Q + D/AUC_{oral}} \quad (5)$$

where Ae is the amount of drug excreted in the urine. Renal clearance is not ignored, and it can always be determined. The assumption of approximately complete absorption and reduced systemic availability exclusively due to hepatic elimination must still be fulfilled.

Application and Discussion

Grahnen (1984) showed that variation in the renal clearance of cimetidine during a typical cross over study of its intravenous and oral administration could give doubtful absolute bioavailability results. He stated that correction of the bioavailability for the differences in renal clearance was necessary, using the method proposed by Øie and Jung (1979). Those data have been used to check the usefulness of Eq. (5).

The results for bioavailability estimation using the different formulae are presented in Table 1 for mean and individual values where available. The first and second columns show the dose and whether mean or individual values were used. For the mean values (100, 400, 800 mg) relative total clearance was computed from the dose and the reported AUC values (Grahnen et al. 1979). For the individual values (200 mg), the ratio of dose over AUC after oral administration was calculated from the total clearance and absolute bioavailability (f_{AUC}), as presented by Somogyi et al. (1980). The last line gives the means of these individual values. f_{AUC} is the dose-corrected area ratio after intravenous and oral administration. f_{corr} represents the bioavailability after correction for differences in renal clearance on the two trial days according to Øie and Jung (1979), as reported by Grahnen (1984). $f_{Eq.(5)}$ means application of Eq.(5). Since renal clearance is used in Eq.(5) it has also been entered in the table, as reported by Grahnen (1984). For Eq.(5) hepatic plasma flow rate was assumed to be 750 ml/min.

f_{corr} must be considered as the best estimate of bioavailability in the presence of variable renal clearance; the estimates using Eq.(5) are in good agreement with f_{corr} for all mean values. For individual values, however, f_{corr} and $f_{Eq.(5)}$ differed by up to about 19% (Subject PD), although in some individuals the two methods led to identical results (Subjects GR, MA, PE).

The assumption of an average liver plasma flow rate of about 750 ml/min may be reasonable, even though the individual liver flow rate may differ markedly from the average value (Wilkenson and Shand 1975). This may be the reason why f_{corr} and $f_{Eq.(5)}$ differ less for the means than for the individual estimates. Although it is not necessary to know liver flow rate when estimating bioavailability by a conventional cross-over design and area ratios, it is still assumed to be the same for both trial days.

The large coefficient of variation of f_{AUC} was clearly reduced when renal clearance was con-

Table 1. Comparison of bioavailability estimated by three different methods. D/AUC_{oral} was computed using the AUC-values reported by Grahnen et al. (1979) and Somogyi et al. (1980). CL_R, f_{AUC} and f_{corr} were taken from Grahnen (1984). f_{AUC} for the individuals were taken from Somogyi et al. (1980). f_{AUC} and f_{corr} are taken from Grahnen (1984) and are entered in the table to facilitate comparison with the $f_{Eq.(5)}$ values; for the latter values only the data after oral administration were used

Dose [mg]	Subject	D/AUC_{oral} [ml·min^{-1}]	CL_R [ml·min^{-1}]	f_{AUC} [%]	f_{corr} [%]	$f_{Eq.(5)}$ [%]
100	Mean	877	533	85	80	79
400	Mean	641	256	123	73	72
800	Mean	833	469	99	71	77
200	GR	692	284	49	70	72
	PD	1325	345	33	72	53
	MA	1353	609	53	64	65
	MO	613	278	51	65	75
	MU	442	71	67	59	69
	PE	800	386	100	71	73
200	Mean	871	329	59	67	68
	SD			23	5	8

sidered and was broadly the same for f_{corr} and $f_{Eq.(5)}$.

A typical application of the proposed calculation when information from intravenous administration is lacking is shown in Table 2. The data were taken from a study in young healthy volunteers and in the elderly of a drug under development. Since a formulation for intravenous administration was not available, absolute bioavailability could not be determined.

The areas under the curves (AUC) differed more than twofold and the question arose whether this was due solely to altered elimination in elderly, which is apparent from the terminal half-life ($t_{1/2,z}$) and the renal clearance values (CL_R). Despite the fact that renal clearance was smaller in the elderly, a larger fraction of the dose in this group was excreted in the urine (Ae/D).

The dose was 50 mg. Systemic availability of 15% for the young volunteers and 29% for the elderly was estimated using Eq.(5) ($f_{Eq.(5)}$). Total clearance (CL) and hepatic clearance (CL_H) were calculated using this value of f. Although the difference in hepatic clearance between the young volunteers and the elderly was small, it had a pronounced effect on availability. The difference in f was also reflected in the peak concentration of 40 ng/ml in the young volunteers and 75 ng/ml in the elderly.

The fraction of dose excreted in the urine (Ae/D) was also predicted from the estimated systemic availability and the ratio of renal to total clearance ($f \cdot CL_R/CL$). The prediction must be in good agreement with the observed values (Ae/D) since the computation of f used CL_R and thus indirectly Ae. However, the prediction shows that the difference in availability is responsible for the larger amount excreted in the urine in the elderly, although renal clearance in that group was smaller.

It must be pointed out that the systemic availability estimated by Eq.(5) reflects the upper limit of availability, provided that hepatic and renal clearance are the only routes of elimination. A formula which also takes into account absorption of only a fraction f_a of the dose is presented in Eq.(6).

$$f = f_a \cdot f_{fp} = f_a \cdot \frac{Q + CL_R}{Q + f_a\, D/AUC_{oral}} \qquad (6)$$

where f_a is the fraction of the administered dose absorbed, and f_{fp} is the fraction of the absorbed dose reaching the systemic circulation in the presence of first-pass elimination. Availability, therefore, is the product $f_a \cdot f_{fp}$.

Vaughan and Trainor (1975) presented an analogue of Eq.(6), using a different nomenclature, and pointed out that the fraction absorbed f_a could be estimated with data from an additional intravenous dose.

With any value for f_a between its upper and lower limits, smaller values for f are estimated from Eq.(6) than from Eq.(5). The upper limit is 100% and the lower is at least the percentage of the dose excreted in the urine. A better estimate of the lower limit of f_a can be obtained from a study employing oral administration of the radiolabelled compound.

For the drug concerned the renal recovery of radioactivity was 70% after oral administration. With this value for f_a, the numbers presented in brackets in Table 2 were computed. They reflect the same general property of the drug, namely low availability. Both values signal the need carefully to consider first-pass elimination in dosage adjustment using the oral route of administration.

In summary, it has been pointed out that with Eq.(5) and (6) only the upper and lower limits of systemic availability can be estimated. This may be of particular value for a drug under development, to serve as a guide for further decisions, or if an intravenous formulation is not available. To apply the equations correctly requires that the assumption outlined above are met by the drug considered.

Nevertheless, even in cases where an intravenous formulation can be used in a common crossover design, the calculation of f proceeds from the assumption that hepatic flow rate and thus hepatic clearance and also renal clearance do not change from one trial period to the other, an assumption which is as debatable for the individual, as is the assumption of a fixed hepatic flow rate in the equations discussed.

Table 2. Estimating availability f and other pharmacokinetic characteristics accessible through f using apparent oral clearance and renal clearance. AUC, $t_{1/2,z}$, CL_R and Ae/D were taken from a study which compared pharmacokinetics in young healthy volunteers and the elderly. Characteristics in the second part of the table were computed using the equations given here

		Young		Elderly	
AUC	[ng·h·ml^{-1}]	120		300	
$t_{1/2,z}$	[h]	1.9		2.5	
CL_R	[ml·min^{-1}]	420		280	
Ae/D	[%]	6		12	
D/AUC	[ml·min^{-1}]	6944		2778	
$f_{Eq.(5)}$	[% of dose]	15.2	(14.6)	29.2	(26.8)
CL	[ml·min^{-1}]	1055	(1014)	811	(743)
CL_H	[ml·min^{-1}]	635	(594)	531	(463)
$\frac{CL_R}{CL} f$	[% of dose]	6	(6)	10	(10)

Equations (5) or (6) estimate systemic availability from apparent oral clearance values more accurately than does Eq. (2), which is not appropriate if renal clearance plays an important role in total clearance.

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