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A method for the calculation of bioavailability in slow release formulations in the presence of within-individual variability

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Summary

In the present study we propose a model-independent method based on the combination of the area under the curve of serum drug levels and the mean residence time for evaluating the amount of bioavailability when within-individual variability is present in the serum clearance of the drug, administered as a slow release formulation (SRF), and this follows linear pharmacokinetic behaviour. The method assumes that the modifications in the area under the curve of the serum levels induced by the within-individual variability in the kinetic behaviour of the drug lead to a variation of the same proportions in the mean residence time of the serum levels curve and that this parameter can be used as a correction factor in the ratio of the areas under the curve of serum levels in bioavailability studies. The method allows one to calculate the fraction of dose absorbed from the SRF without having to measure the disposition clearance of the drug either when using the reference formulation or when the drug is administered as a SRF. The method is easy to apply and has a minimum mathematical complexity. The validity of the method was evaluated using simulated data with either no error or containing a random error of 10%.

Introduction

In recent years considerable developments have been made in calculation methods designed to evaluate the amount and rate of bioavailability of drugs administered by different routes and in different pharmaceutical formulations. Initially, most of these methods were based on the use of the area under the serum levels curve (Wagner, 1977; Smolen and Ball, 1984) although, recently, other model-independent techniques have been developed, such as those employing statistical moments or numerical deconvolution for similar purposes (Cutler, 1978; Yamaoka et al, 1978; Veng-Pedersen, 1980; Proost, 1985).

A usual problem in the evaluation of the amount of bioavailability of a drug is the possible within-individual variability in the kinetic behaviour of drugs; this may provide misleading results in this kind of study if the pharmacokinetic calculations are not suitably corrected as a function of the variability observed.

In practice, several methods have been proposed that should allow one to overcome this problem (Chiou et al., 1981; Veng-Pedersen,

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1987), although their application is only effective when conventional dosing forms, that produce a rapid release of the active principle, are employed.

The control of the pharmacokinetic behaviour of drugs by slow release formulations (SRF) involves the use of specific criteria when dealing with the analysis of the behaviour of such systems. The problem is exacerbated in studies of bioavailability and bioequivalence, where application of conventional methods has certain limitations, especially when there is a problem of within-individual variability in the pharmacokinetic behaviour. This problem derives from the strong influence of the kinetic process of release on the kinetic profile of the active principle in the SRF, which hinders correction of the within-individual variability in the disposition processes.

In the present study a model-independent method is proposed that is based on a combination of the area under the serum levels curve and the mean residence time; the method allows one to evaluate the amount of bioavailability when the drug is administered as a SRF and follows linear pharmacokinetic behaviour.

Methods

Theoretical considerations

Clearance and mean residence time

The mean residence time is a model-independent parameter that can be applied in pharmacokinetic studies (Yamaoka et al, 1978; Brockmeier and Von-Hattingberg, 1986; Cutler, 1987) and whose stochastic properties in the analysis of pharmacokinetic processes have been criticized by several authors who believe that serum levels curves of drugs cannot always be treated as statistical distribution curves (Chanter, 1985). Regardless of the interpretation of this parameter with statistical criteria, its efficacy – although debated – has been admitted in the analysis of drug position processes (Yamaoka et al., 1978; Cutler, 1987), even when the drug is administered as a SRF (Nüesch, 1984; Bialer et al, 1986).

As has already been defined (Cutler, 1987), the elimination rate of a drug (dQ/dt) administered intravenously in a bolus type injection can be expressed as:

$$\frac{dQ}{dt} = D \cdot f(t) \tag{1}$$

where D denotes the dose of the drug administered and $f(t)$ is a function of time.

At the same time, the mean residence time (MRT) can be defined as:

$$\text{MRT} = \int_0^\infty t \cdot f(t) \cdot dt \tag{2}$$

By substituting Eqn 1 into Eqn 2, one has:

$$\text{MRT} = (1/D) \int_0^\infty t \cdot dQ \tag{3}$$

The elimination rate of a drug in a linear system can be expressed as the proportionality between its clearance (CL) and the serum concentration (Ct) by the following equation:

$$\frac{dQ}{dt} = \text{CL} \cdot \text{Ct} \tag{4}$$

By substituting Eqn 4 into Eqn 3, one has that:

$$\text{MRT} = (\text{CL}/D) \int_0^\infty t \cdot \text{Ct} \cdot dt \tag{5}$$

This expression reflects the influence of the disposition clearance of a drug on the mean residence time.

Within-individual variability and mean residence time

Assuming that one is dealing with a drug that has within-individual variability in its serum clearance owing to modifications in its elimination capacity, two values of clearance, called CLa and CLb, can be considered and the following relationship can be written:

$$\text{CLb} = X \cdot \text{CLa} \tag{6}$$

where X is the fraction that quantifies the within-individual variability of CLb with respect to CLa.

Considering the classical relationship between the dose administered (D) and the area under the serum levels curve (AUC), we have:

$$\mathrm{CL} = \frac{D}{\mathrm{AUC}} \tag{7}$$

Combining Eqns 6 and 7, we then write:

$$(\mathrm{AUC})\mathrm{b} = \frac{(\mathrm{AUC})\mathrm{a}}{X} \tag{8}$$

As was already proposed by Yamaoka et al. (1978), the MRT can be expressed as the following equation:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}} \tag{9}$$

where

$$\mathrm{AUMC} = \int_0^\infty t \cdot c \cdot \mathrm{d}t \text{ or AUMC}$$

$$= \int_0^\infty t \sum_{i=1}^{n} a_i \cdot e^{-b_i t}\, \mathrm{d}t = \sum_{i=1}^{n} \frac{a_i}{b_i^2} \tag{10}$$

and

$$\mathrm{AUC} = \int_0^\infty c \cdot \mathrm{d}t \text{ or AUC}$$

$$= \int_0^\infty \sum_{i=1}^{n} a_i \cdot e^{-b_i t}\mathrm{d}t = \sum_{i=1}^{n} \frac{a_i}{b_i} \tag{11}$$

a_i and b_i being the coefficients and exponents, respectively of the polyexponential equation of 'n' exponential terms that characterized the serum levels curve.

By solving Eqns 10 and 11 in terms of within-individual variability in AUC and AUMC, one again obtains Eqn 8 with respect to the within-individual variability in AUC and the following expression for the within-individual variability of AUMC:

$$\mathrm{AUMCb} = \frac{\mathrm{AUMCa}}{X^2} \tag{12}$$

Combining Eqns 8, 9 and 12 one has:

$$\mathrm{MRTb} = \frac{\mathrm{MRTa}}{X} \tag{13}$$

This expression is similar to Eqn 8 and shows that the within-individual variability in serum clearance induces changes of the same magnitude in the area under the curve of serum levels and in the mean residence time of that curve when the drug is administered through the i.v. route and in the absence of input processes.

These deductions show that the mean residence time after bolus i.v. administration is able to reflect within-individual variations in the disposition of the drug and that it can be used as a correction factor in bioavailability studies.

Mean residence time and bioavailability in SRF

Using the linear system analysis theory and moment theory to analyze the disposition of a drug administered intravenously in a bolus injection, by the extravascular route in the form of a solution and through the extravascular route in the form of a SRF with first order dissolution and absorption, the MRT for each administration route can be written:

Bolus i.v. administration: MRTi.v.

Extravascular administration: MRText = MRTa + MRTi.v.

Administration as an SRF: MRTsrf = MRTd + MRTa + MRTi.v.

where MRTa and MRTd are the mean residence time of the absorption and dissolution processes, respectively. MRTsrf is the mean residence time after administration of SRF.

MRTi.v. is affected by the within-individual variation of the disposition parameters of the

drug, but MRTa and MRTd are independent of this variability.

When SRF are employed, based on the control of the kinetic profile of the drug by the slow dissolution of active principle, the MRTd acquires a high value with respect to the MRT of the drug when administered by the same or another route, with a rapid dissolution of the drug. Accordingly, the mean residence time of the SRF is only partially affected by the possible within-individual variability in clearance.

In view of the foregoing considerations, it is possible to propose a method for calculating the fraction of dose absorbed in bioavailability studies of slow release formulations with an assumed within-individual variability in serum clearance, combining the area under the curve and the corrected mean residence time obtained with rapid and slow release formulations.

To do so, values of MRText and MRTsrf should be used that must be corrected, eliminating those components that are not affected by the within-individual variability in the disposition process such as MRTa and MRTd. Accordingly, it is possible to calculate corrected values of the mean residence time for formulations of rapid ((MRText)corr) and slow ((MRTsrf)corr) dissolution through the following expression:

$$(\text{MRText})\text{corr} = \text{MRText} - \text{MRTa} \qquad (14)$$

$$(\text{MRTsrf})\text{corr} = \text{MRTsrf} - \text{MRTd} - \text{MRTa} \qquad (15)$$

The values of (MRText) corr and (MRTsrf)corr should reflect the within-individual variability in serum clearance better than MRText and MRTsrf. The corrected values of MRT can be used directly to correct the areas under the curve and to calculate the relative bioavailability (F) of a slow release formulation as compared with one of rapid dissolution, eliminating the modifications in the area under the curve induced by within-individual variability, according to the following equation:

$$F = \frac{(\text{AUC})\text{srf} \cdot (\text{MRText})\text{corr} \cdot \text{Dext}}{(\text{AUC})\text{ext} \cdot (\text{MRTsrf})\text{corr} \cdot \text{Dsrf}} \qquad (16)$$

where (AUC)srf and Dsrf are the area under the curve and the dose used with the slow release formulation and (AUC)ext and Dext are the area under the curve and the dose used with the rapid dissolution formulation.

When there is no within-individual variability in clearance, the MRTd can easily be calculated by the difference between the MRTsrf and the MRText. However, this form of calculating the MRTd is not applicable in SRF when the existence of within-individual variability is suspected. As a consequence, the calculation of the MRTd in such situations should be carried out from the serum levels curve of the drug following administration of the SRF.

Usually, when serum level curves of drugs administered as SRF are analyzed, the terminal phase of the curve reflects the 'in vivo' release kinetics of the drug. Accordingly, this terminal phase of the curve can be used to calculate the MRTd.

However, it is difficult to calculate the MRTa in the plasma level curves obtained after the administration of the slow release formulation, above all considering that in this kind of formulation MRTa $\ll$ MRTd, such that it is more appropriate to calculate MRTa in the serum level curve obtained following administration of the fast release formulation.

The method proposed for the correction of the within-individual variability in bioavailability studies can also be applied to studies on absolute bioavailability of formulations administered through an extravascular route as compared with bolus type i.v. administration by a modification in Eqn 16, as follows:

$$F = \frac{(\text{AUC})\text{ext} \cdot \text{MRTi.v.} \cdot \text{Di.v.}}{(\text{AUC})\text{i.v.} \cdot (\text{MRText})\text{corr} \cdot \text{Dext}} \qquad (17)$$

Simulation study

In order to check the validity of the method proposed, simulated data were employed, with and without random error, with a view to studying the effect of within-individual variability in

serum clearance on the kinetic behaviour and on the calculation of bioavailability using different administration routes, especially when a SRF is employed.

To perform the simulation study a two-compartment disposition model was employed, with linear and first-order release, absorption, distribution and elimination; the pharmacokinetic parameters of these were as follows:

$K_r = 0.1\,h^{-1}$, $K_a = 3\,h^{-1}$, $\alpha = 5\,h^{-1}$,

$\beta = 0.3\,h^{-1}$, CL = 3.44 l/h, $V_c = 5$ l,

$K_{12} = 2.43\,h^{-1}$, $K_{21} = 2.18\,h^{-1}$, $K_{10} = 0.69\,h^{-1}$,

$V_p = 5.57$ l,

Dose = 100 mg

where K_r and K_a are the constants of release and absorption, respectively; α and β are the disposition macroconstants corresponding to the two compartment kinetic model, CL denotes serum clearance of the drug, K_{12}, K_{21} and K_{10} are distribution and elimination rate constants and V_c and V_p represent the distribution volumes of the central and peripheral compartments.

Fig. 1 shows a scheme of the pharmacokinetic model used in the simulation.

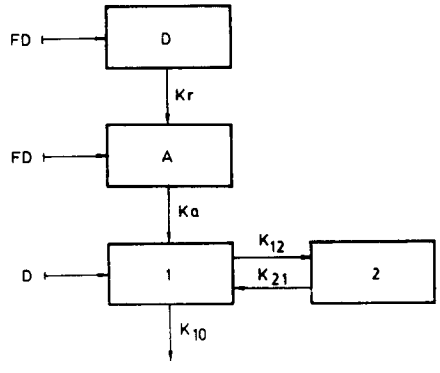

Fig. 1. Two-compartment pharmacokinetic model with sequential first-order dissolution and absorption. To simulate intravenous data, the dose was entered into compartment (1); for oral solution data, the dose was entered into the absorption compartment (A); and SRF, the dose was entered into the dissolution compartment (D).

The simulations were performed following i.v. bolus administration in the form of an oral solution (absorption constant $k_a = 3\ h^{-1}$) and in the form of a SRF administered orally (release constant $k_r = 0.1\ h^{-1}$), in all cases at a dose of 100 mg.

Estimation of the serum concentration of the drug in the different situations was carried out at the following simulated times: (1) oral solution: 0.1, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 h; (2) SRF: 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 36.0 and 48.0 h. Calculations were carried out using the NONLIN program on simulation mode (Weiner, 1986).

Calculation of the area under the curve In bioavailability studies, based on measuring the area under the curve of the serum drug levels, the method of calculation used in the evaluation of this parameter may affect the results obtained. Accordingly, the proposed method using simulated data was applied, conducted utilizing four different methods for calculating the area under the curve of the serum levels: the trapezoidal, log-trapezoidal, Lagrange and natural splines methods (Yeh and Kwan, 1978).

Estimation of bioavailability Serum level curves of the drug were simulated for bioavailabilities ranging from 25 to 100% of the dose administered in the SRF and with different within-individual variabilities. Calculation of the amount of bioavailability (F) of the drug incorporated into the SRF was performed for the different situations on the basis of Eqn 16.

The MRT was calculated from the serum levels curve by model-independent analysis according to Eqns 9–11. The MRTd was calculated using the terminal phase of the serum levels curve, assuming that the release rate is a single exponential function and that this is reflected in the terminal phase of the concentration-time profile. The MRTa was calculated from the plasma levels curve obtained after administration of the oral solution using the method proposed by Riegelman and Collier (1980). Considering the important contribution of the MRTd to the value of the MRT in SRF, the MRTd should be calculated with maximum statistical precision using the

greatest number of data points from the terminal phase of the serum levels curve to do so.

Within-individual variability The influence of within-individual variability in serum clearance on the pharmacokinetic profile of the drug administered as a SRF was studied. The interval of variation studied ranged between −30 and +30% of the serum clearance. The within-individual variability assumed only affected the processes of drug elimination, not considering modifications in serum clearance due to alterations in the apparent distribution volume. The pharmacokinetic parameters studied were the area under the curve (AUC) and the mean residence time (MRT).

Random error Calculation of the fraction absorbed from the SRF was made using data without error as compared with data using an added random error of 10%.

Results

Fig. 2 shows the curve of simulated serum levels of a drug developing according to an open two-compartment kinetic model after i.v. bolus administration in the form of an oral solution and SRF. The same figure shows the influence of the release and absorption processes on the kinetic profile of the drug administered in the form of a SRF.

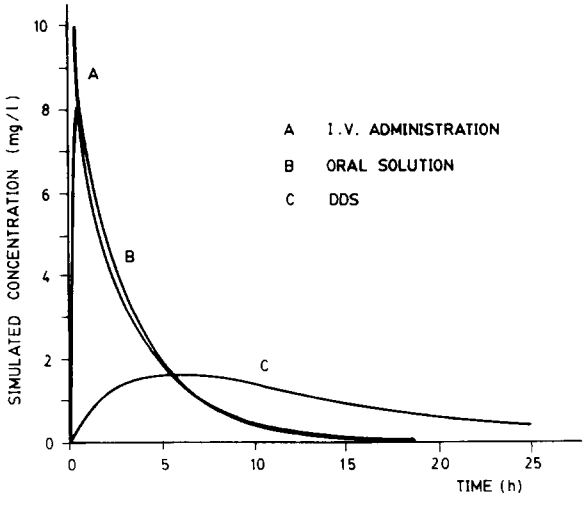

Fig. 2. Simulated serum levels of the drug after i.v. administration, oral solution and SRF.

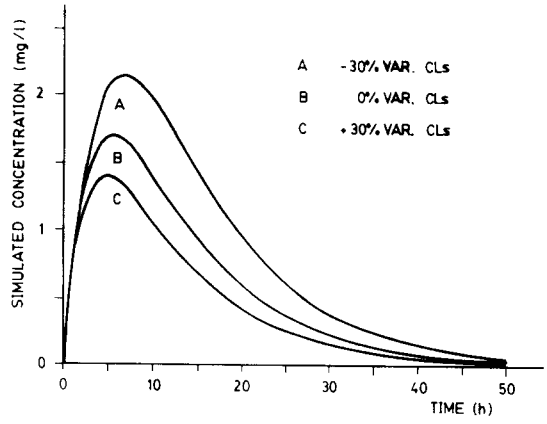

Fig. 3. Influence of within-individual variation of serum clearance of drug (−30 and 30%) on simulated serum levels after administration of SRF.

Fig. 3 shows the curve of simulated serum levels following administration of the drug in the form of a SRF with a bioavailability of 100%, when a within-individual variability of −30 to +30% is present in the serum clearance.

Fig. 3 also shows how within-individual variability in serum clearance – owing to modifications in the elimination capacity – causes important alterations in the serum levels of the drug. These affect the area under the curve, even when there are no modifications in the amount or rate of bioavailability of the drug considered. A parallel can be seen in the terminal phase of the serum levels curve of the drug; the slope of this is unaffected by the modifications occurring in its serum clearance, unlike what happens when conventional formulations are employed. These findings show that it is not possible to apply conventional methodology for calculating the amount of bioavailability in the presence of within-individual variability.

Table 1 lists the F values calculated according to the proposed method for an amount of bioavailability of 100%, calculating the AUC of the serum levels by four different methods. The table also shows that in all cases, and for the different methods used for calculating the area under the curve, the proposed method allowed us

TABLE 1

F values for an amount of bioavailability of 100% between − 30 and + 30% of within-individual variability

	F^a	F^b	F^c	F^d
SRF 0% VAR Cls	1.02	1.02	1.02	1.02
SRF −5% VAR Cls	1.02	1.02	1.02	1.02
SRF −10% VAR Cls	1.03	1.02	1.02	1.02
SRF −20% VAR Cls	1.04	1.03	1.03	1.03
SRF −30% VAR Cls	1.05	1.04	1.04	1.04
SRF +5% VAR Cls	1.02	1.01	1.01	1.01
SRF +10% VAR Cls	1.01	1.01	1.01	1.00
SRF +20% VAR Cls	1.01	1.00	1.00	1.00
SRF +30% VAR Cls	1.00	0.99	0.99	0.99

AUC calculated by: [a] Trapezoidal method, [b] log-trapezoidal method, [c] Lagrange method, [d] natural splines method.

to suitably calculate the fraction of dose absorbed from the SRF, even when the within-individual variability in serum clearance was ±30%. The error of the method under the conditions assayed was in all cases lower than 6%.

Table 2 shows the *F* values for the four bioavailabilities assayed, using the proposed method and calculating the AUC of the serum levels curve by the natural splines method; this proved to be the best method for calculation of the AUC, and was selected on the basis of results of residuals analysis performed.

Table 3 shows the values of the AUC, (MRTsrf)corr and *F* calculated for a bioavailability of 100%, this time using serum level curves to which a random error of 10% had been added. It may be seen that the proposed method works

TABLE 2

F values for simulated bioavailabilities between 25 and 100% of the dose administered as a SRF

	F_{25}	F_{50}	F_{75}	F_{100}
SRF 0% VAR Cls	0.25	0.51	0.76	1.02
SRF −5% VAR Cls	0.25	0.51	0.76	1.02
SRF −10% VAR Cls	0.26	0.51	0.77	1.02
SRF −20% VAR Cls	0.26	0.52	0.77	1.03
SRF −30% VAR Cls	0.26	0.52	0.78	1.04
SRF +5% VAR Cls	0.25	0.50	0.76	1.01
SRF +10% VAR Cls	0.25	0.50	0.75	1.00
SRF +20% VAR Cls	0.25	0.50	0.75	1.00
SRF +30% VAR Cls	0.25	0.49	0.74	0.99

TABLE 3

AUC, (MRTsrf)corr, and F values calculated for a bioavailability of 100% using serum levels curves with an added random error of 10%

	AUC	(MRTsrf)corr	*F*
SRF 0% VAR Cls	29.01	3.59	0.95
SRF −5% VAR Cls	31.02	3.83	0.95
SRF −10% VAR Cls	32.22	3.88	0.98
SRF −20% VAR Cls	36.14	4.02	1.06
SRF −30% VAR Cls	41.68	4.55	1.08
SRF +5% VAR Cls	28.43	3.18	1.05
SRF +10% VAR Cls	26.82	2.81	1.12
SRF +20% VAR Cls	24.21	2.96	0.96
SRF +30% VAR Cls	22.37	2.40	1.10

suitably even in the presence of a residual variability in the data. In this case, the AUC was also calculated using the natural splines method.

Discussion

The results obtained, using simulated data, show that the proposed method allows one to assume the existence of within-individual variability in the kinetic behaviour of drugs and to remove this from the calculation of the fraction of dose absorbed in conventional formulations and, specifically, slow release formulations, in which conventional methods for calculating bioavailability in the presence of within-individual variability cannot be applied. The method allows one to calculate the fraction of drug absorbed from the SRF without having to measure the disposition clearance of the drug or the reference formulation or when the drug is administered as a SRF. It is also easy to use and its mathematical complexity is small.

One of the principal limitations of the method lies in correctly calculating the area under the curve of the serum levels and of the mean residence time. Several authors have previously analyzed the problems involved in calculating bioavailability based on calculation of the area under the curve and/or the mean residence time (Cutler, 1978; Riegelman and Collier, 1980; Urso and Aarons, 1983). In those works discussion is

made of the errors involved in the calculation of both parameters owing to the existence of the cut-off error, in turn due to the use of somewhat imprecise methods for calculating the area, such as the trapezoidal method (Yeh and Kwan, 1978), or using unsuitable sampling times (Wagner, 1977).

As can be seen from the results offered in Table 3, the use of methods for calculating the area under the curve that employ polynomial expressions, such as the natural splines method, reduces the errors involved in calculating the area under the curve. At the same time it is essential to make a suitable experimental design that will optimize sampling times in order to reduce the errors involved in calculating the mean residence time, as already proposed by other authors (D'Argenio and Katz, 1983).

Conclusions

In the experiments in which the area under the curve and the mean residence time of the formulations under study, and especially SRF, can be calculated with sufficient reliability and in which the system satisfies the criterion of linearity, the proposed method may be of use for calculating the fraction of the dose of drug absorbed from the SRF, when within-individual variability is suspected in the drug's pharmacokinetic behaviour.

Under the conditions in which the method has been developed, its limits of application would be as follows:

(1) Linear pharmacokinetic systems.

(2) The absence of saturable or dose-dependent kinetic processes.

(3) Processes of single dissolution and absorption, according to a first-order exponential kinetic process.

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