ELSEVIER

International Journal of Pharmaceutics 146 (1997) 225–232

international journal of pharmaceutics

Calculation of the blister fluid-time history with ciprofloxacin administered orally or by infusion

A. Bakhouya, M. Saïdna, J.M. Vergnaud*

Laboratory Materials and Chemical Engineering, Faculty of Sciences 23, rue du Docteur Paul Michelon, University of St-Etienne, St-Etienne 42023, France

Received 7 June 1996; revised 21 November 1996; accepted 29 November 1996

Abstract

The drug level-time history was calculated either in the blood compartment or in the blister fluid through the skin, when the drug was administered through various ways: orally with immediate release dosage forms or with controlled release dosage forms, through infusion with a constant rate. These drug-time histories were found to be in good agreement with experimental results shown in the literature, with the immediate release oral dosage forms and with infusion. A numerical model was built, taking into account all the known facts concerned with the pharmacokinetic parameters of the drug, with the kinetics of absorption and elimination, as well as the stage through which the drug is transported from the blood compartment to the blister fluid in the skin, assumed to be governed by transient diffusion with constant diffusivity. A parameter of interest appears with the ratio of the diffusivity and the mean length of tissue over which the diffusional transport takes place. © 1997 Elsevier Science B.V.

Keywords: Blister fluid; Ciprofloxacin administration; Modelling; Diffusion

1. Introduction

As already said (Meulemans et al., 1989), it is important to get good knowledge on the diffusion of antibiotics in the extracelluar fluid, since this is the obligatory path to infections loci. The diffusion of antibiotics has been studied in normal and pathological situations through various extracelluar fluid samples: cerebrospinal fluid (Nau et al., 1990), prostatic fluid, bone and bradytrophic tissues such as meniscus and other cartilage (Wacha et al., 1990), bronchial secretions (Saux et al., 1994). Various experimental studies have been especially made on the penetration of the drug into the chemically induced blister fluid which has been shown to be similar in composition to the exudate of a mild inflammatory reaction (Wise et al., 1980).

* Corresponding author.

PII S0378-5173(96)04829-6

Only the diffusivities of oxygen have been evaluated (Blum, 1960; Klitzman et al., 1983; Kreuzer, 1982) with the help of mathematical models simulating the oxygen concentration in tissues and around capillaries. There is little information about the diffusivity of antibiotic through the tissues in the literature. Some authors showed that the penetration of antibiotics into tissues is governed by the Fickian diffusion (Bergan, 1978; Bergan, 1981; Bergeron, 1986). The concentration of ciprofloxacin was measured either in the blood compartment or in blister fluids of healthy male volunteers after they were given a single oral dose of 500 mg with immediate release (Crump et al., 1993). The concentrations of ciprofloxacin in the plasma and in cantharides induced blister fluid on healthy volunteers after IV and oral administration were determined (Catchpole et al., 1994). Following these studies, the pharmacokinetics and the suction-induced blister fluid penetration of ciprofloxacin were compared after single oral dose and after multiple doses (Le Bel et al., 1986).

An attempt was made for a theoretical approach by taking into consideration the fact that the transport of ciprofloxacin from the blood compartment to the blister fluid was driven by transient diffusion (Meulemans et al., 1989). The equation of diffusion through a semi-infinite medium with a constant concentration on the surface was selected, in order to simplify the problem. However, it must be said that this equation does not correspond with a finite thickness of the tissue and a constant concentration on the surface (Vergnaud, 1993, 1991).

The first purpose of this work was to study the process of transport of the drug from the plasma compartment through the tissue to the blister fluid by considering the transient diffusion as the driving force (Vergnaud, 1993). In order to simplify the problem, the transport was assumed to be unidirectional and the diffusivity constant. Various ways of administering the drug were examined: oral dosage forms with immediate release and with controlled release; infusion with a constant rate. As no analytical solution exists, a numerical model with finite differences was built (Vergnaud, 1993, 1991) and tested by comparing the kinetic curves obtained by calculation and from experiments shown in the literature (Catchpole et al., 1994) either in the blood compartment or in the blister fluid. The model of diffusion through the tissue takes into account the known facts, namely, the drug level-time history in the blood compartment and the two parameters of diffusion such as the constant diffusivity and the length over which the diffusion takes place.

The other objective in this paper was to express the results obtained by calculation in terms of curves describing the drug level-time histories of ciprofloxacin in the blood compartment and in the blister fluid. These curves were compared to the experimental data obtained with a single oral dose (Crump et al., 1993), multiple oral dose (Le Bel et al., 1986) or with infusion with a constant rate (Catchpole et al., 1994). As it was not possible to evaluate the thickness of the tissue, the diffusional transport of the drug through this tissue was defined by the diffusivity as a fraction of the square of the length of diffusion through the tissue. This ratio has the dimension of $(\text{time})^{-1}$, in the same way as the rate constant of a first order kinetics.

2. Theoretical

Two kinds of calculation are made, the one concerned with the diffusional transport from the plasma compartment to the blister fluid, the other with the determination of the drug-time history in the plasma volume.

2.1. Calculation of the diffusional transport through the tissue

2.1.1. Assumptions

The following assumptions are made in order to make the process clear:

(1) the diffusional transport is unidirectional, through the tissue, over a mean length L,
(2) the diffusion is Fickian with a constant diffusivity,
(3) the concentration of drug on the surface of the tissue in contact with the plasma volume is the same as that in the plasma volume,

(4) the concentration of the drug on the surface of the tissue in contact with the blister fluid is constantly equal to that of the blister fluid.

2.1.2. Mathematical treatment

The equation of unidirectional diffusion through the tissue of thickness L with constant diffusivity is

$$\frac{\partial c}{\partial t} = D \cdot \frac{\partial^2 C}{\partial x^2} \tag{1}$$

The initial conditions are

$$t = 0 \qquad 0 < x < L \qquad C = 0 \tag{2}$$

The boundary conditions are for the surface in contact with the plasma

$$t > 0 \qquad x = 0 \qquad C_{0,t} \quad \text{plasma concentration} \tag{3}$$

and for the surface in contact with the blister fluid

$$t > 0 \ , \qquad x = L$$

$$C_{L,t} \quad \text{blister fluid concentration} \tag{4}$$

2.1.3. Numerical analysis

No analytical solution exists for the problem with fluctuating concentrations on each surface. A numerical method with finite differences was used to resolve the problem (Vergnaud, 1991, 1993).

The basis of calculation is only given, as it was developed elsewhere. The sheet of thickness L is divided into N slices of thickness Δx, while increments of time Δt are considered.

2.2. Calculation of the drug level in the plasma

Two ways of calculation are used, depending on the administration of the drug: one-compartment model with the oral dosage form, two compartment model with the infusion.

2.2.1. One-compartment model with the oral dosage form with immediate release

The drug in the gastro-intestine is transferred in the plasma volume and eliminated through 2 first-order kinetics:

$$\frac{dY}{dt} = k_a \cdot X_t - k_e \cdot Y_t \tag{5}$$

where Y_t, X_t are the amount of drug in the plasma volume, and in the gastrointestine at time t, and k_a and k_c are the rate constants of absorption and elimination.

2.2.2. One-compartment model with the oral dosage form with controlled release

With the oral dosage form whose release is controlled by erosion, the rate of release is constantly proportional to the actual area of the dosage form:

$$-\frac{d(\text{volume})}{dt} = k(\text{area}) \tag{6}$$

In the case of the dosage form, spherical in shape, the kinetics of release in the gastrointestine is given by (Vergnaud, 1993):

$$\left(1 - \frac{X_t}{M_{in}}\right)^{1/3} = 1 - k_{er}.t \tag{7}$$

The kinetics of absorption of the drug in the plasma volume is also given by Eq. (5).

2.3. Two-compartment model with the drug infusion

Following the principle of the two-compartment model (Cours National de Pharmacologie., 1983) the rate of delivery of the drug in the plasma is given :

(1) during the stage of infusion by:

$$\frac{dY}{dt} = K_0 - k_e \cdot Y \tag{8}$$

whose solution is:

$$Y_t = \frac{K_0}{k_e}[1 - \exp(-k_e t)] \tag{9}$$

(2) after the end of the stage of infusion by:

$$\frac{dY}{dt} = -(k_{12} + k_e)Y + k_{21} \cdot Y_2 \tag{10}$$

whose general solution is:

$$Y_t = A \cdot \exp(-\alpha t) + B \cdot \exp(-\beta t) \quad (11)$$

The values of the coefficients A, B and α, β are determined in the usual way (Cours National de Pharmacologie., 1983).

3. Experimental

Experiments made in a previous study by other authors are summarized (Catchpole et al., 1994).

Six healthy volunteers were submitted to either ciprofloxacin 400 mg delivered through IV infusion over 1 h, or ciprofloxacin 750 mg taken orally with water. Blood and blister liquid fluid samples were taken for analysis at intervals (Catchpole et al., 1994).

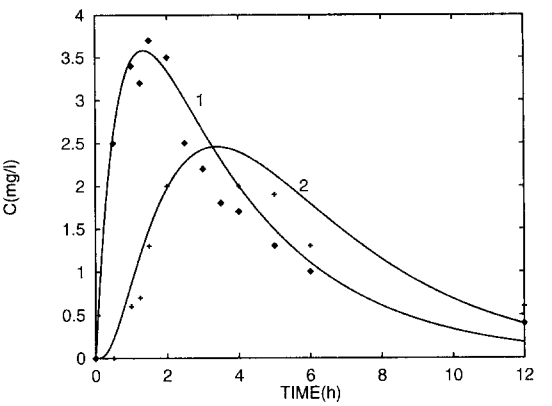

Fig. 1. Drug level-time histories of ciprofloxacin in the serum (1) and blister fluid (2), with the oral dosage form with immediate release (750 mg): ——: calculated: ◆, +: experimental.

4. Results

Two kinds of results are considered: the comparison between the drug level-time histories in the serum and in the blister fluid obtained either by experiments or by calculation with single dose enabling one to test the model and the accuracy of the data; the other with the calculation of the drug level-time histories in other cases, with different dosage forms and especially with multiple dose.

4.1. Comparison between the experimental and calculated drug level-time histories in the serum and the blister fluid

The drug level-time histories in the serum (1) and the blister fluid (2) obtained either by experiments (Catchpole et al., 1994) or by calculation when the drug was administered through an immediate release dosage form are shown in Fig. 1, with an amount of ciprofloxacin of 750 mg. The same curves are shown in Fig. 4 when the drug (400 mg) was administered through infusion with a constant rate over a period of 1 h.

These experimental values correspond with the mean response to drug of six healthy volunteers (Catchpole et al., 1994). The values of the pharmacokinetic parameters and of the diffusion parameters through the tissue which we obtain by calculation are listed in Table 1.

The values of some characteristics of the experimental and calculated curves are also shown in Table 2, for comparison.

The curves drawn in Figs. 1 and 2 and the values in Table 1 and 2 can lead to some conclusions:

(i) Rather good agreement is obtained between the experimental and calculated drug level-time histories in the plasma and in the blister fluid whatever the way of administration: oral with immediate release in Fig. 3, or with infusion in Fig. 4.

(ii) With the oral administration with immediate release, a maximum is attained at 1.33 h in the plasma with a concentration around 3.6 mg/l either in the experimental or calculated curves. In

Table 1
Pharmacokinetic and diffusion parameters

Oral dosage form	$k_a = 1.5$/h	$k_e = 0.3$/h	$V_p = 140$ l
Diffusion	$D/L^2 = 0.2$/h		
Infusion	$\alpha = 2$ h $\beta = 0.3$/h	$k_e = 0.3$/h	$V_p = 52$ l
Diffusion	$D/L^2 = 0.22$/h		

Table 2
Characteristics of the drug level

	IV (400 mg)		PO (750 mg)	
	Calc.	Exp.	Calc.	Exp
Plasma				
C_{max} (mg/l)	6.64	6.7	3.6	3.7
t_{max} (h)	1	1	1.33	1.5
$AUC_{0-\infty}$	12.15	14.2	17.8	19.2
Blister				
C_{max} (mg/l)	2.32	2.4	2.5	2.3
t_{max} (h)	1.66	1.5	3.66	3
$AUC_{0-\infty}$ (mg h/l)	12.12	13.8	17.8	20.8

the same way, the drug level in the blister fluid passes through a maximum at around 3.66 h for the calculated curve; it is difficult to determine exactly the corresponding time in the experimental curve. The maximum concentration of drug in the blister fluid is 2.5 mg/l on the calculated curve, and it can be evaluated at 2.3 mg/l on the experimental curve.

(iii) With infusion, the drug level-time history in the plasma is typical, with a high peak at 6.7 mg/l attained at the end of the stage of infusion (1 h). In the blister fluid, the maximum is reached at around 1.6 h on the experimental and calculated curves at a level around 2.3–2.4 mg/l.

(iv) The values obtained for the parameters of diffusion, and especially for their ratio, namely D/L^2, is about the same whatever the way of administration: 0.2 h with the oral dosage form, and 0.22/h with the infusion. It must be noticed that the dimension of D/L^2 is the same as that of a rate constant of a 1st order kinetics.

(v) Of course, the diffusion of the drug through the tissue is responsible for the drug level-time history in the blister fluid to lag behind the corresponding curve in the plasma.

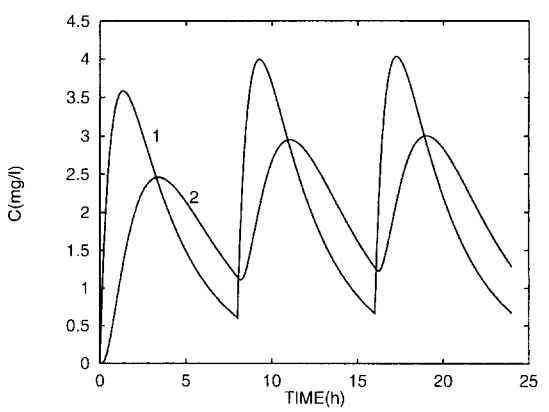

Fig. 2. Drug level-time histories of ciprofloxacin calculated in the serum (1) and blister fluid (2) with the immediate release oral dosage form (750 mg) taken three times a day.

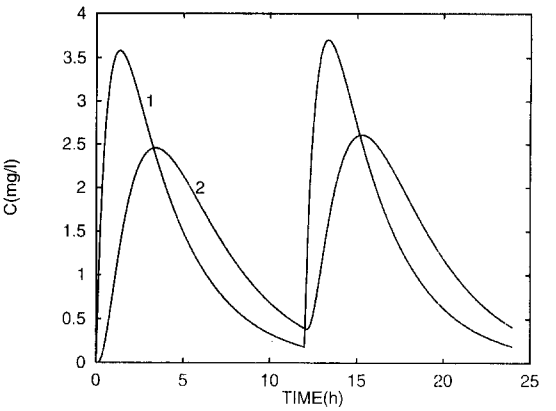

Fig. 3. Drug level-time histories of ciprofloxacin calculated in the serum (1) and blister fluid (2) with the immediate release oral dosage form (750 mg) taken twice a day.

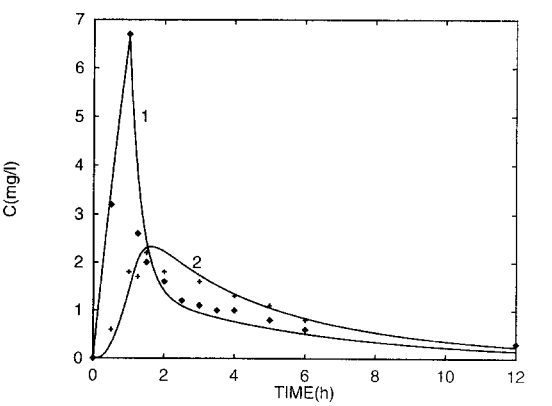

Fig. 4. Drug level-time histories of ciprofloxacin in the serum (1) and the blister fluid (2) with 400 mg administered through infusion over 1 h with a constant rate. ——: calculated: ◆, +: experimental.

4.2. Calculation of the drug level-time histories with various ways of drug administration

4.2.1. Oral dosage form with immediate release

With the oral dosage form with immediate release, the drug level reaches the maximum value at around 1.3 h in the plasma, and at around 3.6 h in the blister fluid. With multiple dose, a trough appears when the following dose is taken. Thus the dose frequency is of great importance either for the drug level in the plasma or for the drug level in the blister fluid. Two dose frequencies are considered: three times a day in Fig. 2 and twice a day in Fig. 3, showing the effect of the dose frequency on the drug level:

(i) The plasma drug level at the peak is about the same with these two dose frequencies at the peak, but it differs largely at the trough.

(ii) The peak of the drug in the blister fluid reaches 2.6 mg/l with the twice a day dose and 3 mg/l with the three times a day dose, these two values being of the same order of magnitude.

(iii) The trough of the drug in the blister fluid is highly influenced by the dose frequency in the same way as in the plasma. From around 0.45 mg/l with the twice a day dose it increases up to 1.2 mg/l with the three times a day dose.

(iv) The process of diffusion reduces the peak and increases the trough in the blister fluid as compared with the corresponding values in the plasma.

4.2.2. Drug administered through infusion with constant rate (400 mg) over 1 h

The drug level-time histories are calculated either in the serum (1) or in the blister fluid (2) in the case of infusion of the drug with a constant rate over 1 h. Multiple infusions are also calculated with various frequencies: twice a day in Fig. 5 and three times a day in Fig. 6. These calculations are made by using the pharmacokinetic parameters with the double compartment and the diffusion parameters through the tissue shown in Table 1. A few conclusions can be given from these curves:

(i) The so-called 'steady state' when the drug level-time history become reproducible, is obtained after the second administration with the twice a day dose and after the third administration with the three times a day dose.

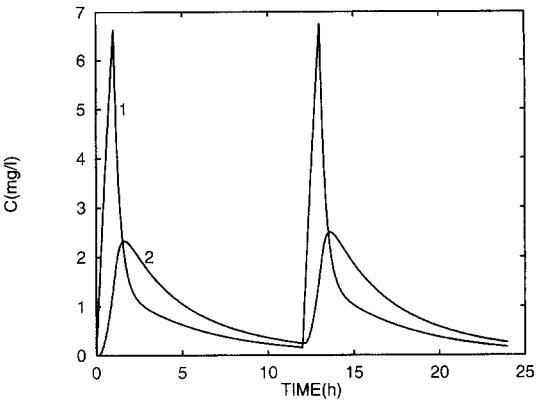

Fig. 5. Drug level-time histories of ciprofloxacin in the serum (1) and the blister fluid (2) with 400 mg administered (through infusion over 1 h with a constant rate, twice a day). ——: calculated: ◆, +: experimental administered twice a day.

(ii) The peaks are about at the same level either in the serum or in the blister fluid, whatever the dose frequency.

(iii) The level at the trough in the serum and the blister fluid depends on the frequency. Of course, it is higher for the three times a day than for the twice a day dose.

(iv) The drug level at the trough is higher in the blister fluid than in the serum, in the same way as for the oral dosage form.

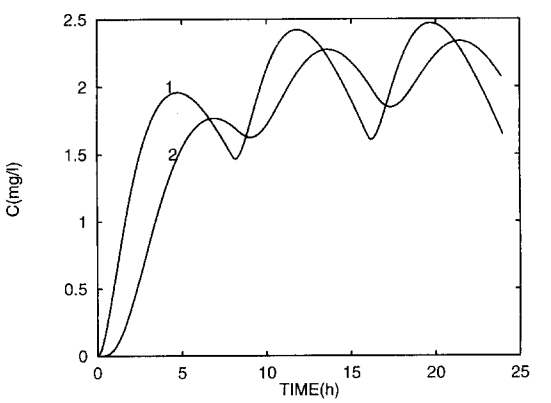

Fig. 6. Drug level-time histories of ciprofloxacin calculated in the serum (1) and the blister fluid (2) with a dosage form with controlled release (400 mg).

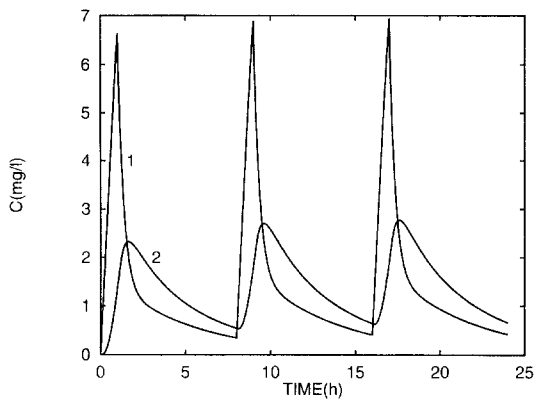

Fig. 7. Drug level-time histories of ciprofloxacin in the serum (1) and the blister fluid (2) with 400 mg administered (through infusion over 1 h with a constant rate, three times a day). ——: calculated: ◆, +: experimental + administered.

4.2.3. Drug orally administered with a controlled release dosage form

Calculation has been made for the drug level-time histories in the serum and the blister fluid in the case of a drug orally administered with a controlled release dosage form. The release is controlled by erosion with a value of the constant k_{er} of 0.08 l/h, meaning that the drug is completely released out of the dosage form after 12 h. The drug level-time histories are drawn in the serum (1) and the blister fluid (2) in Fig. 7 with multiple dose taken twice a day, leading to the following conclusions:

(i) The effect of the controlled release appears for the drug level-time histories in the serum and the blister fluid. The drug level alternates between lower peaks and higher troughs either for the serum and the blister fluid.

(ii) Of course, the first peak is attained after a longer time, e.g. nearly 5 h in the serum and 7 h in the blister fluid.

5. Conclusions

The process of transfer of the drug from the serum into the blister fluid can be explained by transient diffusion. As the thickness or rather the mean thickness over which the diffusion takes place is not known, the results are expressed in terms of the diffusivity as a fraction of the square of the mean thickness, D/L^2. The dimension of this ratio is the same as that of the rate constant of a first-order kinetics, in the same way as for the rate constant of absorption or of elimination. The value of this ratio was found to be about the same when it was calculated either with an oral dosage form with immediate release or when the drug was administered through infusion.

The numerical model used for these calculations was tested by comparing the drug time-histories obtained in the serum and the blister fluid either by calculation or from experiments shown in the literature.

It was thus possible to evaluate the drug level-time histories in the serum and the blister fluid by considering various ways of administration of the drug: oral dosage form with immediate release, infusion with constant rate over 1 h, oral dosage form with release controlled by erosion. In all cases, the drug level-time history in the blister fluid is lagging behind the corresponding curve in the serum, resulting from the diffusion process. The way of administration and the dose frequency were found to play an important role for regulating the drug level in the blister fluid.

6. Nomenclature

A, B	concentration with the bi-compartment model
C	concentration of drug
C_n	concentration of drug at position n
D	diffusivity of the drug through the tissue
$\Delta x, \Delta t$	increments of space, of time, respectively
k_{12}	transfer constant of drug from the plasma to the peripheric compartment
k_{21}	transfer constant of drug from the peripheric compartment into the plasma
k_a, k_e	rate constant of absorption, elimination
k_{er}	rate constant of erosion
K_0	constant rate of infusion
L	thickness of the tissue
X	amount of drug in the gastrointestine
X_t	amount of drug in the gastrointestine at time t

Y amount of drug in the blood compartment

Y_2 amount of drug in the peripheric compartment

Y_t amount of drug in the plasma at time t

Greek letters

α, β rate constants of distribution and elimination

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