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Non-linear Intestinal Absorption Kinetics of Cefadroxil in the Rat

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Abstract—Absorption of cefadroxil in a selective intestinal absorption area (the proximal third of the small intestine) of the anaesthetized rat, at seven initial perfusion concentrations, ranging from 0·01 to 10·0 mg mL^{-1}, is shown to be a non-linear transport mechanism. With the aid of computer-fitting procedures based on differential and integrated forms of Michaelis-Menten equation, V_m and K_m values of 36·7–37·3 mg h^{-1} and 12·0–13·0 mg, respectively, were found. The statistical parameters were better than those obtained both for first-order and for combined Michaelis-Menten and first-order kinetics. There is no evidence for substantial passive diffusion processes. The results reported here, together with allometric considerations and literature data analysis, may help to explain some particular non-linear features of plasma level curves associated with the administration of fairly high oral doses of cefadroxil to humans.

Cefadroxil, an aminocephalosporanic antibiotic with excellent oral bioavailability characteristics (Pfeffer et al 1977; Lode et al 1980), shows extremely hydrophilic properties in the pH range of the digestive tract, so that its absorption profile cannot be explained merely on the basis of passive diffusion mechanisms controlled by the partition hypothesis (Tsuji et al 1981a). Intestinal loop and recirculation in-situ studies suggest the existence of a carrier-mediated disappearance of cefadroxil and other oral cephalosporins from perfusion solutions (Tsuji et al 1979, 1981a; Nakashima et al 1984a; Kimura et al 1985). In-vitro everted sac and homogenate studies also suggest this type of transport (Nakashima et al 1984b; Kimura et al 1985; Tsuji et al 1987); a widely held view is that simultaneous Michaelis-Menten and simple diffusion kinetics are involved in cefadroxil absorption. The opinion of the present authors, however, is that in spite of the excellent studies that have been done, further investigation is desirable to clarify the exact role of active and passive components in cefadroxil absorption, as well as the possible existence of selectivity phenomena (i.e. absorption windows) in the intestinal tract, and their possible practical implications.

Non-linearities in the kinetic behaviour of cefadroxil, as deduced from plasma level curves obtained after oral administration to humans, have occasionally been reported (La Rosa et al 1982) but none of them has been related to absorption. Nevertheless, when current literature data are analysed—as will be discussed later—some features arising from the curves are, at least, intriguing, such as the progressive reduction in dose-normalized C_{max} values and flattening of the curves when doses ranging from 0·5 to 4 g are administered. Such features could become important in certain clinical situations.

To gain an insight into this problem, a series of experiments were designed in our laboratory, based on the perfusion of cefadroxil solutions at different concentrations, including four orders of magnitude, in an anaesthetized rat gut preparation. The results, found from two-phase experiments, were analysed to characterize possible selectivity phenomena in cefadroxil absorption, to ascertain whether there were non-linearities (as deduced by fitting apparent linear kinetics to the data), and, finally, to elucidate the true absorption kinetics of the drug on the basis of statistical criteria, through the comparison of mixed-type, first-order and combined mixed and first-order equations, according to computer procedures.

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Materials and Methods

Absorption studies

The in-situ rat gut technique (Doluisio et al 1969), modified as reported previously (Martín-Villodre et al 1986), was used for absorption experiments. The choice of this procedure instead of others which have been frequently used for active absorption tests (Tsuji et al 1981b; Kimura et al 1983; Nakashima et al 1984a) will be explained later.

Male Wistar rats, 200 to 280 g, anaesthetized 1 h before surgery with i.p. ethylurethane, were treated as follows.

Phase-1 experiments. The small intestine was divided into three fractions of equal lengths of about 33 cm, which were designed as proximal, middle and distal segments. Perfusion was developed in one of these segments or in the whole colon, with solutions of the same cefadroxil concentration (0·01 mg mL^{-1}) buffered to pH 6·7 (proximal), 7·6 (middle), 8·2 (distal) or 7·5 (colonic), as indicated by Sánchez-Picó et al (1984), to detect selectivity phenomena in absorption, i.e. the possible existence of a preferential absorption area for cefadroxil.

Phase-2 experiments. Perfusion was performed in the proximal segment of the small intestine in all cases, but at seven different initial cefadroxil concentrations (0·01, 0·20, 1·00,

Table 1. Reabsorption equations found for the different data sets in independent 12-animal tests for each particular condition. Reabsorption equation is: $V_r = -k_o.t + V_o$, being V_r the remaining volume at time t, V_o the initial volume and k_o a zero-order rate constant.

Phase experiences	Data sets	Equation parameters[a] k_o (mL min^{-1})	V_o (mL)	r
1	Proximal	0·0465	5·17	0·995
Selected	Middle	0·0524	5·28	0·997
intestinal	Distal	0·0432	5·24	0·999
segments	Colonic	0·0105	5·00	0·990
2	10	0·0465	5·17	0·995
Starting	200	0·0386	5·16	0·994
cefadroxil	1000	0·0415	5·18	0·994
concentration	2500	0·0460	5·16	0·996
(mg mL^{-1})	5000	0·0391	5·19	0·999
	7000	0·0297	5·22	0·996
	10000	0·0306	5·20	0·993

[a]Values found at 0, 5, 15 and 25 min were used for the regression (means of 3 animals per time).

2·50, 5·00, 7·00 and 10·00 mg mL^{-1}), to detect non-linearities in absorption and to ascertain the best cefadroxil absorption kinetics.

Perfusion was carried out in these segments at 37°C with 5 mL of the suitable antibiotic solution. The drug concentration in perfusates was measured every 5 min for a total of 30 min. When proximal segments of the small intestine were used, the biliary duct was ligated. Five animals for each lot were employed in phase-1 experiments and ten in phase-2 experiments; the average concentration values were used for calculations.

Variable but in general significant water reabsorption effects were noted. To evaluate its extent and characteristics, the time course of this process was followed separately in 12 animals for each data set (intestinal segments and cefadroxil concentrations in perfusion fluids) by means of a previously reported procedure (Martín-Villodre et al 1986); as pointed out by these and, more recently, by other authors (Gabus-Sannié & Buri 1987), water reabsorption was identified to be an apparent zero-order process, indeed important because of its magnitude except for the colonic segment (see Table 1). Cefadroxil concentrations remaining in the luminal solutions at each time unit were then corrected according to the particular reabsorption pattern found for each set of data (Martín-Villodre et al 1986).

Analytical procedure

Intestinal cefadroxil samples were assayed for drug content by high-pressure liquid chromatography. The apparatus was a Waters HPLC constituted by a Model 590 pump with a Model 481 Lambda-Max detector (at 254 nm) and a Data Module. A variable-volume injector and a 150:3·9 mm analytical column packed with Novapak C-18, in conjunction with a Guard-Pak RC5S C-18 precolumn, were employed.

A mixture of methanol and aqueous phosphate buffer 1/15 M, of pH 2·8 in proportions 10:90 (v/v) was used as elution fluid at a flow rate of 1 mL min^{-1}, at room temperature (20°C). After study of a variety of literature recommended mobile phases the solvent mixture was selected as being the most suitable to avoid interferences due to endogenous contaminants, presumably histaminoid substances (Casabó et al 1987).

The intestinal samples were centrifuged at 3000 rev min^{-1} for 10 min to remove particulate material, and 40 μL of the supernatant was injected into the chromatograph. Calibration curves covering the entire range of concentrations in the biological samples were prepared in triplicate; excellent linear plots relating peak area and concentration were found, with practically no intercepts. Coefficients of variation ranging from 1·7 to 5·9 were obtained from standard cefadroxil samples (98·0% active matter content). Owing to the limited sample manipulation, no internal standard was used for chromatographic determinations.

Data fitting and statistical procedures

To detect selectivity phenomena (phase-1 experiments) or non-linearities (phase-2 experiments) in cefadroxil absorption, the first-order kinetics equation was fitted to data:

$$\ln A = -k_{ap}.t + \ln A_o \quad (1)$$

Initial non-perfused samples (i.e. concentrations at zero time) were not considered for regression to avoid membrane adsorption phenomena and dilution effects (Doluisio et al 1969; Martín-Villodre et al 1986); as a result, in equation 1, A_o values are extrapolated intercepts, and k_{ap} is an apparent first-order rate constant.

To analyse selectivity phenomena (i.e. significant differences in absorption efficiency between segments), the apparent rate constants (means of 5 animals) found in each particular segment were subjected to a two-way ANOVA test and to a subsequent Peritz-F test, which is, undoubtedly, a most robust statistical test for multiple comparisons (Harper 1984). To ascertain non-linearities in absorption, the comparison between the average k_{ap} values (means of 10 animals) found in phase-2 experiments was done according to the same statistical procedure.

In addition, fits of zero-order kinetics, which represents a limiting condition for some absorption processes, were performed:

$$A = -k_o.t + A_o \quad (2)$$

where k_o represents an apparent zero-order rate constant. The zero-order equations are used for some fitting operations and can be also of some interest in discriminating, in addition to the above test, about non-linearity phenomena, as will be pointed out later.

Subsequently, absorption kinetics of cefadroxil were investigated through two general computer procedures. First, the Michaelis-Menten classical differential equation:

$$\frac{\Delta A}{\Delta t} = \frac{V_m \cdot A_m}{K_m + A_m} \quad (3)$$

was fitted to data found in phase-2 experiments. In equation 3, ΔA is the decrease in cefadroxil luminal concentration between the A value found at a given time (for example, at 20 min) and the following (at 25 min) for a given set of data; Δt is the time elapsed between samplings (5 min in all cases), and A_m represents the concentration, A, calculated at the mean time interval (i.e. 7·5 min for the values between 5 and 10 min) according to the best apparent linear kinetics previously

assayed (first or zero-order). The MULTI program (Yamaoka et al 1981) was used for fitting equation 3 to these data; calculations were performed globally for all remaining concentrations by using the average values at each time (means of 10 animals).

Based on the same principle, but employing A_m values found by applying apparent first-order kinetics in preliminary adjustments, global fits to the classical first-order differential equation:

$$\frac{\Delta A}{\Delta t} = -\text{kap}.A_m \tag{4}$$

were performed and compared with those found for equation 3, through the Akaike information criterion, namely AIC (Akaike 1976); the smaller AIC value indicates the best fit. In equation 4, k_{ap} represents the first-order apparent absorption rate constant which globally satisfies the data found for all cefadroxil concentrations in the proximal intestinal segment.

Secondly, in addition to this fitting method, the integrated Michaelis-Menten equation:

$$t = \frac{1}{V_m}(A_o - A + K_m.\ln\frac{A_o}{A}) \tag{5}$$

was fitted to the experimental data found in phase-2 experiments, in a global form. The fit was achieved through a non-linear least-squares procedure based also in the MULTI program (Yamaoka et al 1981). To treat the concentration, A, as a dependent variable and the time, t, as an independent variable, a subroutine based on combined iteration- and half-procedures (Demidovich & Maron 1985) was written and incorporated into the program, which, for a given parameter (A_o, V_m, K_m) and experimental time, t, values, allows the calculation of any theoretical concentration, A, so that a difference less than 0·001 μg mL^{-1} between these latter and the actual concentration is obtained. The difference between these theoretical and experimental concentrations at the corresponding time is squared and accumulated to the remainder to obtain the sum of squares; the convergence criteria are not modified since they act only on the parameter values.

At the end of the fitting, V_m and K_m parameters that globally satisfied the data available, as well as the corrected A_o intercepts for each perfusion set were obtained. When these parameters have been found, the time values for a given cefadroxil concentration can be calculated through equation 5 by using the final V_m and K_m estimates, as well as the A_o value found for the perfusion set of higher cefadroxil concentration; the theoretical concentrations, A, found by means of the preceding procedure for each perfusion data series are substituted in equation 5. In this way, complete and continuous plots of A *vs* t were obtained, as shown in Fig. 1.

Based on the same principle, global fits of first-order kinetics (eqn 6) and of combined Michaelis-Menten and first-order kinetics (eqn 7) (Wagner 1979; Gibaldi & Perrier 1982) to the experimental A, t data:

$$A = A_o.\, e^{-\text{kap}.t} \tag{6}$$

$$t = \frac{1}{k_{ap}.K_m + V_m}K_m.\ln\frac{A_o}{A} + \frac{V_m}{k_{ap}}\ln\frac{(A_o + K_m)\,k_{ap} + V_m}{(A + K_m)\,k_{ap} + V_m} \tag{7}$$

were performed and compared with that found from equation 5 through the same statistical tests as above (Akaike 1976). The use of subroutine for equation 6 is, of course, unnecessary since in this expression, the remaining concentrations, A, are in explicit form.

Results

Phase-1 experiments. The time course of disappearance of the average remaining cefadroxil concentrations (A, means of 5 animals), as well as the apparent first-order rate constants, k_{ap}, according to equation 1, found in the different intestinal segments, are indicated in Table 2. The statistical comparison of the apparent rate constants is shown in Table 3.

Phase-2 experiments. The average remaining cefadroxil concentrations (A, means of 10 animals) found at different

Table 3. Statistical comparison between apparent first-order rate constants, k_{ap}, found in the different intestinal segments (phase 1 experiences), through the Peritz F-test.

Segments compared	Reference α_p-values	Significance (P value)
Proximal–Middle	0·025	0·67 (NS)
Proximal–Distal	0·038	<0·0001
Proximal–Colonic	0·050	<0·0001
Middle–Distal	0·025	<0·0001
Middle–Colonic	0·038	<0·0001
Distal–Colonic	0·025	<0·0001

Table 2. Percent average cefadroxil concentrations (±s.d.) relative to initial (10 μg mL^{-1}) remaining in the intestinal lumen, apparent first-order rate constants fitting each data set and correlation coefficients found (n = 5).

Sampling time (min)	Percent remaining cefadroxil in lumen (eqn 1)			
	Proximal	Middle	Distal	Colonic
5	71·13 (±1·44)	63·73 (±3·78)	81·67 (±2·84)	89·11 (±5·72)
10	52·29 (±4·26)	48·93 (±4·31)	69·53 (±1·76)	87·82 (±6·21)
15	39·18 (±2·56)	34·87 (±4·37)	61·27 (±2·80)	86·76 (±5·51)
20	28·42 (±2·78)	26·64 (±4·34)	53·05 (±1·95)	85·23 (±4·09)
25	22·09 (±2·33)	19·70 (±4·12)	47·99 (±2·16)	84·83 (±4·66)
30	15·27 (±2·84)	15·07 (±3·40)	43·38 (±1·89)	84·81 (±3·17)
k_{ap} (h^{-1})	3·634 (±0·34)	3·500 (±0·43)	1·515 (±0·15)	0·126 (±0·11)
r	0·999	0·999	0·996	0·961

Table 4. Percent average cefadroxil concentrations, relative to initial (±s.d.; means of 10 animals), remaining in intestinal lumen of the proximal segment at each sampling time. Pseudo first- and zero-order rate constants fitting each data set and correlation coefficients found are also given.

Sampling time (min)	% remaining cefadroxil in lumen at the indicated initial perfusion concentration, μg mL^{-1}						
	10	200	1000	2500	5000	7000	10 000
5	71·00 (±1·76)	78·83 (±3·09)	81·39 (±3·02)	78·88 (±3·80)	82·98 (±3·14)	86·24 (±1·36)	87·81 (±1·79)
10	52·91 (±4·52)	65·09 (±3·35)	66·77 (±3·05)	66·44 (±3·36)	73·48 (±3·04)	79·56 (±1·81)	80·96 (±1·84)
15	39·72 (±3·97)	51·59 (±3·85)	55·25 (±3·01)	55·56 (±4·20)	65·62 (±3·56)	73·03 (±1·54)	75·46 (±1·45)
20	28·69 (±3·38)	42·19 (±3·94)	45·13 (±3·74)	46·16 (±4·08)	58·96 (±3·86)	67·19 (±2·27)	70·57 (±1·66)
25	21·91 (±3·15)	34·33 (±3·97)	37·66 (±4·36)	38·62 (±3·91)	52·70 (±4·10)	63·24 (±2·30)	65·83 (±1·67)
30	15·85 (±3·33)	28·21 (±3·84)	31·32 (±3·89)	31·90 (±4·49)	47·46 (±4·50)	58·96 (±2·40)	61·32 (±2·32)
k_{ap} (h^{-1})	3·589 (±0·42)	2·489 (±0·29)	2·295 (±0·29)	2·173 (±0·25)	1·336 (±0·16)	0·917 (±0·10)	0·851 (±0·07)
r	0·999	0·999	0·999	0·999	0·999	0·998	0·999
k_o (% min^{-1})	2·170 (±0·09)	2·027 (±0·13)	1·987 (±0·15)	1·873 (±0·10)	1·409 (±0·10)	1·093 (±0·10)	1·044 (±0·07)
r	0·979	0·988	0·989	0·993	0·994	0·994	0·997

Table 5. Statistical comparison between the apparent first-order rate constants found in the proximal segment at different initial perfusion concentrations (phase-2 experiments) through the Peritz F-test.

Initial perfusion concentrations compared	Significance (*P* value)
200 vs 1000	0·152 (NS)
1000 vs 2500	0·052 (NS)
7000 vs 10 000	0·099 (NS)
All remainder combinations	<0·0001

initial perfusion concentrations in the proximal segment are given in Table 4; the apparent rate constants representing the two limiting linear kinetics (eqns 1, 2) are also given. The statistical analysis of the apparent first-order slopes is schematized in Table 5. In Table 6, the parameter values and statistical figures found after fitting Michaelis-Menten and first-order differential expressions (eqns 3, 4) to the rate, concentration data, as well as those obtained after fitting Michaelis-Menten, first-order and combined mixed-type and first-order integrated expressions to the concentration, time data, are shown. In Figs 1, 2, representative continuous plots of the time course of cefadroxil absorption in the proximal segment, according to equations 5 and 6, have been reproduced; the plot for equation 7 is similar to that found for equation 5 (Fig. 1).

Table 6. Parameter values found after fitting the selected equations to the data. Standard deviations are indicated in brackets. Statistical figures found for each fit are also given.

Working equation	Parameter values (±s.d.)	AIC	r
Michaelis-Menten (eqn 3)	V_m = 124·3 (±12·4) μg mL^{-1} min^{-1} K_m = 2604 (±667·6) μg mL^{-1}	2·3	0·967[a]
First-order (eqn 4)	k_{ap} = 1·200 (±0·001) h^{-1}	71·7	0·946[a]
Michaelis-Menten (eqn 5)	V_m = 122·5 (±7·68) μg mL^{-1} min^{-1} K_m = 2395 (±401·4) μg mL^{-1} A_o = 8999 (±56·7) mL μg mL^{-1}	−102·6	0·999[b]
First-order (eqn 6)	k_{ap} = 1·944 (±0·181) h^{-1} A_o = 12472 (±622·9) μg mL^{-1}	−12·4	0·983[b]
Combined kinetics (eqn 7)	V_m = 128·5 (±3·28) μg mL^{-1} min^{-1} K_m = 2507 (±247·6) μg mL^{-1} k_{ap} = 0·007 (±0·0012) h^{-1} A_o = 9115 (±52·4) μg mL^{-1}	−100·8	0·999[b]

[a] Between experimental and model-predicted ΔA/Δt values.
[b] Between experimental and model-predicted A values.

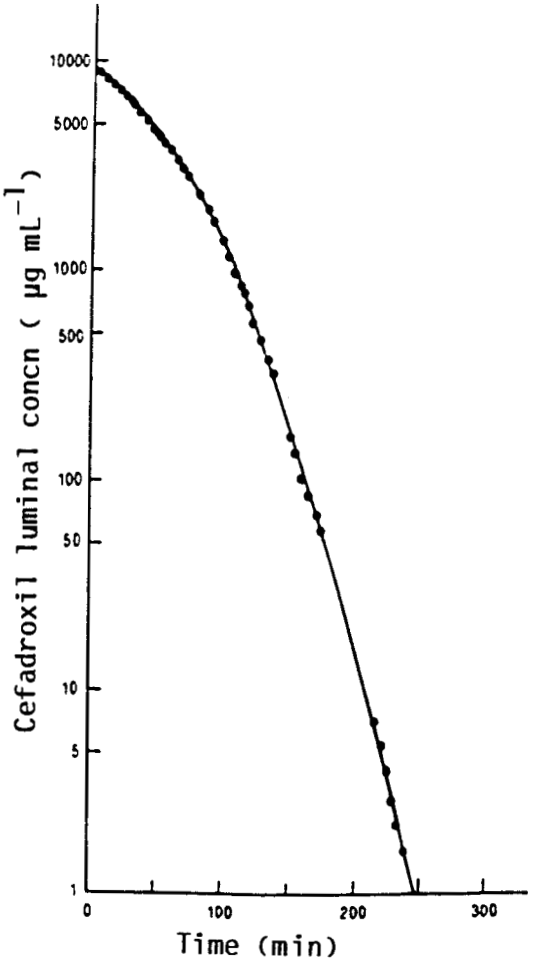

FIG. 1. Semilogarithmic continuous plot representing cefadroxil absorption from the proximal intestinal segment, according to Michaelis-Menten kinetics (eqn 3). Parameter values are shown in Table 6.

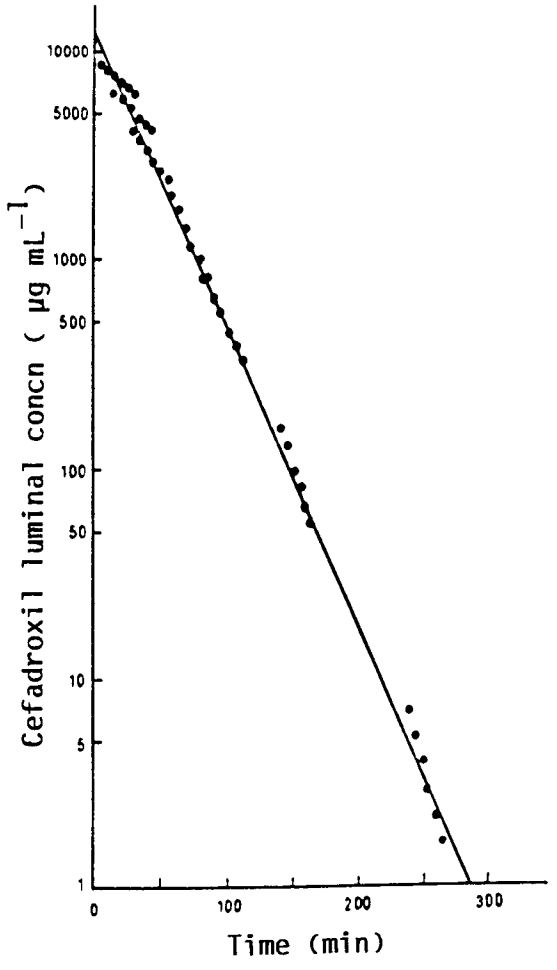

FIG. 2. Same as Fig. 1 but assuming that absorption follows first-order kinetics (eqn 4).

Discussion

Experimental absorption technique

In-situ perfusion or recirculation techniques (Tsuji et al 1981b; Kimura et al 1983) have been widely used instead of the kind of "static" perfusion procedure more or less like the one employed in the present study (Tsuji et al 1981a) to characterize active absorption mechanisms for antibiotics. It has been shown, however, that the intrinsic permeability constants obtained by these two types of methods, when normalized for perfused volumes and intestinal lengths, give virtually identical results, provided that suitable correction for water reabsorption is done (Houston & Wood 1980). Since the static methods would allow absorption rates several times greater (Plá-Delfina & Moreno 1981), nearer to in-vivo values (Doluisio et al 1969), and much more suitable for kinetic calculations, the non-circulating static technique was selected as the routine working procedure to characterize the possible non-linearities in absorption better, and to fit absorption model equations more easily and accurately to experimental data.

Selectivity phenomena in absorption

As shown in Table 3, significant differences are found between k_{ap} values for distal and colonic segments, and that found for proximal and middle segments, where these latter show about the same absorption capacity. From these results it can be concluded that there is a definite absorption window for cefadroxil in the first two-thirds of the rat small intestine. For practical purposes, cefadroxil absorption could be considered as merely complementary in character (in the distal segment) or residual and even irrelevant (in the colonic fraction). One could reasonably assume that absorption in these two later segments does not substantially contribute to the global cefadroxil bioavailability in-vivo.

As far as the results in proximal and middle segments are concerned, it can be observed from Table 2 that the apparent k_{ap} average constant is somewhat higher and the coefficient of variation lower (9·4 vs 12·3%) for the proximal segment. In view of these features, the proximal intestinal fraction was selected for phase-2 experiments.

Assessment of non-linearities

The statistical analysis of the apparent first-order constants found in phase-2 experiments as a function of the initial cefadroxil concentration in the perfusion fluid (Table 5) is clearly discriminatory. As can be observed, the differences that have been found are, undoubtedly, highly significant in global terms, thus demonstrating the non-linear nature of cefadroxil absorption in our conditions.

As seen from Table 4, k_{ap} values decrease as the initial cefadroxil concentration in the perfusion fluid is increased. In these cases, fitting Michaelis-Menten kinetics to the data is strongly recommended (Wagner 1979) since this behaviour could be indicative of the existence of a saturable, carrier-mediated transport mechanism. The advisability of fitting Michaelis-Menten kinetics to the data is also, in the opinion of the authors, evidenced by the fact that the correlation coefficient found for the zero-order fits (eqn 2) to each set of data increases as the initial cefadroxil concentration in the perfusion fluid is increased.

Fitting equations to data

As can be seen from Table 6, the differential and integrated forms of Michaelis-Menten equation give similar values for the V_m and K_m parameters. They coincide also in appointing Michaelis-Menten expressions as the best models to describe cefadroxil absorption kinetics rather than the alternative first-order equations. The relative value of these two types of fitting procedures (differential vs integrated) cannot be elucidated, however; the working variables are not the same, thus making irrelevant the comparison of the respective statistical figures.

In view of the reported results, it can be concluded with a great deal of probability that cefadroxil absorption in its absorption window is a selective, carrier-mediated mechanism, without evidence of a substantial intervention of passive diffusion processes. The negligible k_{ap} value found in the fitting of combined mixed-type and first-order integrated expression (eqn 7) to the data, as seen in Table 6, seems to support this view, as does the small value found for the absorption rate constant in tests developed on the colonic segment, an intestinal area where active absorption processes have never been identified (phase-1 experiments, Table 2).

The features of the different fits found through the integrated equations are conclusve, not only from the

statistical figures found but even intuitively, from a visual inspection of the graphs. In Fig. 1 it can be observed that the experimental points are situated practically on the theoretical line, with an A_o value of somewhat less than 10 mg mL^{-1}. This effect is, undoubtedly, a consequence of some initial adsorption of the compound on the mucosal surface (Doluisio et al 1969), and, very probably, of some dilution effect on the test solution due to the practical impossibility of completely emptying the rinsing solution used for previous cleansing of the intestine (Martín-Villodre et al 1986). On the other hand, the global first-order plot shown in Fig. 2 is not satisfactory; the average first-order rate constant found ($k_{ap} = 1{\cdot}944\ h^{-1}$, clearly lower than the limiting quotient V_m/K_m, see Table 6) fits well only, as was to be expected, the concentrations of mean order of magnitude (from 200 to 2000 $\mu g\ mL^{-1}$ approximately). Concentrations above and below these values fit poorly, as can be clearly observed from the graph; as a consequence of this poor fit, an A_o value much higher than expected and not kinetically explainable is obtained, thus demonstrating that this model is mostly artifactual in nature.

Allometric considerations

According to allometric equations as applied to active absorption processes (Peris-Ribera et al 1986), the K_m constant in humans, K_{mh}, could be related to that found in rats, K_{mr}, through the following expression:

$$K_{mh} = K_{mr}\ (W_h/W_r)^{0{\cdot}94} \qquad (8)$$

where W_h and W_r are the average weight population values estimated for men and rats (70 and 0·25 kg, respectively).

As has been reported herein, a K_{mr} value of 2·395 mg mL^{-1} was obtained according to the Michaelis-Menten integrated equation (Table 6). Since the perfused volume per animal was 5 mL, the K_{mr} value in terms of amounts of cefadroxil at the absorption site would be 11·975 mg of antibiotic per rat. Thus the predicted Michaelis constant in man could be approximated to:

$$K_{mh} = 11{\cdot}975\ (70/0{\cdot}25)^{0{\cdot}94} = 2{\cdot}39\ g$$

That is, for an oral dose of cefadroxil of about 2·4 g, the enzymatic system responsible for cefadroxil absorption would attain its K_m value in humans or, in other words, for doses of about 2·4 g, cefadroxil kinetics in man will be in a fully non-linear range. If we assume that equation 5 virtually collapses to a linear first-order equation when approximately 0·2 K_m remains in the absorption site, we would obtain a value of about 0·5 g as the maximal dose below which linear kinetics should be maintained. From Fig. 1, it can be seen that above 500 mg mL^{-1} (equivalent to a rat dose, D_r, of 2·5 mg since $D_r = 500{\cdot}5 = 2500\ \mu g$, and to a human dose, D_h, of 500 mg since $D_h = D_r\ (W_h/W_r)^{0{\cdot}94}$, that is, $D_h = 2{\cdot}5\ (70/0{\cdot}25)^{0{\cdot}94} = 499$ mg) the A values would be clearly out of linearity. Therefore, the doses above 0·5 mg could result in non-linearities in absorption when cefadroxil is administered to man.

The above considerations are, of course, open to severe criticism and should be considered only as merely orientative since many assumptions which have been made are, undoubtedly, not fully justified: (1) absorption is probably not complete in the first proximal fraction of the small intestine in-vivo either in rats or in humans; (2) the transport mechanisms cannot be identical in the two species, and (3) there is probably no exact parallelism between absorption rates found in-situ and those found in-vivo. However, in light of the results reported by Venturini & Barbanti (1982), it can be deduced that cefadroxil absorption patterns in rats and men are basically similar. Therefore, the dose of 0·5 g can be assumed to represent, in principle, a rough limit for cefadroxil absorption non-linearities.

Pharmacokinetic and clinical implications

Data reported in the literature indicate that the peak plasma levels in curves obtained after the administration of oral 1 g doses to humans are clearly flatter than those found for other oral cephalosporins (Lode et al 1980; Simon 1980); these plateau-like maxima are not observed when lesser doses, such as 250 or 500 mg, are administered (LaRosa et al 1982). These types of maxima are precisely those that can be expected when saturable absorption prevails.

On the other hand, the data compiled by Tanrisever & Santella (1986) and reproduced in Table 7, demonstrate that the C_{max} values found at high cefadroxil oral doses are lower than expected when linear kinetics exists, whereas the total areas under the curves seem to remain just about dose-proportional. It should be remembered here that the linearity in areas can be expected to exist when bioavailability is similar, regardless of the absorption kinetics, whereas C_{max} values should be lower for high doses when saturation phenomena are at work in the absorption process.

Brisson & Fourtillan (1982) also found significantly lower dose-normalized C_{max} values after the administration of 1 g doses than after 0·5 g doses ($P < 0{\cdot}001$). The corresponding

Table 7. Normalized peak levels and total areas in plasma level curves after administration of oral cefadroxil to humans[a].

Dose (g)	Normalized C_{max} $(mg\ L^{-1}D^{-1}) \times 10^3$	Normalized AUC $(mg\ L^{-1}hD^{-1}) \times 10^3$
0·5	32·4	94·8
1·0	33·8	114·5
2·0	21·3	94·5
4·0	19·9	102·4

[a] Calculated from compilative data reported by Tanrisever & Santella (1986).

Table 8. Normalized individual and average peak levels and total areas under the curves found after oral cefadroxil administration to volunteers[a].

Dose (mg)	Normalized C_{max} $(mg\ L^{-1}D^{-1}) \times 10^3$	Normalized AUC $(mg\ L^{-1}hD^{-1}) \times 10^3$
498·2	28·1	108·8
497·0	30·4	84·3
499·2	41·7	101·8
500·5	32·4	93·5
496·8	37·2	108·4
498·34 ± 1·55	33·96 ± 5·47	99·36 ± 10·46
999·0	16·3	58·56
999·6	23·0	78·63
1001·0	25·0	98·90
998·2	27·7	101·18
999·6	26·7	84·03
999·48 ± 1·03	23·74 ± 4·53	84·26 ± 17·27

[a] Calculated from the data of Brisson & Fourtillan (1982).

normalized areas under the curves were also different, but the probability level was much lower, as can be inferred from the data given in Table 8. Again, the non-linearity in C_{max} is demonstrated (in this case, even for the 1 g dose); the apparent non-linearity in areas may be associated with a slight reduction in bioavailability for the higher dose.

As occurs with C_{max}, the apparent absorption rate constants, k_{ap}, calculated according to first-order approaches, should become progressively lower as the dose increases. From the results reported by La Rosa et al (1982), we have calculated apparent k_{ap} values of about 3·0, 2·6 and 0·9 h^{-1}, respectively, for doses of 250, 500 and 1000 mg.

It must be pointed out here that some other non-linearities in cefadroxil global kinetics, such as the saturation of the active renal tubular secretion of the antibiotic, have been reported to arise at high oral doses, as deduced from the analysis of plasma level curves (La Rosa et al 1982). This could lead to somewhat reduced elimination half-lives and clearances as dose increases. This effect may, in fact, be balanced if there is a parallel reduction in bioavailability, which would explain the apparent dose proportionality of areas in Table 7 data. But these apparent non-linearities in elimination could merely be due to the incidence of residual absorption processes in the terminal disposition phase, leading to an artifactual reduction in the half-lives when calculated from the terminal portion of the plasma level curves. In fact, distribution and elimination parameters should only be calculated from plasma levels found after intravenous administration.

Be that as it may, these and other data from the literature strongly suggest, as do the allometric considerations already discussed, that cefadroxil absorption is just barely within the limits of linearity when oral doses ranging from 0·5 to 1·0 g are administered. This feature can be clinically important if the cefadroxil steady-state levels in plasma should be greater than customary. In such cases, the administration of usual doses (up to 1 g as much) at shorter time intervals could be recommended instead of higher maintenance doses, to reach effective plateau values throughout a given dosage regimen.

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