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Research Papers

Pharmacokinetics of cefadroxil in patients with terminal renal impairment

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Summary

The pharmacokinetics of cefadroxil were studied in 15 subjects divided into 3 groups: healthy volunteers, patients with terminal renal impairment in interdialysis sessions and patients with terminal renal impairment undergoing hemodialysis sessions.

The serum levels of the antibiotic were determined by a microbiologic plate diffusion method using *Bacillus subtilis* (ATCC no. 6633) as the test organism.

Renal impairment causes a decrease in the elimination rate of the antibiotic. The serum half-life has a value of 1.20 ± 0.21 h in the healthy volunteers, 26.56 ± 8.00 h in patients in interdialysis periods and 2.45 ± 0.72 h in patients undergoing hemodialysis sessions.

Hemodialysis partially restores absorption and elimination of cefadroxil to levels which approach those established in healthy volunteers.

Introduction

Cefadroxil is a semi-synthetic cephalosporin destined for oral use whose chemical structure is 7-[D-(−)-α-(4-hydroxyphenyl)-acetamido]-3-methyl-3-cephem-4-carboxylic acid. Its antimicrobial spectrum is similar to that of other oral cephalosporins and is effective against Gram (+) and Gram (−) germs frequently associated with respiratory tract infections (Santella et al., 1979), genito-urinary tract infections (Santella et al., 1978) and infections of the skin and soft tissues (Cordero,

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1976). Several clinical studies have shown its efficacy in various infectious processes and the scarcity of side-effects, which are limited to nausea, vomiting and abdominal pain, does not make it necessary to discontinue treatment (Paul et al., 1977).

When administered orally, more than 80% of the antibiotic dose is absorbed (Lode et al., 1979) and the kinetics the antibiotic follows are not dose-dependent (Mariño et al., 1980). The antibiotic is not metabolized within the body and is principally excreted via the kidney, high concentrations being found in the urine (Buck et al., 1977). Cutler et al. (1979) studied the pharmacokinetics of cefadroxil in patients with varying degrees of renal impairment, establishing the following relationship between the elimination constant of the antibiotic and the creatine clearance:

$$K_e(h^{-1}) = 0.06 + 0.008\ Cl_{Cr}(ml/min/m^2);\ r = 0.920$$

The purpose of the present study is to elucidate the effect of hemodialysis on the pharmacokinetics of cefadroxil in patients with terminal renal impairment.

Materials and methods

Patients with normal renal function (NRF) and with terminal renal impairment in the interdialysis period (TRI)

Five healthy volunteers were included in the study with ages ranging between 19 and 22 years and weights between 56 and 73 kg. Their serum urea and creatinine concentrations were the following: Ur = 43.40 ± 5.55 mg/dl; Cr = 0.64 ± 0.14 mg/dl. Creatinine clearances were greater than 110 ml/min.

The clinical characteristics of the patients with TRI in the interdialysis periods are shown in Table 1.

In all cases the patients received a single oral dose of cefadroxil (one 500 mg capsule of cefadroxil monohydrate). Blood samples were withdrawn at the following times: (a) patients with NRF; 0 (immediately before administration of the antibiotic), 0.5, 1.0, 2.0, 2.5, 3.0, 4.0, 5.0 and 6.0 h; (b) patients with TRI; 0, (see above), 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0, 24.0 and 48.0 h.

Blood samples were centrifuged and the plasma separated and frozen at −20°C until analysis.

TABLE 1

Clinical characteristics of the patients with renal impairment during interdialysis periods

Patients	Age (years)	Sex	Weight (kg)	Urea (mg/dl)	Creatinine (mg/dl)	Creatinine clearance (ml/min)
S.M.G.	64	M	64.0	110	11.1	<1
L.M.M.	68	M	53.5	87	4.7	<5
A.E.F.	55	F	59.5	262	11.7	<5
B.M.S.	60	M	62.5	82	10.7	<5
M.P.B.	18	F	39.5	160	6.7	<5

Patients undergoing hemodialysis (TRI^H)

The study also included 5 patients with TRI (creatinine clearance < 5 ml/min) undergoing hemodialysis sessions lasting 4 h.

The clinical characteristics of the patients in this group are shown in Table 2. In all cases the patients received a single oral dose of cefadroxil (one 500 mg capsule of cefadroxil monohydrate) just at the beginning of the hemodialysis session.

Blood samples were collected at the input and the output of the dialyzers (arterial and venous blood) at the following times: 0, (see above), 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00 and 4.00 h. Serum was separated by centrifugation and stored at $-20°C$ until analyzed.

Hemodialysis was performed using a plate dialyzer with 25 blood compartments, a 13.5 μm thickness Cuprophan membrane and a working membrane surface area of 1.5 m^2 (Gambro Lundia, Rahms, Lund). The average blood flow rate was 230 ± 27 ml/min. Ultrafiltration of fluid from the blood during transit through the dialyzer was negligible and did not influence the venous concentrations of cefadroxil.

Assays

The determination of the antibiotic was carried out using a microbiologic plate diffusion method with *Bacillus subtilis* (ATCC no. 6633) as the test organism.

Standard curves of cefadroxil in pooled human serum were prepared with known concentration values. Repeated analyses of standard solutions indicated that the precision of the technique, expressed as the relative standard deviation, was 7% or less. The lower sensitivity limit was established at 2 μg/ml. All assays were repeated at least 4 times.

Pharmacokinetic analysis

Following oral administration, serum levels of cefadroxil follow a single-compartment open kinetic model. The pharmacokinetic parameters corresponding to this model were calculated according to the equations of Gibaldi and Perrier (1975) and Wagner (1975) using a programmable Hewlett-Packard 97 calculator.

The evaluation of the efficiency of hemodialysis was calculated from the pharmacokinetic parameters of cefadroxil and from the conditions under which dialysis was carried out, using the following equations (Takki et al., 1978):

$$\text{E.C.} = \frac{C_A - C_V}{C_A}$$

where E.C. represents the extraction coefficient of the antibiotic and C_A and C_V are the arterial and venous blood concentrations of the antibiotic.

$$Cl_D = B_F \times \text{E.C.}$$

Cl_D being dialysis clearances and B_F the blood flow used. The amount of antibiotic remaining in a dialysis session (A_t) is:

$$A_t = D \times e^{-\frac{Cl_s + Cl_d}{V_d} \times \tau}$$

where D represents the amount of antibiotic administered, Cl_s is the serum clearance

TABLE 2

Clinical characteristics of patients with renal impairment during hemodialysis sessions

Patients	Age (years)	Sex	Weight (kg)	Urea		Creatinine		Creatine clearance (ml/min)	Blood flow (ml/min)
				(mg/dl) [a]	(mg/dl) [b]	(mg/dl) [a]	(mg/dl) [b]		
S.S.M.	69	M	68.0	160	50	9.5	5.3	1.50	200
G.G.C.	42	F	50.0	117	30	7.6	3.3	5.60	250
F.M.C.	16	M	55.0	174	42	10.8	6.4	1.00	250
C.M.	63	M	84.0	140	64	11.7	8.4	2.60	200
M.M.S.	66	M	53.0	122	42	16.3	7.2	0.81	250

[a] The beginning; and [b] the end of the hemodialysis session.

of the antibiotic, τ is the duration of the hemodialysis session and V_d represents the apparent distribution volume.

The dialysis half-life ($t_{1/2}$ D) represents the time necessary for the elimination by dialysis of half the amount of the antibiotic remaining in the organism, and is derived from:

$$t_{1/2}\,D = \frac{0.693 \times V_d}{Cl_s + Cl_d}$$

Results and discussion

Subjects with normal renal function (NRF) and with terminal renal impairment during interdialysis periods (TRI)

Administered orally, cefadroxil follows a single-compartment open-kinetic model.

Fig. 1 shows the average serum level curves obtained from individuals with NRF and from patients with TRI during interdialysis periods as defined by the following equations:

$$C = 38.194 \times e^{-0.542 \times t} - 60.674 \times e^{-1.704 \times t} (\text{NRF})$$

$$C = 25.527 \times e^{-0.029 \times t} - 41.870 \times e^{-1.140 \times t} (\text{TRI})$$

The average values of the pharmacokinetic parameters obtained from the individuals included in these two groups are shown in Table 3.

In all cases there is a lag-time, but no statistically significant difference ($P = 0.05$) between those obtained in the two groups studied.

The analysis of the ascending phase of the serum level curve in patients with TRI suggests the possibility that the decrease observed in the absorption rate of the antibiotic may take place at the moment at which a particular serum level of the

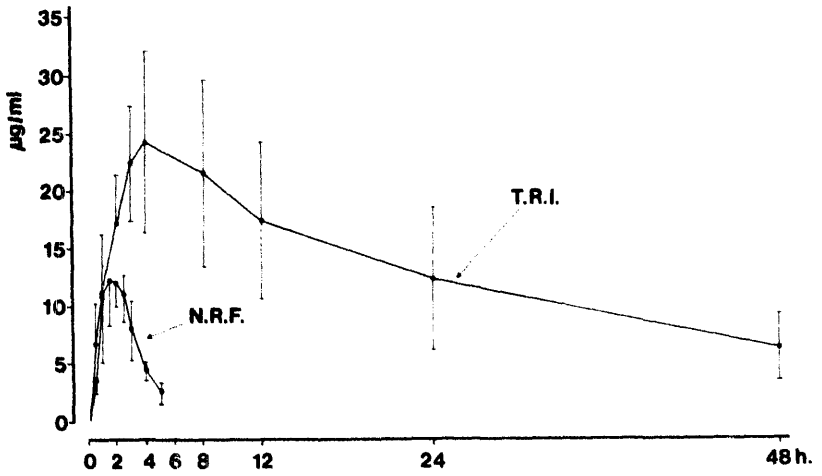

Fig. 1. Average serum level curves of cefadroxil obtained in subjects with NRF and in patients with TRI in interdialysis periods.

TABLE 3

Average pharmacokinetic parameters of cefadroxil obtained from patients with NRF and from patients with TRI in interdialysis periods

		N.R.F.	T.R.I.
K_a	(h^{-1})	= 1.265 ± 0.090	1.364 ± 1.186
t_0	(h)	= 0.252 ± 0.021	0.267 ± 0.219
t_{max}	(h)	= 1.139 ± 0.090	4.266 ± 2.650
C_{max}	(μg/ml)	= 10.072 ± 2.274	22.199 ± 6.895
K_e	(h^{-1})	= 0.592 ± 0.121	0.028 ± 0.008
$t_{1/2}$	(h)	= 1.204 ± 0.214	26.560 ± 8.002
V_d	(l)	= 22.073 ± 4.834	21.598 ± 5.933
Cl_p	(ml/min)	= 215.221 ± 48.497	10.403 ± 5.240
$(AUC)_0^\infty$	(μg/ml)h	= 40.602 ± 10.296	908.931 ± 382.027

antibiotic is reached, when the amount of the antibiotic accumulated within the organism becomes manifest. Fig. 2 shows the serum concentration curve of the patient A.E.F. It may be seen how the serum concentration increases rapidly during the first 60 min after administration. During this time, the serum concentrations of the antibiotic found in the TRI group reach an average value of 17.10 μg/ml; while 4 h after administration, these serum levels only undergo an increase of 5.31 μg/ml.

Bearing in mind that cefadroxil is principally eliminated in an undegraded state from the kidney, the greatest foreseeable variation, as a consequence of renal impairment, would be the decrease in the elimination constant. It may be seen, indeed, how this constant undergoes a decrease of 95% of its numerical value in the patients in interdialysis periods with respect to the value of the same constant in individuals with NRF. As a result of this modification, the elimination half-life of cefadroxil has an average value of 26.560 h in renal impairment, much greater than in the case of NRF; 1.204 h. The quotient of these two values is 22, similar to that obtained with other beta-lactam antibiotics such as Cefalexin-20 (Nightingale et al.,

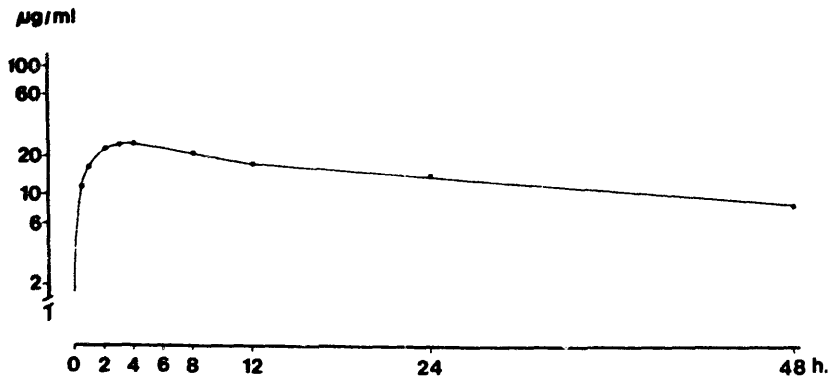

Fig. 2. Serum level curve of cefadroxil obtained from one patient (A.E.F.) with TRI during an interdialysis period.

1975); Cefoxitin-18 (Garcia et al., 1979); CPG-9000-27 (Nieto et al., in press).

The decrease in the elimination rate makes it necessary to correct the dosage regimen in the circumstances of multiple doses in order to avoid an accumulation of the antibiotic within the organism.

Table 4 shows the maximum and minimum predicted serum levels at steady-state together with the accumulation factor calculated for individuals of the NRF and the TRI groups with a maintenance dose of 500 mg of cefadroxil, orally in capsule form and with a 6 h dosage interval.

The apparent distribution volume of cefadroxil is not modified in renal impairment, contrary to what has been observed in the case of other oral cephalosporins (Klotz, 1976). Nevertheless, the accessibility of the antibiotic to the various organs and tissues must increase significantly in renal impairment as a consequence of the greater permanence of the antibiotic in the systemic circulation. This fact has been confirmed in our own laboratory with experimental animals (Dominguez-Gil et al., 1981).

The variation observed in the values of C_{max} and t_{max} are a consequence of the effect that renal impairment causes on the absorption and elimination processes of the antibiotic.

Patients undergoing hemodialysis (TRI^H)

Fig. 3 shows the average serum level curves of cefadroxil obtained after oral administration of the antibiotic to patients with TRI undergoing hemodialysis sessions lasting 4 h with later sampling of blood at the input and output of the dialyzer. Both follow a single-compartment open-kinetic model, and are defined by the following equations:

$$C = 24.434 \times e^{-0.242 \times t} - 94.842 \times e^{-2.566 \times t} \text{(input)}$$

$$C = 21.038 \times e^{-0.276 \times t} - 39.174 \times e^{-1.911 \times t} \text{(output)}$$

In all cases the serum antibiotic concentrations at the input of the dialyzer are greater than those at the output ($P < 0.005$).

The pharmacokinetic parameters obtained for the antibiotic concentrations at the input of the dialyzer for this group of patients are shown in Table 5.

The elimination serum half-life of the hemodialysis sessions has an average value of 2.542 h, similar to that obtained for cefaloridine, 2–4 h (Anderson et al., 1976);

TABLE 4

Maximum and minimum concentration values of cefadroxil at steady-state and accumulation factor value for the three groups studied

		N.R.F.	T.R.I.
C^{ss}_{max}	(μg/ml)	= 13.02	146.49
C^{ss}_{min}	(μg/ml)	= 1.24	132.49
Accumulation factor		= 1:03	6.47

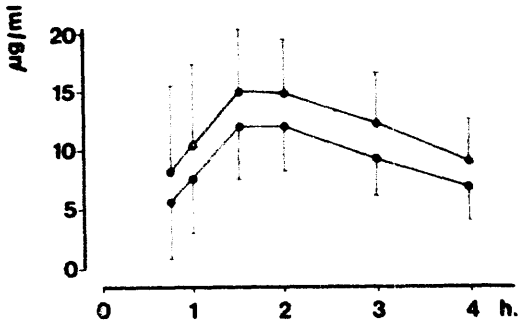

Fig. 3. Average serum levels of cefadroxil at the input and output of the dialyzer obtained from patients with TRI in hemodialysis sessions.

less than that for cefalexin, 4–6 h (Bailey, 1972); cefoxitin, 4 h (Garcia et al., 1979) and CGP-9000, 3–4 h (Nieto et al., in press) and greater than that of cefacetrile, 1.5 h (Dominguez-Gil et al., 1979).

The extraction coefficient for cefadroxil has an average value of 0.218, which is similar to that of cefoxitin, 0.255 (Garcia et al., 1979); CGP-9000, 0.248 (Nieto et al., in press) and cefacetrile, 0.251 (Dominguez-Gil et al., 1979).

In patients undergoing hemodialysis sessions, it may be seen that there are variations in the values obtained for C_{max}; they range between those values obtained for C_{max} in the NRF and TRI groups.

The average value of t_{max} in the TRI^H group is similar to that obtained for the NRF group and lower that of the TRI group. The lag-time (t_0) is greater in the patients of the TRI^H group than that established for the NRF and TRI groups.

All these variations observed in the absorption process of cefadroxil in the 3 groups studied become manifest in Fig. 4 which shows the amount of antibiotic remaining at the absorption site calculated from the average serum levels of cefadroxil for each of the 3 groups of patients (Wagner et al., 1963). It may be seen how in the individuals with normal renal function, absorption is completed in 3 h; in 8 h in patients with TRI and 4 h in the hemodialysis group.

TABLE 5

Average pharmacokinetic parameters of cefadroxil obtained at input (arterial blood) of the dialyzer in patients with TRI during hemodialysis sessions

K_a (h^{-1})	= 2.330± 0.836	E.C.	= 0.218± 0.103
t_0 (h)	= 0.582± 0.235	Cl_p (ml/min)	= 129.824±66.900
t_{max} (h)	= 1.121± 0.405	Cl_D (ml/min)	= 48.450±21.004
C_{max}(µg/ml)	= 15.463± 4.362	A^r_0 (mg)	= 100.086±37.722
k_e (h^{-1})	= 0.289± 0.074	$t_{1/2}D$ (h)	= 1.741± 0.410
$t_{1/2}$ (h)	= 2.542± 0.724	$(ABC)^{\infty}_0$(µg/ml)h	= 77.210±32.716
V_d (l)	=26.715±11.562		

E.C. = extraction coefficient; Cl_D = dialysis clearance; A^r_0 = amount of antibiotic extracted by dialysis.

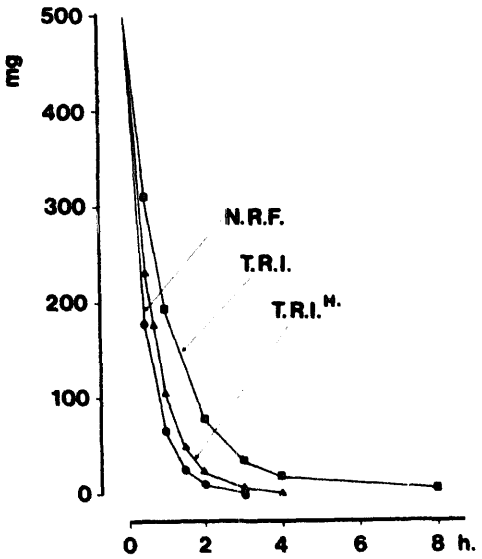

Fig. 4. Average disappearance curves of cefadroxil from the absorption site in the 3 groups studied.

This decrease in the absorption rate may be attributed to changes in the concentration gradient of the antibiotic at the absorption site due to its accumulation in the systemic circulation as a consequence of renal impairment.

Hemodialysis increases the elimination of the antibiotic. The serum half-life has an average values of 2.542 h in this group of patients. The quotient of this value with the NRF group is 2.110; 10-fold lower than that established for the TRI group.

Due to the fact that patients suffering from TRI periodically undergo hemodialysis sessions, upon correcting the dosage regimen, it would be necessary to consider

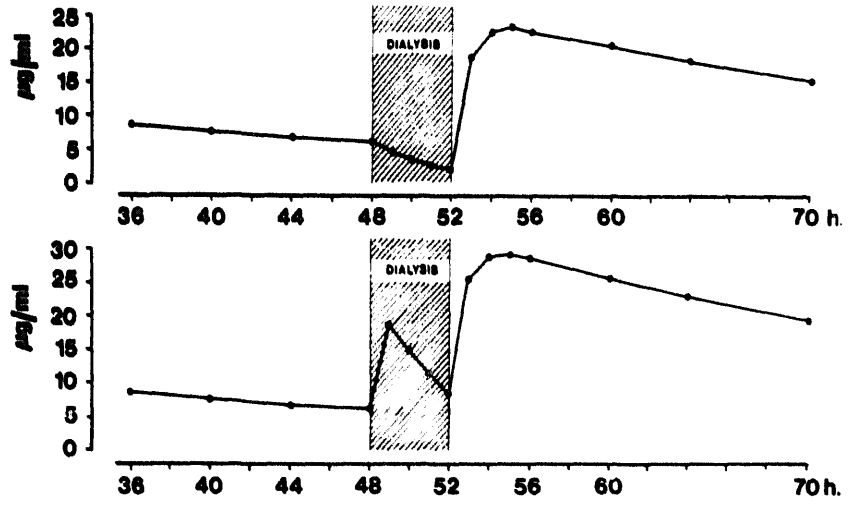

Fig. 5. Average serum levels curves of cefadroxil calculated for an individual with TRI during inter- and intra-dialysis periods undergoing two different dosage regimens: (a) administering a dose of the antibiotic at the end of the dialysis sessions; and (b) administering a dose of the antibiotic at the beginning and the end of the hemodilysis session.

the existence of alternative and clearly differentiated kinetic processes.

Fig. 5 shows the serum level curve of cefadroxil obtained in this kind of patient subject to different kinds of dosage regimen; the first consisting of a dose of 500 mg of cefadroxil at the end of the hemodialysis session while in the second, the patients are administered the same amount at the beginning and the end of the session. In both cases, the patient would be suffering from TRI and would have received a previous 500 mg, dose of antibiotic 48 h before beginning the hemodialysis session.

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References

Anderson, R.J., Gambertoglio, J.G. and Schrier, R.W., In Clinical Use of Drugs in Renal Failure, C.H. Thomas, Springfield, IL., 1976, p. 38.

Bailey, G.C., Hemodialysis Principles and Practice, Academic Press, New York, London, 1972, p. 134.

Buck, R.E. and Price, K.E., Cefadroxil, a new broad-spectrum cephalosporin. Antimicrob. Agents Chemother., 11 (1977) 324–330.

Cordero, A., Treatment of skin and soft tissue infection with cefadroxil a new oral cephalosporin. J. Int. Med. Res., 4 (1976) 176–178.

Cutler, R.E., Blair, A.D. and Kelly, M.R., Cefadroxil kinetics in patients with renal insufficiency. Clin. Pharmacol. Ther., 25 (1979) 514–521.

Dominguez-Gil, A., Lanao, J.M., Tabernero, J.M., Rodriguez-Commes, J.L. and De Castro, S., Pharmacokinetics of cefacetrile in patients undergoing haemodialysis. Eur. J. Clin. Pharmacol., 16 (1979) 49–52.

Dominguez-Gil, A.A., Garcia, M.J., Cepeda, M., Lanao, J.M. and Dominguez-Gil, A, Influence of renal impairment in the penetration of cefoxitin into interstitial tissue fluid in rabbits. Clin. Ther., 3 (1981) 413–424.

Garcia, M.J., Dominguez-Gil, A., Tabernero, J.M. and Sanchez-Tomero, J.A., Pharmacokinetics of cefoxitin in patients with normal or impaired renal function. Eur. J. Clin. Pharmacol., 16 (1979) 119–124.

Gibaldi, M. and Perrier, D., In Pharmacokinetics, Vol. I, Marcel Dekker, New York, 1975.

Klotz, V., Pathophysiological and disease-induced changes in drug distribution volume: pharmacokinetic implications. Clin. Pharmacokin., 1 (1976) 204–218.

Lode H., Stahlmann, R. and Koeppe, P., Comparative pharmacokinetics of cephalexin, cefaclor, cefadroxil and CGP-9000. Antimicrob. Agents Chemother., 16 (1979) 1–6.

Mariño, E.L. and Dominguez-Gil, A., Influence of dose on the pharmacokinetics of cefadroxil. Eur. J. Clin. Pharmacol., 18 (1980) 505–509.

Nieto, M.J., Lanao, J.M., Dominguez-Gil, A., Tabernero, J.M. and Macias, J.F., Elimination of CGP-9000 in patients undergoing dialysis. Eur. J. Clin. Pharmacol., in press.

Nightingale, C.H., Greene, D. and Quintiliani, R., Pharmacokinenetics and clinical use of cephalosporin antibiotics. J. Pharm. Sci., 64 (1975) 1899–1927.

Paul, P.A.D., Santella, J. and Berman, E., Cefadroxil: a multi-center clinical evaluation. Invest. Med. Int., 4 (1977) 143–147.

Santella, P.J., Tanrisever, B. and Berman, E., An overview of results of world-wide clinical trials with cefadroxil. J. Int. Med. Res., 6 (1978) 441–451.

Santella, P.J. and Tanrisever, B., Treatment of upper and lower respiratory tract infections with cefadroxil, a new orally active cephalosporin. Curr. Ther. Res., 25 (1979) 210–220.

Takki, S., Gambertoglio, J.G., Honda, D.H. and Tozer, T.N., Pharmacokinetics evaluation of hemodialysis in acute drug overdose. J. Pharmacokin. Biopharm., 6 (1978) 427–442.

Wagner, J.G. and Nelson, E., Percent absorbed time plots derived from blood level and/or urinary excretion data. J. Pharm. Sci., 52 (1963) 610–611.

Wagner, J.G., Fundamentals of Clinical Pharmacokinetics, Drug Intelligence Publications, Hamilton, IL., 1975.