International Journal of Pharmaceutics, 19 (1984) 345–348
Elsevier

IJP 00672

Pharmacokinetics of cefotiam after i.v. administration to healthy volunteers

I.G. Alonso, E.L. Marino and A. Dominguez-Gil

Department of Pharmacy, University of Salamanca, Salamanca (Spain)

(Received October 11th, 1983)
(Modified version received January 10th, 1984)
(Accepted January 14th, 1984)

Cefotiam is a recently developed semi-synthetic cephalosporin antibiotic destined for parenteral use with a chemical structure of 7-β-[2-(2-aminothiazol-4-yl)-acetamide]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]thio]methyl]ceph-3-em-4-carboxylic acid.

In vitro studies have shown it to have a broad antimicrobial spectrum and to be especially effective against Gram (−) microorganisms (Nozaki et al., 1979; Bodey et al., 1981).

The percentage of cefotiam excreted in urine has an average value of 54% after 24 h (Rouan et al., 1981); its excretion principally takes place during the first 6 h after administration (Daschner et al., 1981).

Its use in clinical practice has revealed it to be efficient in the treatment of infections of the urinary tract (Iwahi and Tsuchiya, 1980) and of gynecological (Takase, 1981) and respiratory tract (Kahn and Del Rio, 1981) infections.

In our study cefotiam in solution at a dose of 1 g was administered by bolus type i.v. injection.

Our subjects were 2 women and 8 men with an age range between 21 and 30 years and weights ranging between 53 and 83 kg.

All subjects were judged healthy as determined by history, physical examination and standard laboratory testing carried out within 30 days of the study. None of the subjects had a history of sensitivity to penicillins or cephalosporins and they had not received antibiotics or other drugs for 48 h before the study.

Blood specimens were taken just before administration and 5, 10, 15, 20 and 45 min, and 1.0, 1.5, 2.0 and 3.0 h after each injection for drug level analysis. Samples were collected in heparinized test-tubes; plasma was separated by centrifugation, placed in labelled tubes and frozen at −20°C until determination.

Correspondence: A. Dominguez-Gil Hurle, Departamento de Farmacia Galénica, Facultad de Farmacia, Universidad de Salamanca, Salamanca, Spain.

Urine was collected fractionally from 0.0 to 0.5, 0.5 to 1.0, 1.0 to 2.0, 2.0 to 3.0, 3.0 to 5.0, 5.0 to 7.0 and 7.0 to 9.0 h after each injection. Urine volumes were measured and a portion stored frozen until assayed.

Determination of the antibiotic in biological fluid was carried out by a plate diffusion method using *Bacillus subtilis* (ATCC no. 6633) as the test organism.

The experimentally determined plasma concentrations of cefotiam were subjected to the MAICE test (Yamaoka et al., 1978) in order to select the most suitable kinetic model. A two-compartment open kinetic model was seen to provide the best estimate for the evolution of the plasma levels of the antibiotic. An iterative least-squares method was used to find the parameters α, β, A_0 and B_0 where α and β represent the rapid and slow disposition constants, respectively, and A_0 and B_0 represent the zero-time intercepts for the concentration–time curve. The remaining pharmacokinetic parameters were calculated from these values according to the method of Wagner (1975).

The average curve of the plasma levels of cefotiam after i.v. administration are shown in Fig. 1. The pharmacokinetic parameters established are shown in Table 1.

The equation defining the average plasma level–time curve may be expressed as:

$$C_p = 28.34 \cdot e^{-1.03t} - 63.33 \cdot e^{-4.56t}$$

The rapid and slow disposition phases are defined by the constants α and β, which have average values of 4.56 h^{-1} and 1.03 h^{-1}, respectively, and the balance between distribution and elimination occurs at 0.44 h after administration.

The half-life of the slow disposition phase ($t_{1/2}\,\beta$) has an average value of 0.69 h, similar to that of some other cephalosporins such as cephalothin—0.56 h (Nightingale et al., 1975) and cephamandole—0.40 h (Aziz et al., 1978), but lower than that of more recently developed cephalosporins, such as cefoperazone—1.60 h (Craig, 1980), ceftriaxone—6.60 h (Patel et al., 1981), cefonicid—3.46 h (Pitkin et al., 1981) and ceftizoxime—1.85 h (Dubb et al., 1981). This low value of the slow disposition phase half-life, together with the high value for the constant K_{13} of 2.43 h^{-1} are clearly indicative of the rapid disappearance of cefotiam from the systemic circulation.

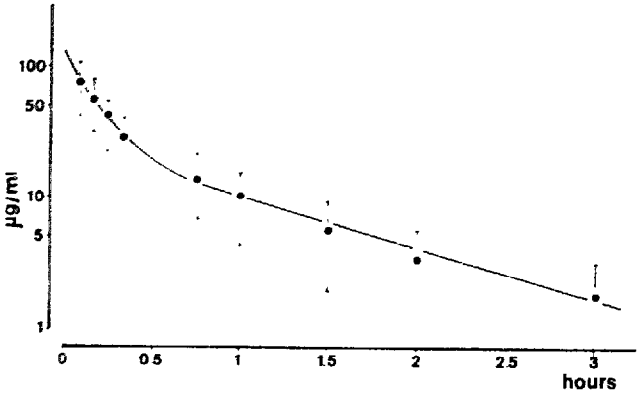

Fig. 1 Average plasma level curve of cefotiam administered i.v.

TABLE 1

PHARMACOKINETIC PARAMETERS OF CEFOTIAM DETERMINED IN OUR STUDY

α	(h^{-1})	=	4.56 ± 1.12
β	(h^{-1})	=	1.03 ± 0.16
$t_{1/2}\beta$	(h)	=	0.69 ± 0.10
K_{12}	(h^{-1})	=	1.12 ± 0.57
K_{21}	(h^{-1})	=	2.03 ± 0.68
K_{13}	(h^{-1})	=	2.43 ± 0.85
V_c	(l)	=	12.74 ± 4.82
V_p	(l)	=	6.55 ± 3.21
Vd_{ss}	(l)	=	19.29 ± 7.57
Cl_p	(ml/min)	=	532.33 ± 336.11
$(AUC)_0^\infty$	(h·μg/ml)	=	41.79 ± 20.67
Δ	(l/kg)	=	0.29 ± 0.09
K_u	(h^{-1})	=	0.50 ± 0.13
K_{nr}	(h^{-1})	=	0.42 ± 0.08
Cl_r	(ml/min)	=	375.02 ± 266.96
% Excreted at 9 h		=	68.81 ± 6.96

α and β hybrid rapid and slow disposition constants; K_{12} distribution constant from the central to the peripheral compartment; K_{21} distribution constant from the peripheral to the central compartment; K_{13} overall elimination rate constant; V_c and V_p distribution volumes of the central and peripheral compartment; Vd_{ss} distribution volume at steady-state; Cl_p plasma clearance; $(AUC)_0^\infty$ area under the curve of the plasma level–time plot; Δ distribution coefficient; K_u urinary excretion rate constant; K_{nr} no renal excretion rate constant; Cl_r renal clearance.

The values obtained for the pharmacokinetic microconstants K_{12} and K_{21} with a quotient of 0.53, together with the results of the distribution volumes of the central and peripheral compartments, 12.74 liters and 6.55 liters, respectively, shows a lesser distribution of the drug in the peripheral compartment than in the central one, principally due to high elimination rate of cefotiam from the organism.

The values obtained for serum clearance of cefotiam are very high with an average value of 532.33 ml/min, once again confirming the rapid elimination of the drug from the organism.

From the determination of cefotiam in urine it was possible to establish its urinary excretion kinetics. This study shows that the amounts of the antibiotic accumulated in urine where it may be seen that at 9 h after administration, 68.81% of the original dose is found. This suggests that though renal excretion is essential for the elimination of the drugs, it is not the only route involved.

From the plot of the urinary excretion rate of cefotiam it was possible to calculate the values of the urinary excretion constant (K_u) and the elimination constant (K_e) or rather the β constant, since one is dealing with a two-compartment model.

The lower value observed for the urinary excretion constant with respect to the elimination constant again shows the existence of other elimination routes, apart from the renal mechanism, which contribute to the elimination of cefotiam from the

organism. Similarly, renal clearance was also seen to be lower than serum clearance, with average values of 375.02 ml/min and 532.33 ml/min, respectively.

References

Aziz, N.S., Gambertoglio, J.G., Lin, E.T., Grausz, H. and Benet, L.Z., Pharmacokinetics of cefamandole using a HPLC assay. J. Pharmacokin. Biopharm., 6 (1978) 153–164.

Bodey, G.P., Fainstein, V. and Heikle, A.M., Comparative in vitro study of new cephalosporins. Antimicrob. Ag. Chemother., 20 (1981) 226–230.

Craig, W., Single-dose pharmacokinetic of cefoperazone following intravenous administration. Clin. Ther., 3 (1980) 46–49.

Daschner, F.D., Hemmer, K.A., Offerman, P. and Slanicka, J., Kinetics of cefotiam following intravenous of 0.5, 1 and 2 g in healthy volunteers. Proceedings of the 12th International Congress of Chemotherapy, Florence, 1981, p. 584.

Dubb, J., Actor, P., Pitkin, D., Alexander, F., Familiar, R., Erlich, S. and Stote, R., Ceftizoxime kinetics and renal handling. Clin. Pharmacol. Ther., 31 (1981) 516–521.

Findlay, C.D., Brown, R.M., Allock, J.E., Lowe, P.A. and Wise, R., A study of the relationship between dose and pharmacokinetics of ceftriaxone. J. Antimicrob. Chemother., 9 (1982) 57–62.

Iwahi, T. and Tsuchiya, K., Comparative activities of cefotiam and cefazolin against urinary tract infections with *Proteus mirabillis* in mice. Antimicrob. Ag. Chemother., 18 (1980) 257–263.

Kahn, M. and Del Rio, G., Treatment of urinary tract infections using cefotiam or cefamandole. Proceedings of the 12th International Congress of Chemotherapy, Florence, 1981, p. 590.

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

Nozaki, Y., Imada, A. and Yoneda, M., SCE-963, a new potent cephalosporin with high affinity for penicillin-binding protein 1 and 3 of *Escherichia coli*. Antimicrob. Ag. Chemother., 15 (1979) 20–27.

Patel, I.H., Miller, K., Weinfeld, R. and Spicehandler, J., Multiple intravenous dose pharmacokinetics of ceftriaxone in man. Chemotherapy, 27 (Suppl. 1) (1981) 147–156.

Pitkin, D., Dubb, J., Actor, P., Alexander, F., Ehrlich, S., Familiar, R. and Stote, R., Kinetics and renal handling of cefonicid. Clin. Pharmacol. Ther., 30 (1981) 587–593.

Rouan, M.R., Lecaillon, J.B., Abadie, F., Juge, F., Schoeller, J.P., Guibert, J. and Modal, J., Pharmacokinetics of cefotiam in humans. Proceedings of the 12th International Congress of Chemotherapy, Florence, 1981, p. 771.

Takase, Z., Antimicrobial activity, pharmacokinetics and clinical studies with cefotiam in the field of obstetrics and gynecology. Proceedings of the 12th International Congress of Chemotherapy, Florence, 1981, p. 586.

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

Yamaoka, K., Nakagawa, T. and Uno, T., Application of Akaike's information criterion in the evaluation of linear pharmacokinetic equations. J. Pharmacokin. Biopharm., 6 (1978) 165–175.