DECREASED EXTRARENAL CLEARANCE OF CEFOPERAZONE IN HEPATOCELLULAR DISEASES

Cefoperazone, a cephalosporin with a spectrum extended to *P. aeruginosa*, *E. cloacae* and *S. marescens* (Auckenthaler & Waldvogel, 1980), is a drug extensively eliminated through extrarenal processes. Decreased renal function has practically no influence on its apparent half-life of elimination (Balant, Dayer, Rudhardt, Allaz & Fabre, 1980). Reduced extrarenal clearance of cefoperazone however has been reported in one patient with bile duct obstruction (Balant *et al.*, 1980) and in two others with a slight increase of alkaline phosphatase (Dayer, Balant, Rudhardt, Allaz & Fabre, 1980). A study was thus conducted to document the kinetics of this drug in patients with hepato-cellular diseases. Present results were compared to those previously obtained in healthy volunteers (Allaz, Dayer, Fabre, Rudhardt & Balant, 1979).

Six patients, four men and two women, aged 23 to 57 (mean 37) years, weighing from 48 to 87 (mean 60) kg, ranging from 162 to 177 (mean 170) cm in height, were selected because of mild liver function impairment due to viral hepatitis in four cases (1 A, 2 B, 1 non-A non-B), and biopsy-proven alcoholic fatty liver and alcoholic cirrhosis in 2 cases. Serum values ranged from 13 to 119 μmol for total bilirubin (normal < 17), 39/16 to 244/336 U/l for aspartate/alanine transaminases (normal $< 19/23$), 69 to 219 U/l for alkaline phosphatase (normal < 48), 68 to 100% for prothrombine time. Care was taken to choose patients whose liver function tests were progressively improving; the tests were repeated 1 and 2 days after the cefoperazone infusion and disclosed persistent improvement in every case. All patients were on usual diets. No other drugs were given during the trial period with the exception of the patient with an alcoholic fatty liver who received chlordiazepoxide, 75 mg daily per os on the 3 days preceding cefoperazone infusion. The healthy volunteers were eight adult males (medical students), weighing from 64 to 77 (mean 71.8) kg, ranging from 173 to 183 (mean 177) cm in height; physical examination, routine blood and urine analysis were within the normal range. Patients and volunteers were hospitalized for the study. None had a history of allergy to penicillin. All gave informed consent for the study.

All subjects received a 2 h intravenous infusion of 2 g of cefoperazone sodium in 500 ml of 5% dextrose (Infusomat^R pump). The volunteers, who took part in a larger study, received a second infusion of cefoperazone, 10 h after the end of the first one. These results are not reported here. Twelve blood samples were obtained before infusion and at regular intervals

Table 1 Pharmacokinetic parameters of cefoperazone

	AUC ($\mu\text{g ml}^{-1} \text{h}$)	$T_{1/2}$ (h)	k_e (h^{-1})	C_s (2h) ($\mu\text{g ml}^{-1}$)	V_d (l)	Cl_T (ml min^{-1})	Cl_R (ml min^{-1})	Cl_{ER} (ml min^{-1})	Ae_x (mg)
Eight normals	Mean	1.60	0.447	134	10.4	77.7	18.3	59.4	473
	CV %	19	18	12	6	20	8	25	16
Six patients	Mean	4.30	0.169	208	11.7	32.5	25.5	7.3	1580
	CV %	24	24	27	41	46	41	88	12
	$P <$	0.0001	0.0001	0.01	NS	0.001	NS	0.0001	0.0001

CV, coefficient of variation
AUC, area under the serum concentrations-time curves
 $T_{1/2}$, apparent half-life of elimination
 k_e , elimination rate constant
 C_s (2h), serum concentrations at the end of the 2 h infusion
 Cl_T , total clearance
 V_d , volume of distribution
 Cl_R , renal clearance
 Cl_{ER} , extrarenal clearance
 Ae_x , amount of cefoperazone eliminated in the urine

Figure 1 Cumulative urinary excretion (mean $\pm$ s.d.) after a 2-h infusion of 2 g cefoperazone in normal volunteers (●) showing the extremes of the range and in patients with hepatic diseases (■).

up to 24 h. The serum was separated and stored at -18°C until assayed. Fractionated urine specimens were obtained as indicated in Figure 1, and aliquots were frozen until assayed.

Cefoperazone concentrations were measured by a bioassay using *Sarcina lutea* (Fabre, Blanchard & Rudhardt, 1977). The values are the mean of 6 measurements of the same sample, each at two dilutions. The detection limit of cefoperazone is about 1 $\mu\text{g}/\text{ml}$ in serum, and the coefficient of variation of the assay is in the range of 10%. The assay is not specific for cefoperazone but, as evidenced by the blank

serum and urine samples, no other antibiotic was present to interfere with our determinations.

Pharmacokinetic parameters of cefoperazone, expressed as mean and coefficient of variation in normal volunteers and patients, are shown in Table 1. The total clearance, derived from the dose and the serum concentration-time curves, is reduced in patients with hepatic diseases as compared with normal volunteers ($P < 0.001$, Student's *t*-test). The renal clearance is calculated from the urinary excretion rate and the corresponding serum concentration of the drug. No significant difference is found between the two groups for this parameter. The extra-renal clearance, estimated on the basis of the differences between the total and the renal clearances, is greatly reduced in patients with liver impairment ($P < 0.0001$). The apparent half-life of elimination shows a three-fold increase in those patients as compared with normals ($P < 0.0001$). No difference between the two groups is found for the volume of distribution, which is derived from the total clearance and the apparent half-life of elimination.

The changes of the pharmacokinetic parameters of cefoperazone observed in the patients are of similar magnitude, whether the hepatic lesion is viral hepatitis, alcoholic fatty liver or cirrhosis. No relation was found between these changes and any particular liver function test or serum albumin concentration.

As a consequence of the reduction of the extrarenal clearance of cefoperazone, there is a marked increase in the urinary excretion of the biologically active drug (Figure 1). In view of the prolonged apparent half-life of elimination and increased urinary excretion, the question arises as to the opportunity and modalities of dosage adjustment of cefoperazone in patients with impairment of liver function.

B. COCHET, J. BELAIEFF, A.-F. ALLAZ, M. RUDHARDT, L. BALANT & J. FABRE

Policlinique Universitaire de Médecine, Geneva, Switzerland

Received August 8, 1980

References

- ALLAZ, A.F., DAYER, P., FABRE, J., RUDHARDT, M. & BALANT, L. (1979). Pharmacocinétique d'une nouvelle céphalosporine, la céfopérazone. *Schweiz. med. Wschr.*, **109**, 1999–2005.
- AUCKENTHALER, E. & WALDVOGEL, F.A. (1980). *In vitro* activity of a new semisynthetic cephalosporin: cefoperazone. *Clin. Ther.*, **3**, special issue, 89–97.
- BALANT, L., DAYER, P., RUDHARDT, M., ALLAZ, A.F. & FABRE, J. (1980). Cefoperazone: pharmacokinetics in humans with normal and impaired renal function and pharmacokinetics in rats. *Clin. Ther.*, **3**, special issue, 50–59.
- DAYER, P., BALANT, L., RUDHARDT, M., ALLAZ, A.-F. & FABRE, J. (1980). Behavior of cefoperazone (a new cephalosporin) in man: influence of renal insufficiency. Presented at the Swiss Society of Nephrology, Basel, Switzerland, December 8, 1979. Abstracts. *Kidney Int.*, **17**, 857.
- FABRE, J., BLANCHARD, P. & RUDHARDT, M. (1977). Pharmacokinetics of ampicillin, cephalothin and doxycycline in various tissues of the rat. *Chemotherapy*, **23**, 129–141.