ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1981, p. 526-531
0066-4804/81/040526-06$02.00/0

Vol. 19, No. 4

Pharmacology of Cefotaxime and Its Desacetyl Metabolite in Renal and Hepatic Disease

R. WISE,[1] N. WRIGHT,[2]* AND P. J. WILLS[1]

Departments of Medical Microbiology[1] and Medicine,[2] Dudley Road Hospital, Birmingham, B18 7QH, United Kingdom

Received 27 August 1980/Accepted 2 January 1981

The pharmacology of cefotaxime and the metabolite desacetyl cefotaxime was studied in 40 patients with various degrees of renal and hepatic failure who received 0.5 or 1 g of cefotaxime intravenously. Patients with severe renal impairment (creatinine clearance, 3 to 10 ml/min) had a cefotaxime serum half-life of 2.6 h and desacetyl cefotaxime serum half-life of 10.0 h. The equivalent figures were 1.0 and 1.5 h, respectively, in subjects with normal renal function. The presence of an acute coexisting illness together with severe renal impairment was associated with a further prolongation of the serum half-lives. Hepatic dysfunction was accompanied by a reduction in desacetyl metabolite formation. A reduction of cefotaxime dosing to 0.5 g twice a day would appear prudent when the creatinine clearance is 5 ml/min or less to avoid accumulation of the parent compound and the metabolite.

The novel cephalosporin cefotaxime combines a broad antibacterial spectrum with considerable antimicrobial potency (2, 10). This compound, like cephalothin and cephacetrile, possesses an acetoxy group on the 3 position of the cephem nucleus and undergoes desacetylation in animals and humans (7). Desacetyl cefotaxime has a good antibacterial spectrum and potency, being similar to cefamandole and cefuroxime (11). As little is known of the pharmacology of both the parent drug and the metabolite, this study was designed to investigate both cefotaxime and desacetyl cefotaxime in patients with various degrees of renal failure and also in patients with hepatic necrosis. A dosing regime is proposed.

MATERIALS AND METHODS

Patients. A total of 40 patients (19 males; mean age, 51.4 years) were studied after informed consent had been obtained. Thirty-four of these were under investigation for acute or chronic renal failure, and six patients had acute hepatocellular damage related to self-administered drugs such as acetaminophen and carbon tetrachloride. Thirty-eight patients received 1 g and 2 patients received 0.5 g of cefotaxime diluted in sterile water intravenously over 3 to 5 min. Creatinine clearance studies were performed during and after each investigation. Routine screening tests performed before and after the investigation consisted of a full blood count, blood urea, electrolytes, and liver function tests. In addition, the extent of the hepatocellular damage in five patients was gauged by the peak alanine-amino transferase activity measured daily. These six patients were all studied in the early recovery phase of their disease.

Three of the 34 patients with renal dysfunction were studied while undergoing hemodialysis with an Ultraflow (Travenol Laboratories S.A., Castlebar, County Mayo, Ireland) 1-m^2 coil and a blood flow of 140 to 250 ml/min. Five patients underwent peritoneal dialysis (1.5-liter exchanges every 40 min) while being studied.

Repeated intravenous doses of 0.5 or 1 g of cefotaxime at 12- or 24-h intervals over 3 days were given to eight patients with renal dysfunction.

The patients with renal dysfunction were classified into four groups on the basis of their creatinine clearance (Table 1). The group of patients with severe renal failure was further subdivided according to the presence or absence of acute illnesses (these included coexistent heart failure, septicemia, and pulmonary edema).

Sampling. Blood samples for assay were taken from the arm opposite that used for drug administration. In single-dose studies samples were taken at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h. In patients receiving multiple doses the following sampling schedules were used: once daily dosing—0, 2, 6, 8, 12, and 24 h postdosing; twice daily dosing—0, 2, 6, and 12 h postdosing. The serum was separated within 1 h of collection and frozen at −20°C before assay.

Assay. Cefotaxime and its desacetyl metabolite were measured in serum by using a high-performance liquid chromatography system (Applied Chromatography Systems Ltd., Luton, United Kingdom) with a 10-cm octadecylsilane column and a 4-cm precolumn containing copellicular octadecylsilane. Sera were prepared by adding an equal volume of acetonitrile and then mixing and centrifuging. Twenty microliters of supernatant was injected. The mobile phase was 14%

TABLE 1. *Cefotaxime and desacetyl cefotaxime half-lives in patients with various degrees of renal failure*

Renal function (creatinine clearance in ml/min)	No. of patients	Cefotaxime serum half-life (h)		Desacetyl cefotaxime half-life (h)	
		Mean	Range	Mean	Range
Normal (>100)	4	1.0	0.72–1.3	1.5	1.1–1.8
Mild impairment (30 to 100)	3	1.3	1.27–1.34	ND[a]	
Moderate impairment (10 to 30)	6	1.9	1.26–2.4	6.6	2–9.9
Severe impairment (3 to 10)	9	2.6	1.4–3.6	10	8.2–11.8
Severe impairment plus acute illness (<5)	7	5.6	2.2–11.5	30	19.2–56.8

[a] ND, No data available.

methanol and 1% acetic acid in distilled water. The flow rate was 2 ml/min, and an ultraviolet detector at 254 nm, set at 0.005 absorbance units full scale, was used. The retention times of desacetyl cefotaxime and cefotaxime were 4 and 12 min, respectively. Standards of 50, 25, 12.5, 6.25, and 3.125 μg/ml were prepared in pooled human serum (pH 7.4) and injected before the first samples and after every sixth sample. All samples were run in triplicate, and serum levels were calculated from peak height measurements.

The high-performance liquid chromatographic assay had previously been compared with a bioassay designed to measure cefotaxime by using *Proteus morganii* as an indicator organism (8). The correlation coefficient between the two assays was calculated as $r = 0.98$. Deepfreezing for periods of up to 1 week had been shown not to alter assay results.

Hematology and biochemistry. The hematological and biochemical tests were performed by standard methods. In particular the creatinine concentrations in urine and serum were measured by the colorimetric method of Jaffé as described by Bosnes and Tausky (1).

Pharmacokinetic analysis. The data were analyzed by least squares regression line analysis. Pharmacokinetic parameters were calculated by using a two-compartment model (6). Serum half-lives were calculated from analysis of the beta phase of elimination. The central volume of distribution (Vc) was calculated from the formula $Vc = D_0/A + B$, where A and B are the theoretical concentrations obtained by extrapolating the α and β exponentials back to time zero, and D_0 is the dose given (3).

RESULTS

Renal dysfunction. The results of cefotaxime and desacetyl cefotaxime elimination studies in patients with various degrees of renal failure are shown in Table 1. For technical reasons (interfering peaks on high-performance liquid chromatography) it was not always possible to assay the desacetyl metabolite. The serum half-lives of cefotaxime in all patients in the study are shown in Fig. 1. The serum half-life of cefotaxime barely doubled when the creatinine clearance fell from normal to between 10 to 30 ml/min (Table 1). Patients with a severe impairment of renal function (creatinine clearance, 3 to 10 ml/min) had a mean cefotaxime serum half-life of 2.6 h. Patients with severe coexisting disease in addition to severe renal failure had varied but generally more prolonged serum half-lives. The elimination of desacetyl cefotaxime was more markedly reduced in patients with renal failure (Fig. 2). When the elimination constant was plotted against creatinine clearance the relationship approximated towards linearity (for cefotaxime, $r = 0.84$, $n = 32$; for desacetyl cefotaxime, $r = 0.88$, $n = 13$). The mean amount of cefotaxime appearing in the urine in five subjects with normal renal function after intravenous administration of 1 g was 680 mg, whereas the mean amount in five subjects with creatinine clearances of less than 5 ml/min was 147 mg. Calculated volumes of distribution of cefotaxime in these two groups were 0.22 and 0.15 liter/kg, respectively, a slight reduction in the patients with reduced renal function.

Only minimal amounts of cefotaxime appeared in the peritoneal dialysate of five patients. The mean serum cefotaxime half-life during dialysis (2.9 h ± 1.08 [standard deviation]) did not differ significantly from that found in this same group when they were not on dialysis (4.4 h ± 4.1 [standard deviation]). In contrast, hemodialysis caused a mean reduction in cefotaxime serum half-life of 44% as compared with the drug half-life in the same patients when they were not on hemodialysis.

Eight patients were studied after repeated doses (Table 2). The case of a male 42-year-old patient who was given 1 g twice daily is illustrated in Fig. 3. Slight cefotaxime accumulation occurred in patients given 1 g twice daily, but only to a minimal degree in those given 0.5 g twice daily. Accumulation of the desacetyl metabolite occurred in all patients with severe renal failure whatever the dosing regime. It was of a minor degree (48%) in patients given 0.5 g twice daily. There was no evidence that this was accompanied by any toxic effects.

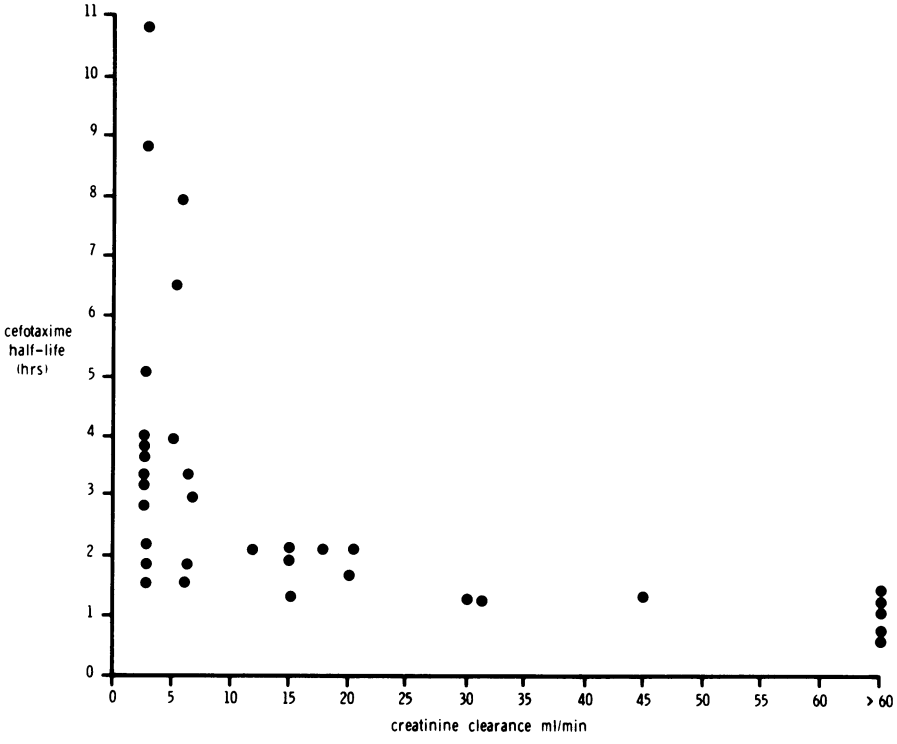

FIG. 1. *Serum half-life of cefotaxime compared with the creatinine clearance.*

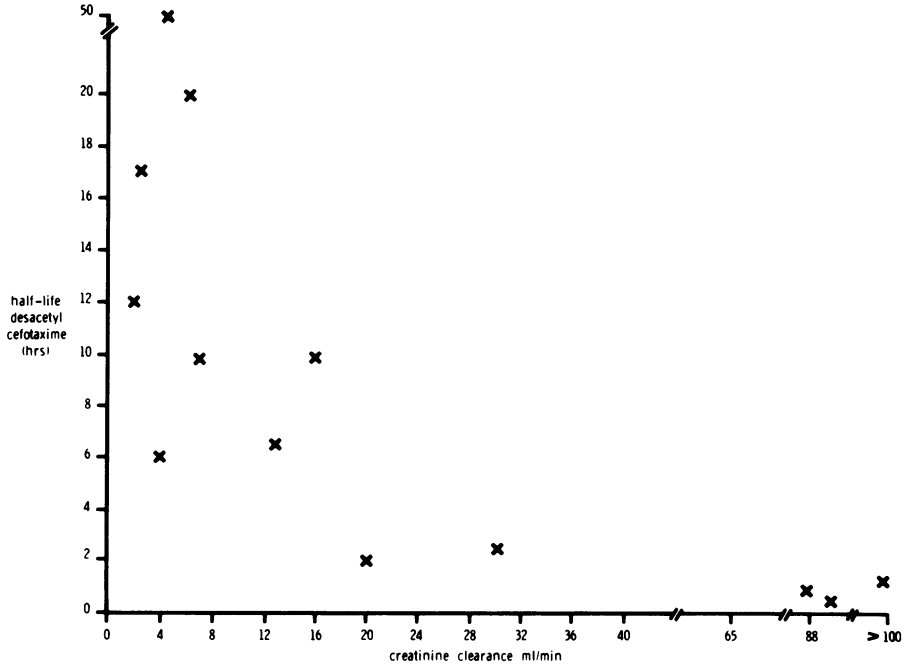

FIG. 2. *Serum half-life of desacetyl cefotaxime compared with the creatinine clearance.*

Hepatic dysfunction. Data on six patients with hepatic damage are summarized in Table 3. The amount of desacetyl cefotaxime formed (as measured by peak levels) was reduced with increasing liver damage when assessed by serum aspartate transaminase. There was also an increase in cefotaxime half-life with a reduction in renal function (assessed by creatinine clearance). This increase was related to the extent of renal function rather than reduced metabolic capacity. Two-hour levels were remarkably high in two patients, but there was no obvious reason for this.

Toxicity. There was no evidence of drug-associated deterioration in renal function, hepatic damage, or hematological disturbance, and no

TABLE 2. *Cefotaxime and desacetyl cefotaxime concentrations during repeated dose regimes in patients with renal failure*

Age/sex	Creatinine clearance (ml/min)	Dose (g)	No. of doses	Dosage interval (h)	Cefotaxime level (μg/ml)		Desacetyl cefotaxime level (μg/ml)	
					2 h after first dose	2 h after last dose	2 h after first dose	2 h after last dose
42/M	5	1	6	12	28	37	19	56
72/F	16	1	6	12	30	33.9	11.5	14.5
57/F	8	1	3	24	36	55	20.5	65
70/F	6	1	3	24	50	45	14	60
68/F	7	1	3	24	25	31	16	18
41/M	20	1	3	24	29	27	27	30
22/M	<5	0.5	6	12	17	22.8	7.2	35
48/M	<5	0.5	6	12	14.5	13.3	4.6	18.7

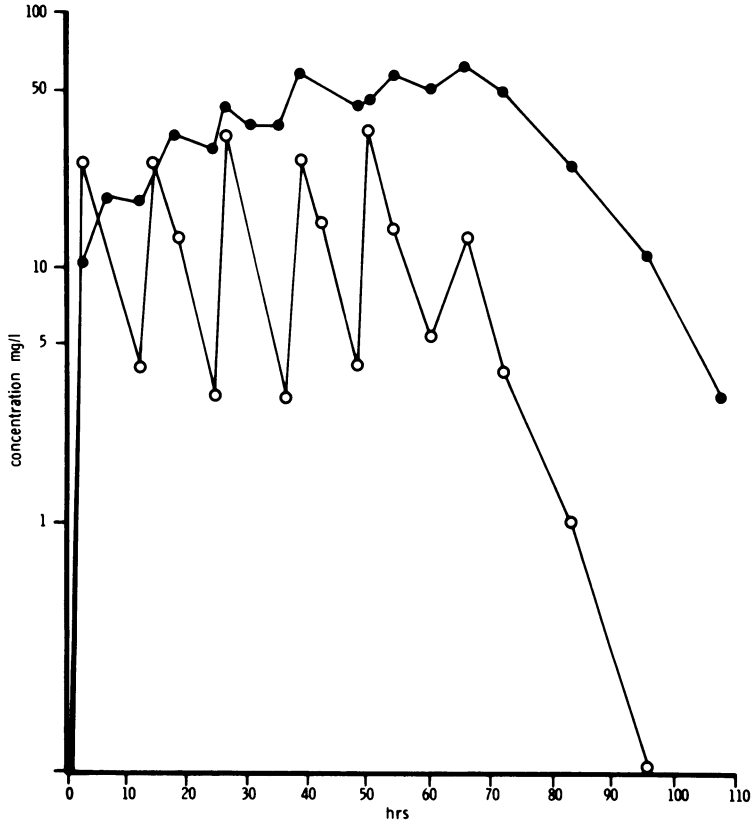

FIG. 3. *Serum concentrations per unit time in a patient receiving 1 g every 12 h (creatinine clearance, 5 ml/min). Symbols: ○, cefotaxime; ●, desacetyl cefotaxime.*

TABLE 3. *Clinical and kinetic features of patients with hepatic damage given 1 g of cefotaxime intravenously*

Age/sex	Creatinine clearance (ml/min)	Peak AST (IU/liter)[a] (Normal < 45 IU/l)	Cefotaxime		Desacetyl cefotaxime 2-h level (μg/ml)
			2-h level (μg/ml)	Half-life (h)	
20/F	88	410	197	0.7	30
21/F	45	437	104	1.3	15
41/M	90	957	52	1.2	7.2
32/M	95	2310	166	1.2	4.1
19/F	65	2279	53	1.4	<1
63/F	<5	2958	85	3.3	<1

[a] AST, Serum aspartate transaminase. Normal AST levels are <45 IU/liter.

phlebitis was noted. Nausea occurred in one patient given the drug more rapidly than usual (over 2 min instead of the standard 5 min).

DISCUSSION

Cefotaxime clearance from serum was reduced in patients with renal failure, but not to the same extent as that occurring with antimicrobial agents that are eliminated solely by the kidneys (9). This difference is presumably related to metabolism of cefotaxime to the desacetyl compound. Cefotaxime clearance was markedly depressed only when renal function fell below a creatinine clearance of 10 ml/min, and drug elimination was unpredictable when the patient also suffered from concurrent severe illness (in one case the half-life was as long as 11.5 h). Others have reported that severe illness alters drug disposition (5) and can greatly reduce overall elimination (4).

Desacetyl cefotaxime would appear to be eliminated almost solely by the kidneys, as the serum half-life was increased to a greater extent in patients with concurrent renal failure. As indicated by multiple dose studies, accumulation occurred to a greater degree with desacetyl cefotaxime than with the parent compound in patients with severe renal failure. Interestingly, concurrent hepatic damage depressed desacetyl cefotaxime formation, but did not affect overall cefotaxime elimination.

In arriving at any conclusions relating to a dosing schedule of an antibiotic the antibacterial activity has to be considered. It is not possible to give a definite dosing schedule but, as many common pathogens are extremely susceptible to cefotaxime (2, 10), and as dosing every 8 to 12 h with 1 g appears to be adequate in clinical trials (7), this would appear to be a reasonable starting point to consider for a dosing schedule for a patient with renal failure. As cefotaxime is eliminated by extrarenal mechanisms (i.e., is metabolized), accumulation hardly occurs with 1-g dosing even when the creatinine clearance falls to 10 ml/min. Below this level of renal function cefotaxime accumulation was only minor. Desacetyl cefotaxime accumulation in patients with severe renal failure after multiple dosing was somewhat more marked, but not excessive (it did not exceed 65 μg/ml even in patients given 1 g twice daily), and was not accompanied by any toxic effects.

When renal function is severely reduced (i.e., a creatinine clearance of 5 ml/min), the half-lives of cefotaxime and its metabolite are extremely variable, and it would appear prudent to reduce dosing to 0.5 g twice daily. Peritoneal dialysis and hepatic necrosis do not materially affect cefotaxime elimination; hence, dosing schedules need not be altered in these conditions. Hemodialysis may require some increase in dose. In all other conditions 1 g of cefotaxime twice daily would appear to be an adequate and safe dosing schedule. Further alterations could be made, for patients without severe renal failure, if indicated by the severity of the infection.

LITERATURE CITED

1. **Bosnes, R. W., and H. H. Tausky.** 1945. On the colorimetric determination of creatinine by the Jaffé reaction. J. Biol. Chem. **158**:581-600.
2. **Fu, K. P., and H. C. Neu.** 1978. Beta-lactamase stability of HR 756, a novel cephalosporin, compared to that of cefuroxime and cefoxitin. Antimicrob. Agents Chemother. **14**:322-326.
3. **Gladtke, E., and H. M. Hattingberg.** 1979. Pharmacokinetics, an introduction, p. 58-59. Springer-Verlag, Berlin.
4. **Hepner, G. W., E. S. Vesell, and K. R. Tantum.** 1978. Reduced drug elimination in congestive cardiac failure. Am. J. Med. **65**:271-276.
5. **Korhonen, U. R., A. J. Jounela, A. J. Pakarinen, P. J. Pentikainen, and J. T. Takkunen.** 1979. Pharmacokinetics of digoxin in patients with acute myocardial infarction. Am. J. Cardiol. **44**:1190-1194.
6. **Levy, G., and M. Gibaldi.** 1975. Pharmacokinetics, p. 6-18. *In* J. R. Gillette and J. R. Mitchell (ed.), Handbook of experimental pharmacology new series: concepts in biomedical pharmacology, vol. 28. Springer-Verlag, Berlin.
7. **McKendrick, M. W., A. M. Geddes, and R. Wise.** 1980. Clinical experience with cefotaxime (HR-756), p. 123-125. *In* J. D. Nelson and C. Grassi (ed.), Current chemotherapy and infectious disease. Proceedings of the 11th International Congress of Chemotherapy and the 19th Interscience Conference on Antimicrobial Agents and

Chemotherapy, vol. 1. American Society for Microbiology, Washington, D.C.

8. **White, L. O., H. A. Holt, D. S. Reeves, M. J. Bywater, and R. P. Bax.** 1980. Separation and assay of cefotaxime (HR-756) and its metabolites in serum, urine, and bile, p. 153–154. *In* J. D. Nelson and C. Grassi (ed.), Current chemotherapy and infectious disease. Proceedings of the 11th International Congress of Chemotherapy and the 19th Interscience Conference on Antimicrobial Agents and Chemotherapy, vol. 1. American Society for Microbiology, Washington, D.C.
9. **Wise, R.** 1978. A review of antibiotic pharmacology, p. 144–150. *In* D. S. Reeves, I. Phillips, J. D. Williams, and R. Wise (ed.), Laboratory methods in antimicrobial chemotherapy. Churchill Livingstone, Edinburgh.
10. **Wise, R., T. Rollason, M. M. Logan, J. M. Andrews, and K. A. Bedford.** 1978. HR756, a highly active cephalosporin: comparison with cefazolin and carbenicillin. Antimicrob. Agents Chemother. 14:807–811.
11. **Wise, R., P. J. Wills, J. M. Andrews, and K. A. Bedford.** 1980. Activity of cefotaxime (HR756) desacetyl metabolite compared with those of cefotaxime and other cephalosporins. Antimicrob. Agents Chemother. 17:84–86.