ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1984, p. 760–763
0066-4804/84/060760-04$02.00/0

Vol. 25, No. 6

Distribution of Ceftazidime in Ascitic Fluid

G. BENONI, E. AROSIO, M. G. RAIMONDI, E. APOLLONI, E. PASSARELLA, A. LECHI, AND G. P. VELO*
Institute of Pharmacology and Clinical Medicine, University of Verona, Policlinico Borgo Roma, 37134 Verona, Italy

Received 20 October 1983/Accepted 27 March 1984

The pharmacokinetics of ceftazidime were investigated in eight normal subjects and eight patients with ascites after intravenous administration of 1 g of the drug. Samples of blood and ascitic fluid were collected for 6 h after dosage, and urine samples were collected for 24 h. Pharmacokinetic data were calculated by using a one-compartment model. The apparent volume of distribution and half-life of elimination ($t_{1/2\beta}$) in patients with ascites were approximately three times those in normal subjects. In contrast, renal clearance was greater in the normal subjects. With respect to ascites, the mean area under the concentration-time curve was 95.3 ± 38.3 μg · h/ml. The mean ratio of the area under the concentration-time curve for ascitic fluid to that for plasma was 69.9% (±38.2). These data show that ceftazidime rapidly diffuses into the peritoneal space, in which concentrations greater than 10 μg/ml were present for at least 6 h.

The results of pharmacokinetic studies of β-lactam antibiotics in different tissue fluids show some discrepancies (2, 5, 9). Since extent of penetration of a β-lactam antibiotic into interstitial fluids is a sound basis for selection for therapy, kinetic studies of spontaneously formed pathological fluids deserve greater attention.

The assay of peritoneal penetration of antibiotics into ascitic fluid allows study of the exchange between the transcellular compartment and the intravascular space. Moreover, this fluid is easily collected. This led to the evaluation recorded in this report of the concentration of ceftazidime in ascitic fluid after parenteral administration. Ceftazidime is a new aminothiazolyl cephalosporin with a marked activity against most gram-negative, β-lactamase-producing bacteria (16).

MATERIALS AND METHODS

Subjects and study design. Eight healthy female volunteers and eight patients with ascites (three males and five females) participated in this study after providing informed consent. The volunteers ranged in age from 25 to 60 years. The patients, two with peritoneal carcinoma and six with hepatic cirrhosis, ranged in age from 42 to 60 years. No patient had a history of hypersensitivity or other adverse reactions to β-lactam antibiotics, and all had normal renal function with averages for blood urea nitrogen of <8 mg/dl, serum creatinine of <105 mg/dl, and glomerular filtration rate of >80 ml/min. Serum albumin concentrations ranged from 2.8 to 3.3 g/dl, and serum bilirubin levels ranged from 0.5 to 3.7 mg/dl. No subject had received a diuretic or antibiotic for at least 1 week before the start of the study. All subjects fasted overnight before the study began and for 1 h after antibiotic administration.

Ceftazidime (Glaxo Laboratories) as the monosodium salt in a 1-g amount was dissolved in 10 ml of saline and injected intravenously over 2 min. An intravenous cannula with a butterfly needle was inserted into the contralateral arm, and a dilute heparin solution was used to maintain the patency of the needle. Serum and ascitic fluid samples (obtained by percutaneous needle abdominal paracentesis) were collected simultaneously.

Collection of blood, peritoneal fluid, and urine. Samples of blood and peritoneal fluid were collected from all patients at 1, 2, 4, and 6 h after drug administration. In addition, peritoneal fluid was collected at 7 and 12 h (three patients), 8.5 h (one patient), and 24 h (two patients). The sampling times were recorded and used in data analysis. Serum was separated by centrifugation at 4°C. Paired serum and ascitic fluid samples were stored at −20°C until they were assayed by the same method at the same time. Urine was collected at 0 to 3, 3 to 6, 6 to 12, and 12 to 24 h after injection of the antibiotic. The urinary volumes were measured, and 10-ml samples were assayed within 96 h.

Antibiotic assay. Ceftazidime concentrations in ascitic fluid, serum, and urine were measured by an agar-well diffusion method (21) with *Proteus morganii* 235 as the test organism. Assay organisms were seeded (0.12 ml of an overnight suspension of 10^6 bacteria per ml) in plates prepared with 65 ml of antibiotic medium 1 (Difco Laboratories). Ceftazidime preparations of certified potency were used for standards. These were prepared in final concentrations of 50, 25, 6.25, 3.13, 1.56, 0.78, 0.39, and 0.18 mg/liter in phosphate buffer (pH 7.0). The sensitivity of the assay method was 0.18 mg/liter, and correlation coefficients of the regression standard curves ranged between 0.94 and 1.00 for replicated curves. Ascitic fluid samples were assayed undiluted, whereas serum and urine samples were diluted in phosphate buffer as necessary to obtain concentrations within the range of the standard curves. All samples were run in duplicate; results were read after 1 night of incubation at 37°C, and inhibition zones were measured and compared with standards. There was no evidence of ceftazidime metabolism, 89% of which was recovered unchanged in the urine (6).

Pharmacokinetic analysis. The elimination rate constant, β, was determined from the regression line of log ceftazidime concentration in serum or ascitic fluid versus time. Serum half-life, $t_{1/2\beta}$, was calculated from the equation $t_{1/2\beta} = 0.693/\beta$. The area under the concentration-time curve (AUC) was measured and C_0 was extrapolated by the method of Magera et al. (13). Plasma clearance (CL_P) was derived from the equation CL_P = dose/AUC. The apparent volume of distribution (V_d) was determined from the equation V_d = dose/AUC × β. Renal clearance (CL_R) was estimated by $CL_R = X_{u_{\Delta t}}/AUC_{\Delta t}$, where $X_{u_{\Delta t}}$ is the amount of ceftazidime recovered unchanged in the urine during a timed collection interval and $AUC_{\Delta t}$ is the AUC during the same interval. The nonrenal clearance was calculated as the difference between plasma and renal clearances (4, 19). Percent penetration of ceftazidime into ascites was calculated by deter-

* Corresponding author.

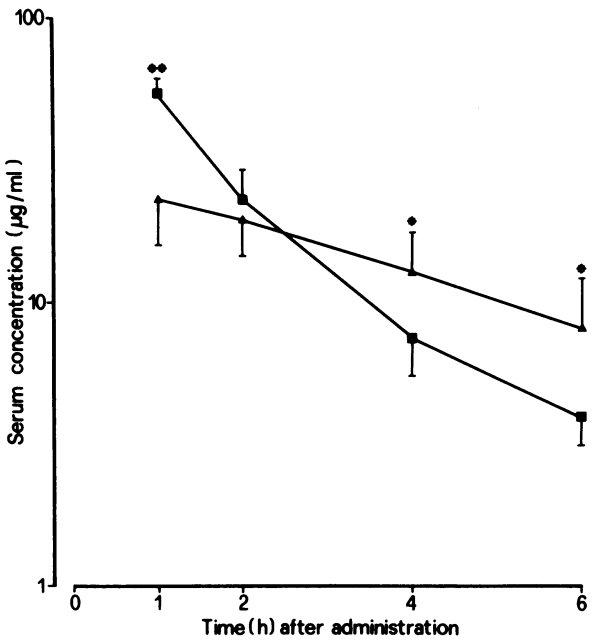

FIG. 1. Mean concentrations of ceftazidime in serum after a 1-g intravenous injection into eight healthy subjects (■) and eight patients with ascites (▲). Bars indicate standard deviations. **, $P < 0.01$; *, $P < 0.05$ by Student's t test.

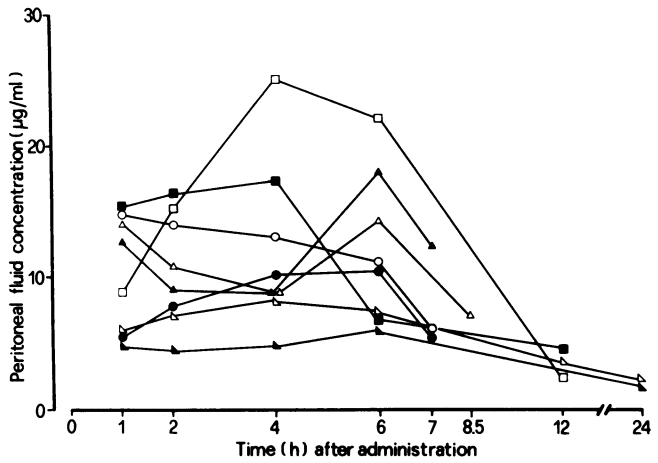

FIG. 2. Concentration of ceftazidime in the peritoneal fluid after a 1-g intravenous injection into eight patients with ascites. Symbols represent results from eight different patients.

mining the ratio of the peritoneal fluid AUC to the serum ceftazidime AUC.

Statistical analysis. Data were expressed as the mean ± the standard deviation, and statistical testing was done by using Student's t test.

RESULTS

The mean concentrations of ceftazidime in serum at different times after administration of the drug to control subjects and patients with ascites are shown in Fig. 1. Pharmacokinetic data are summarized in Table 1. The pharmacokinetics of this drug are more accurately described by a biexponential equation, and thus the pharmacokinetic data of the present study, by monoexponential equation, are only approximate (11). Concentrations of ceftazidime in the serum of controls were significantly greater than those in patients at 1 h, whereas at 4 and 6 h, ceftazidime concentrations in the serum of patients were higher than in volunteers. The plasma elimination half-life was 1.34 h in normal subjects and 4.30 h in patients with ascites. This difference is significant, despite the pronounced intersubject variability. Despite wide ranges in the rates of elimination and distribution volumes in different patients, these pharmacokinetic parameters were significantly different from those of controls. The apparent volume of distribution in patients was about 60% greater than that of controls. Total body clearance was similar for both groups. However, renal clearance values (CL_R), ca. 94% of CL_P in controls and 22% of CL_P in patients, were significantly different. Drug recovery in urine over 24 h amounted to 95% of the dose in controls and 14% in patients (Table 1). In both groups, most of the urinary excretion of ceftazidime occurred during the first 3 h after drug administration. Thus, urinary excretion of ceftazidime is responsible for the almost complete elimination of the drug from the control subjects, whereas in patients with ascites

TABLE 1. Pharmacokinetic data for ceftazidime in normal subjects and in patients with ascites

Subjects	Kinetics in serum				Clearance (ml/min)			Kinetics in ascites			% Elimination in urine	
	β (h^{-1})	$t_{1/2\beta}$ (h)	AUC[a] (μg · h/ml)	V_d (liter)	Plasma	Renal	Nonrenal	β (h^{-1})	AUC (μg · h/ml)	Penetration (%)	0–3 h	0–24 h
Normal (n = 8)												
Mean	0.52	1.34	152	13.5	109	103	6.48				45.1	95.5
SD	0.04	0.09	20.2	2.02	15.0	13.7	5.60				12.6	4.55
Range	0.48–0.60	1.16–1.44	126–188	11.2–16.5	88.3–131	95.6–130	1.30–17.1				28.5–65	86.5–99
Patients (n = 8)												
Mean	0.23	4.30	163	36.7	123	27.2	100	0.28	95.3	69.9	9.0	14.7
SD	0.12	3.04	87.8	13.6	53.4	18.1	51.3	0.18	38.3	38.2	5.3	7.0
Range	0.07–0.35	1.94–9.48	83.8–355	21.4–63.4	46.6–198	11.7–55.2	31.5–165	0.06–0.59	46.0–172	29.5–126	2.7–17.8	6.6–24.5
Significance (P)[b]	<0.001	<0.02	NS[c]	<0.001	NS	<0.001	<0.001				<0.001	<0.001

[a] AUC, Area under serum and ascites concentration-time curve (0 to ∞).
[b] Statistical significances refer to Student's t test.
[c] NS, Not significant.

this process is delayed because the ascitic fluid acts as a drug reservoir.

Ceftazidime concentrations in the peritoneal fluid are shown in Fig. 2. In two patients, ceftazidime peritoneal fluid concentrations greater than 2 μg/ml were measured for at least 24 h after administration, and in four patients, drug levels greater than 4 μg/ml were measured for nearly 8 h. Maximum levels in ascitic fluid were attained between 4 and 6 h after administration. The drug penetrated rapidly into the peritoneal fluid, and at 1 h, the concentrations were about one-half those in serum. The percent penetration of ceftazidime into the peritoneal fluid, calculated as peritoneal fluid-to-serum AUC ratio, averaged 69.9, with a range of 30 to 126 for all eight patients. Percentages for only two of these eight patients were less than 50% (Table 1).

There was a positive correlation between the peritoneal fluid-to-serum level ratio and time (Fig. 3). The regression analysis yields a correlation coefficient of 0.61 ($n = 32$, $P < 0.001$, $y = 0.14x + 0.26$).

DISCUSSION

The direct measurement of antibiotics in various fluid compartments is theoretically the best method to investigate their tissue penetration as the apparent volume of distribution. Although it is considered a reliable measurement for extravascular distribution of the drug, it does not provide information about specific organs and tissues. Accordingly, antibiotic penetration into pathological fluid effusions, such as that in ascites, in various spaces has been investigated (1, 14).

In the current study the apparent volume of ceftazidime distribution was significantly higher in ascitic patients than in control subjects. This finding is consistent with those for other β-lactam antibiotics described by Simon et al. (20) and by Wittman et al. (24).

Ceftazidime has very favorable pharmacokinetic properties (7). Protein binding in human serum averages ca. 20%. The serum half-life of ceftazidime is longer than that of most other β-lactam antibiotics, thereby ensuring prolonged high levels of free drug in the serum. In agreement with Wittman et al. (24), we found that the serum half-life of ceftazidime is longer in patients with ascites than in control subjects. Our data suggest rapid diffusion of ceftazidime into ascitic fluid, the result of low serum protein binding (18), molecular size, and electrostatic charge. High levels of ceftazidime in peritoneal fluid were found within 1 h after administration. This suggests that peritoneal fluid rapidly balances with the vascular compartment. In this dynamic balance, the inflow from the intravascular space into the ascitic fluid is more important than the outflow. As a consequence, the antibiotic is eliminated from ascitic fluid more slowly than from serum. Its accumulation in the ascites may be predicted in the case of a multiple-dosage regimen. In fact, despite the great variability in the group of ascitic patients, total clearance is similar to that of control subjects, whereas renal clearance is greater in normal subjects than in patients. The levels of ceftazidime in the ascitic fluid show an elevated interindividual variability, probably due to the influence of the factors governing entry processes into this compartment, namely, the volume of the ascitic fluid, hypoproteinemia, and anemia (23).

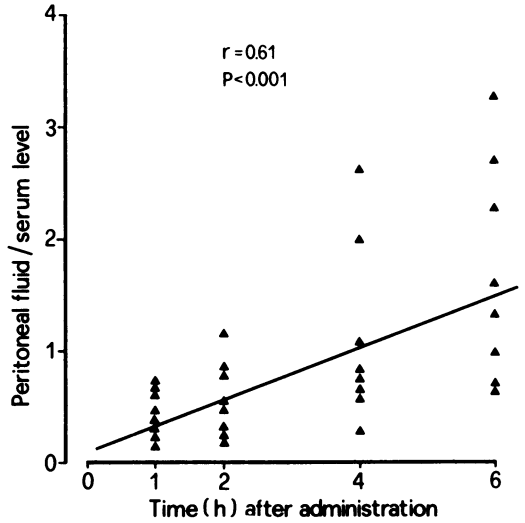

FIG. 3. Ratio of ceftazidime concentration in peritoneal fluid to that in serum as a function of time. Symbols show results for eight different patients at the times indicated.

In a study similar to this on ampicillin administered intravenously, Lewis and Jusko (12) found that cirrhotic patients had lower initial drug concentrations in plasma because of a larger distribution volume. Metabolic-biliary clearance of ampicillin was three times as great in cirrhotic patients, whereas ampicillin clearance from the peritoneal cavity was very slow.

Finally, the observed data deserve a comment from a therapeutic point of view. In the ascitic fluid, a concentration of 10 μg of ceftazidime per ml was maintained for over 6 h. This concentration is sufficient to inhibit the growth of members of the family *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and most other aerobic pathogens, *Streptococcus faecalis* excepted (15, 22). In different cases, the peritoneal fluid may be involved in infectious diseases such as infections secondary to abdominal surgery (C. R. R. Corbett, R. S. McFarland, G. R. Spencer, and D. M. Ryan, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami Beach, Fla., abstr. no. 809, 1982). In outpatients undergoing chronic peritoneal dialysis, some authors have described pseudomonas peritonitis secondary to catheter infection (8) or bacterial contamination of the disinfectant solution (17). As with other β-lactam antibiotics (3, 10), the high diffusion of ceftazidime into ascitic fluid ensures maintenance of therapeutic levels and thereby favors clinical success in the treatment of peritoneal infections.

LITERATURE CITED

1. **Chalas, J., D. Lebayle, J. Macarrio, D. Barrand, A. Lindenbaum, C. Buffet, and J. C. Chaput.** 1980. Métabolisme et cinétique de l'élimination de l'ampicilline dans la cirrhose. Conséquences therapeutiques. Sem. Hop. **56**:464–467.
2. **Eickenberg, H. U.** 1980. Interstitial concentration of antibiotics and their significance for an adequate dosage. Infection **8**(Suppl. 1):39–44.
3. **Garcia, M. J., A. Dominguez-Gil, F. Diaz Perez, F. Perez Rodriguez, and F.Dominguez Moronta.** 1981. Disposition of cefoxitin in patients with ascites. Eur. J. Clin. Pharmacol. **20**:371–374.
4. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics. Marcel Dekker, New York.
5. **Gillett, A. P., and R. Wise.** 1978. Penetration of four cephalosporins into tissues fluid in man. Lancet **i**:962–964.
6. **Harding, S. M., A. J. Monro, J. E. Thornton, S. Ayrton, and M. I. J. Hogg.** 1981. The comparative pharmacokinetics of ceftazidime and cefotaxime in healthy volunteers. J. Antimicrob. Chemother. **8**(Suppl. B):263–272.
7. **Hoffstedt, B., and M. Walder.** 1981. Penetration of ceftazidime

into extracellular fluid in patients. J. Antimicrob. Chemother. 8(Suppl. B):289–292.
8. **Krothapalli, R., W. B. Duffy, C. Lacke, W. Payne, H. Patel, V. Perez, and H. O. Senekjian.** 1982. *Pseudomonas* peritonitis and continuous ambulatory peritoneal dialysis. Arch. Intern. Med. **142**:1862–1863.
9. **Laber, G., E. Schütze, R. Leskova, R. Kolb, and A. Georgopoulos.** 1980. A diffusion chamber technique for measuring concentrations of antibiotics in interstitial fluid. Infection **8**:58–62.
10. **Lechi, A., E. Arosio, L. Xerri, C. Mengoli, G. Montesi, and O. Ghidini.** 1982. The kinetics of cefuroxime in ascitic and pleural fluid. Int. J. Clin. Pharmacol. Ther. Toxicol. **20**:493–496.
11. **Leeder, J. S., M. Spino, A. M.Tesoro, and S. M. MacLeod.** 1983. High-pressure liquid chromatographic analysis of ceftazidime in serum and urine. Antimicrob. Agents Chemother. **24**:720–724.
12. **Lewis, G. P., and W. J. Jusko.** 1975. Pharmacokinetics of ampicillin in cirrhosis. Clin. Pharmacol. Ther. **18**:475–484.
13. **Magera, B. E., J. C. Arroyo, S. J. Rosansky, and B. Postic.** 1983. Vancomycin pharmacokinetics in patients with peritonitis on peritoneal dialysis. Antimicrob. Agents. Chemother. **23**:710–714.
14. **Moreau, L., H. Durand, and P. Biclet.** 1980. Cefotaxime concentrations in ascites. J. Antimicrob. Chemother. **6**(Suppl. A):121–122.
15. **Neu, H. C.** 1981. In vitro activity of ceftazidime, a β-lactamase stable cephalosporin. J. Antimicrob. Chemother. **8**(Suppl. B):131–134.
16. **O'Callaghan, C. H., P. Acred, P. B. Harper, D. M. Ryan, S. M. Kirby, and S. M. Harding.** 1980. GR 20263, a new broad-spectrum cephalosporin with antipseudomonal activity. Antimicrob. Agents Chemother. **17**:876–883.
17. **Parrott, P. L., P. M. Terry, E. N. Whitworth, L. W. Frawley, and R. S. Coble.** 1982. *Pseudomonas aeruginosa* peritonitis associated with contaminated poloxamer-iodine solution. Lancet **ii**:683–685.
18. **Peterson, L. R., and D. N. Gerding.** 1980. Influence of protein binding of antibiotics on serum pharmacokinetics and extravascular penetration: clinically useful concepts. Rev. Infect. Dis. **2**:340–350.
19. **Rowland, M., and T. N. Tozer.** 1980. Clinical pharmacokinetics. Concepts and applications. Lea & Febiger, Philadelphia, Pa.
20. **Simon, C., V. Malerczyk, U. Müller, and G. Müller.** 1972. Zur Pharmakokinetik von Propicillin bei geriatrischen Patienten im Vergleich zu jüngeren Erwachsenen. Dtsch. Med. Wochenschr. **97**:1999–2003.
21. **Trager, G. M., G. W. White, V. M. Zimelis, and A. P. Panwalker.** 1979. LY-127935, a novel beta-lactam antibiotic with unusual antibacterial activity. Antimicrob. Agents Chemother. **16**:297–300.
22. **Verbist, L., and J. Verhaegen.** 1980. GR 20263, a new aminothiazolyl cephalosporin with high activity against *Pseudomonas* and *Enterobacteriaceae*. Antimicrob. Agents Chemother. **17**:807–812.
23. **Wilson D. E., T. C. Chalmer, and M. A. Madaff.** 1967. The passage of cefalothin into and out of ascitic fluid. Am. J. Med. Sci. **253**:449–452.
24. **Wittmann, D. H., H. H. Schassan, F. Kohler, and W. Seibert.** 1981. Pharmacokinetic studies of ceftazidime in serum, bone, bile, tissue fluid and peritoneal fluid. J. Antimicrob. Chemother. **8**(Suppl. B):293–297.