ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1984, p. 201–204
0066-4804/84/020201-04$02.00/0

Vol. 25, No. 2

Pharmacokinetics of Ceftazidime in Patients with Renal Insufficiency

LYNDA S. WELAGE,[1,2] ROBERT W. SCHULTZ,[3] AND JEROME J. SCHENTAG[2,4]*

Division of Clinical Pharmacy Science[1] and Department of Pharmaceutics,[4] School of Pharmacy, State University of New York, and Department of Medicine[3] and Clinical Pharmacokinetics Laboratory,[2] Millard Fillmore Hospital, Buffalo, New York 14209*

Received 22 July 1983/Accepted 21 November 1983

The pharmacokinetics of ceftazidime were studied in 14 adult volunteers with different degrees of renal function. The elimination of ceftazidime was totally dependent on renal excretion. The clearance of ceftazidime ranged from 7.5 to 145.1 ml/min and correlated with both renal ceftazidime clearance and creatinine clearance (Cl_{CR}). It is recommended that 0.5 to 2.0 g of ceftazidime be given in extended dosages, with intervals dependent on the renal function of the patient. Patients with a Cl_{CR} of >50 ml/min should be given ceftazidime every 8 h, those with a Cl_{CR} of 30 to 50 ml/min should be given the drug every 12 h, those with a Cl_{CR} of 15 to 30 ml/min should be given the drug once a day, and individuals with a Cl_{CR} of <15 ml/min should be given the drug on a 36- to 48-h regimen.

Ceftazidime is a beta-lactamase-stable cephalosporin with a high degree of activity against a broad spectrum of organisms including: streptococci, staphylococci, and *Neisseria, Haemophilus, Salmonella, Serratia, Enterobacter, Klebsiella*, indole-positive *Proteus*, and *Pseudomonas* species (1, 6, 7, 9). Its potential use includes a wide variety of infections caused by these pathogens.

In subjects with normal renal function, ceftazidime is primarily excreted by glomerular filtration (1, 4, 5, 10, 12). This study was performed to determine the pharmacokinetics of ceftazidime in patients with renal insufficiency and to employ this data to predict appropriate dosages for similar patients.

MATERIALS AND METHODS

After informed consent was obtained, the elimination kinetics of ceftazidime were studied in 14 adult volunteers with different degrees of renal function, 12 men and 2 women, ranging in age from 27 to 91 years. Demographic characteristics of these patients are shown in Table 1. Premenopausal women, individuals with hepatic dysfunction as determined by abnormal liver function tests or an elevated bilirubin (greater than three times normal), congestive heart failure, hematocrit of less than 22%, and individuals with a history of any drug allergy were excluded. The patients received no other cephalosporin antibiotics while participating in this study. Creatinine clearances (Cl_{CR}s) were determined with 24-h urine collections on at least two separate occasions. Laboratory examinations, including complete blood counts, blood chemistry screening, and urinalyses, were performed both before the study and upon completion of the study.

Dosing and sampling. After fasting for 8 h, subjects were given 1.0 g of ceftazidime intravenously over 2 to 3 min. Blood samples (5.0 ml each) were obtained from an indwelling catheter immediately before the administration of ceftazidime and at 0, 5, 15, and 30 min and at 1, 2, 4, 5, 6, 8, 12, and 24 h. An additional blood sample was collected at 48 h from patients with Cl_{CR}s of less than 75 ml/min. After blood samples were allowed to clot for ca. 1 h, samples were centrifuged, and the serum was separated and frozen at −70°C until assayed.

Urine specimens were collected before ceftazidime administration and at 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h. Additional urine specimens were collected from subjects with Cl_{CR}s of less than 75 ml/min at the following time intervals: 24 to 36 and 36 to 48 h. All urine samples were frozen at −70°C until assayed.

Assay. High-pressure liquid chromatography (HPLC) was performed with a Dupont Zorbax Sil column (4.6 mm by 25 cm). All reagents were HPLC-analytical grade. The mobile phase consisted of 87% 0.1 M sodium acetate buffer, 9.0% methanol, and 4.0% acetonitrile. The 0.1 M acetate buffer was prepared by adding 109 ml of 0.1 M sodium acetate trihydrate to 891 ml of 0.1 M glacial acetic acid, with a resulting buffer pH of 3.8 at 25°C. A Waters 6000A solvent delivery system was used to pump the mobile phase at a flow rate of 1.0 ml/min, and the effluent was monitored by UV absorbance with a Schoeffel model 770 detector set at 254 nm.

Extraction of serum, plasma, or diluted urine was performed by mixing 100 μl of perchloric acid with 0.5 ml of sample and 250 μl of cephaloridine (50 μg/ml) as the internal standard. The mixture was vigorously vortexed for 30 s and then centrifuged at 2,000 rpm for 20 min. The supernatant (10 μl) was injected onto the column. Urine samples were prepared in a similar manner after diluting the samples 25- to 50-fold with deionized distilled water.

A representative chromatogram is shown as Fig. 1. By HPLC assay, samples ranging in concentration from 0.5 to 100 μg/ml were assayed. The maximum within-day coefficient of variation was 1.4% and the between-day coefficient of variation was 6.2%. Sensitivity of this procedure is 0.5 μg/ml with retention times of 10.5 and 14.2 min for ceftazidime and cephaloridine, respectively.

Pharmacokinetic analysis. Ceftazidime concentrations in serum were analyzed by noncompartmental analysis (8). The area under the curve for serum concentration versus time was employed to determine clearance, serum half-life, and volume of distribution at steady state (V_{dss}) as previously described (8). Renal clearance was determined by urinary excretion rate divided by the midpoint serum concentration, and ceftazidime clearance parameters were plotted versus

* Corresponding author.

TABLE 1. Demographic data on the 14 study patients

Patient no.	Age (yrs), sex	Ht (cm)	Wt (kg)	S_{CR} (mg/dl)[a]	Cl_{CR} (ml/min)[b]
1	73 F	172.7	57.1	8.5	4.5
2	51 M	177.8	92.7	7.5	9.1
3	60 M	177.8	80.9	2.8	21.5
4	73 M	172.7	72.3	3.6	24.0
5[c]	91 M	177.8	65.0	1.9	29.5
6	27 M	198.1	91.4	4.3	29.5
7	65 F	160.0	93.0	1.7	34.0
8	51 M	177.8	88.2	2.1	38.1
9	68 M	177.8	86.4	2.3	41.5
10	69 M	175.3	90.9	2.4	48.7
11	49 M	180.3	94.1	1.6	53.3
12	50 M	167.6	73.6	1.4	69.5
13	36 M	167.6	88.6	1.1	109.5
14	30 M	177.8	94.6	1.0	122.3

[a] S_{CR}, Serum creatinine.
[b] Each Cl_{CR} value is the average of two measurements on 24-h collections.
[c] The height and weight of patient 5 were estimated.

Cl_{CR} (8). Nonrenal clearance was determined by ceftazidime total clearance minus renal clearance and from the relationship of ceftazidime clearance to Cl_{CR} (8).

RESULTS

The intravenous bolus dose of ceftazidime actually administered ranged from 833.3 to 1,000 mg, and concentrations of ceftazidime in serum declined in biexponential fashion. During the elimination phase, ceftazidime concentrations in serum increased with decreasing renal function as shown in Fig. 2.

The average V_{dss} of ceftazidime based on ideal body weight was 0.28 liters/kg (range = 0.10 to 0.33 liters/kg) as shown in Table 2. V_{dss} did not change in relation to renal function. The dose-adjusted area under the plasma concentration time curve ranged from 114.9 to 2,233.8 μg · h/ml and increased in proportion to reductions in renal function.

The elimination half-life of ceftazidime increased with decreased Cl_{CR} (Fig. 3). The average elimination half-life of ceftazidime was 1.6 h in subjects with normal renal function and the half-life increased to 24.6 h in subjects with severe renal impairment (Cl_{CR} = 4.5 ml/min).

Total body clearance of ceftazidime ranged from 7.5 to 145.1 ml/min and correlated with both renal clearance of ceftazidime (r = 0.95) and with Cl_{CR} (r = 0.93) as shown in Fig. 4 and 5. Renal clearance of ceftazidime was highly correlated with Cl_{CR} (r = 0.95) and ranged from 6.9 to 121.2 ml/min. Nonrenal clearance, as determined by ceftazidime total clearance minus renal clearance, ranged from 0 to 62.3 ml/min (Table 2). The relationship of ceftazidime total clearance to Cl_{CR} yielded a nonrenal clearance of 6.59 ml/min. Cumulative urinary recovery of ceftazidime ranged from 45 to 100% of the dose, with an average recovery of 73.5%. Cumulative urine recovery did not correlate with renal function.

DISCUSSION

Ceftazidime pharmacokinetics are primarily dependent upon the degree of renal function. Gower et al., have demonstrated that glomerular filtration of unchanged ceftazidime is the major route of elimination, and have demonstrated a prolongation in its serum half-life with decline in Cl_{CR} (2).

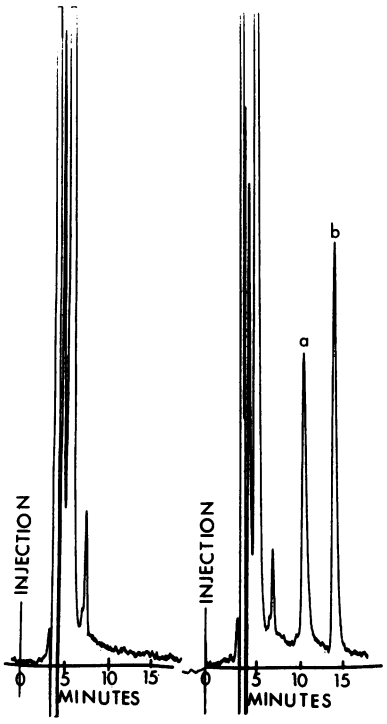

FIG. 1. Chromatograms obtained for perchloric acid-treated blank plasma (left) and plasma spiked with ceftazidime (15 μg/ml) and processed in the normal manner (right). Peak a, ceftazidime peak; peak b, cephaloridine (internal standard).

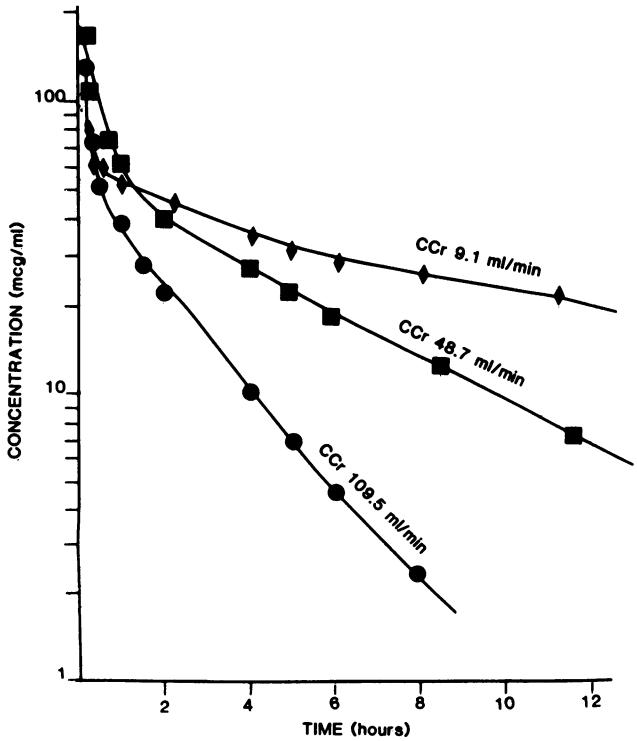

FIG. 2. Plasma concentrations of ceftazidime after a 1.0-g intravenous dose in three representative patients with different degrees of renal function.

TABLE 2. Pharmacokinetic parameters of the 14 study subjects

Patient no.	AUC[a] (μg · h/ml)	$t_{1/2}$ (h)	Clearance (ml/min)			V_{dss} (liters/kg)	Urinary recovery (%)
			Renal	Nonrenal	Total		
1	2233.8	24.6	5.40	2.10	7.5	0.26	72
2	1138.5	19.6	6.71	7.89	14.6	0.33	45
3	443.2	4.8	34.73	2.87	37.6	0.20	92
4	603.3	10.0	19.72	7.88	27.6	0.33	71
5	677.7	3.6	15.33	9.27	24.6	0.10	62
6	603.4	6.6	19.59	8.01	27.6	0.15	71
7	293.1	4.0	47.46	9.44	56.9	0.34	83
8	312.0	3.0	28.05	25.35	53.4	0.16	53
9	318.1	4.3	45.68	6.72	52.4	0.23	87
10	351.8	3.8	45.85	1.55	47.4	0.20	97
11	404.2	3.1	33.55	7.65	41.2	0.14	81
12	236.0	2.0	39.10	31.50	70.6	0.15	55
13	189.8	1.8	88.00	0.00	87.8	0.17	100
14	114.9	1.5	82.80	62.30	145.1	0.22	55

[a] AUC, Area under the curve.

The V_{dss} of ceftazidime has been reported to average 0.21 liters/kg in normal healthy adults (10). Increases in V_{dss} have been reported in patients with renal failure secondary to a decrease in plasma protein binding (11). However, owing to the low protein binding of ceftazidime (ca. 10%), its V_{dss} was not expected to change in patients with renal failure. This hypothesis was supported by our results.

Incomplete and variant urinary ceftazidime recovery may be explained by several hypotheses: (i) 48-h urine collection was inadequate to collect 100% of the excreted dose, (ii) degradation of ceftazidime in urine and blood may occur either in vivo or in vitro, (iii) ceftazidime may be metabolized, or (iv) the drug may be excreted through an alternate pathway such as bile. Hypothesis (iii) is unlikely because no metabolites of ceftazidime have been identified either by HPLC assay or by bioautography (3). Since fecal ceftazidime concentrations were not measured, it is impossible to rule out bilary excretion as an elimination pathway. However, Harding has reported 1% biliary excretion after a 2-g intravenous ceftazidime injection (3). The 48-h urine collection was shown to be inadequate in patients with severe renal insufficiency, as there was a plateau in cumulative urinary excretion in all but three patients by 48 h. Ceftazidime was detectable in urine and serum at the completion of the study in seven patients. Harding similarly has reported cumulative ceftazidime urinary recovery to be 83% and explains the loss of drug by its instability before assay (3). Thus, it seems the most likely explanation for the incomplete urinary recovery in our study appears to be ceftazidime degradation.

Since ceftazidime is predominantly excreted in urine, it will be important to reduce the dose when treating individuals who may have renal failure. Based on the correlation found between ceftazidime clearance and Cl_{CR}, simple alterations in the dosage interval can be made to accommodate decreases in renal function. If peak concentrations equivalent to those obtained in patients with normal renal function (given the recommended standard regimen of 0.5 to 2.0 g every 8 h) are desired in patients with renal insufficiency, then the interval between the maintenance doses should be

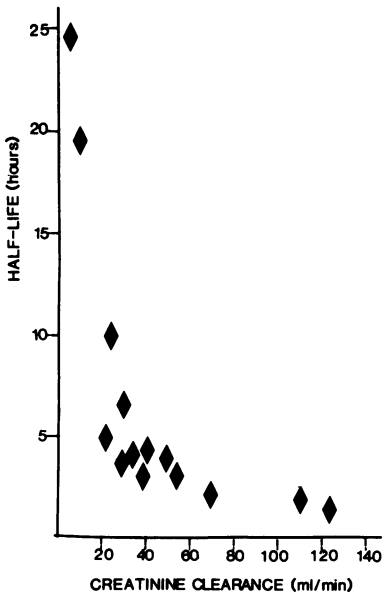

FIG. 3. Relationship between serum elimination half-life (hours) and Cl_{CR} (milliliters per minute).

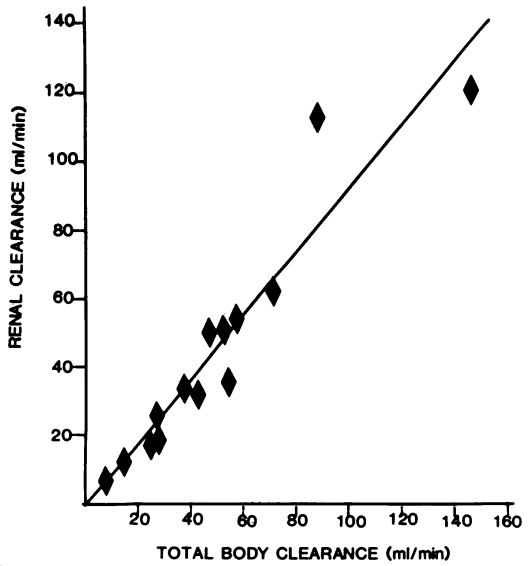

FIG. 4. Relationship between renal clearance of ceftazidime and ceftazidime total body clearance in 14 healthy subjects. Regression line is: slope = 0.95, intercept = −1.17 ($P < 0.001$).

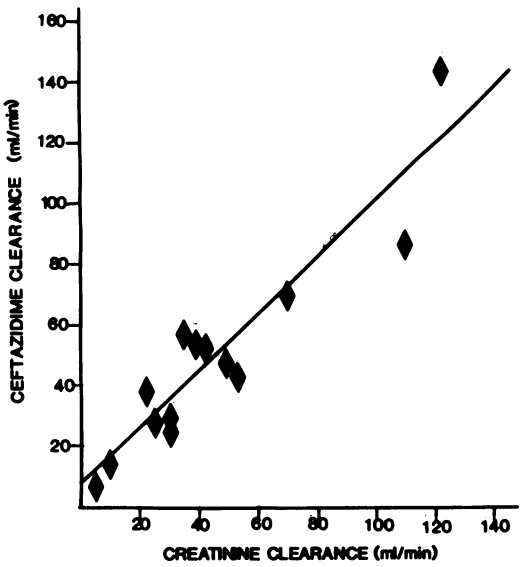

FIG. 5. Relationship between total body clearance and Cl_{CR}. The regression line is: slope = 0.95, intercept = 6.59 ($P < 0.001$).

prolonged. For patients similar to those studied here, patients with Cl_{CR}s of 30 to 50 ml/min should receive a standard maintenance dose (0.5 to 2.0 g) of ceftazidime every 12 h, and individuals with Cl_{CR}s of 15 to 30 ml/min should be given the dose once a day. Patients with Cl_{CR}s of less than 15 ml/min should receive ceftazidime every 36 to 48 h, or alternatively, one-half of the dose every 24 h. Since ceftazidime has not been associated with dose-related adverse effects, dosage recommendations can be substantially rounded to times convenient to clinical practice. More precise dosage regimens can be calculated from the correlation between Cl_{CR} and ceftazidime clearance ($Cl = 0.95\ Cl_{CR} + 6.59$) as shown in Fig. 5.

In conclusion, ceftazidime is totally dependent on renal function for its excretion, and thus its maintenance doses should be reduced in direct proportion to declines in Cl_{CR}. As renal function is relatively easy to quantify, dosage regimens of renally excreted agents can be readily determined.

ACKNOWLEDGMENTS

This study was supported in part by Public Health Service grant 20852 from the National Institute of General Medical Sciences and by a grant-in-aid from Glaxo, Inc.

We gratefully acknowledge the technical support of S. A. Boudinot.

LITERATURE CITED

1. **Daikos, G. K., J. Kosmidis, C. Stathakis, H. Glamarellou, E. Douzinas, S. Kastanakis, and B. Papathanassiou.** 1981. Ceftazidime: therapeutic results in various infections and kinetic studies. J. Antimicrob. Chemother. 8(Suppl. B):331–337.
2. **Gower, P. E., P. M. Hobbs, and S. M. Harding.** 1981. Kinetics of ceftazidime in renal impairment, p. 498–499. *In* P. Periti and C. G. Grassi (ed.), Current chemotherapy and immunotherapy: proceedings of the 12th International Congress of Chemotherapy. American Society for Microbiology, Washington, D.C.
3. **Harding, S. M.** 1981. Clinical pharmacology of ceftazidime, p. 495–498. *In* P. Periti and C. G. Grassi (ed.), Current chemotherapy and immunotherapy: proceedings of the 12th International Congress of Chemotherapy. American Society for Microbiology, Washington, D.C.
4. **Harding, S. M., J. Ayrton, J. E. Thornton, A. J. Munro, and M. I. J. Hogg.** 1981. Pharmacokinetics of ceftazidime in normal subjects. J. Antimicrob. Chemother. 8(Suppl. B):261.
5. **Harding. S. M., A. J. Monro, J. E. Thornton, J. Ayrton, and M. I. J. Hogg.** 1981. The comparative pharmacokinetics of ceftazidime and ceftotaxime in healthy volunteers. J. Antimicrob. Chemother. 8(Suppl. B):263–272.
6. **Harper, P. B.** 1981. The in-vitro properties of ceftazidime. J. Antimicrob. Chemother. 8(Suppl. B):5–13.
7. **Jones, R. N., A. L. Barry, C. Thornberry, E. H. Gerlach, P. C. Fuchs, T. L. Gavan, and H. M. Sommers.** 1981. Ceftazidime, a pseudomonas-active cephalosporin: in-vitro antimicrobial activity evaluation including recommendations for disc diffusion susceptibility tests. J. Antimicrob. Chemother. 8(Suppl. B):187–211.
8. **Jusko, W. J.** 1980. Guidelines for collection and pharmacokinetic analysis of drug disposition data, p. 639–680. *In* W. E. Evans, J. J. Schentag, and W. J. Jusko (ed.), Applied pharmacokinetics. Applied Therapeutics, Inc., San Francisco.
9. **Knothe, H., and G. A. Dette.** 1981. The in-vitro activity of ceftazidime against clinically important pathogens. J. Antimicrob. Chemother. 8(Suppl. B):33–41.
10. **Lüthy, R., J. Blaser, A. Bonetti, H. Simmen, R. Wise, and W. Siegenthaler.** 1981. Comparative multiple-dose pharmacokinetics of cefotaxime, moxalactam, and ceftazidime. Antimicrob. Agents Chemother. 20:567–575.
11. **Welling, P. G., and W. A. Craig.** 1976. Pharmacokinetics in disease states modifying renal function, p. 155–188. *In* L. Z. Benet (ed.), The effect of disease states on drug pharmacokinetics. American Pharmaceutical Association, Washington, D.C.
12. **Wittman, 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):292–297.