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Disposition of Ceftazidime in Surgical Patients with Intra-Abdominal Infection

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The disposition of ceftazidime was assessed in 11 surgical patients with suspected intra-abdominal infection. All patients had normal hepatic function, and creatinine clearances ranged from 43 to 186 ml/min. Patients received 2 g of ceftazidime intravenously every 8 h. Trough and peak concentrations in serum were measured on day 2, and trough and postdose concentrations in serum were determined on 10 samples collected during a dosage interval between days 3 and 6 of therapy. Ceftazidime peak and trough concentrations in serum at steady state determined by high-performance liquid chromatography were 257.4 ± 122.0 (mean ± standard deviation) and 13.1 ± 20.6 mg/liter. The serum-concentration-versus-time profile was multiexponential. The elimination half-life, steady-state volume of distribution, and total body clearance were 2.52 ± 1.39 h, 0.31 ± 0.12 liter/kg, and 0.11 ± 0.05 liter/h per kg, respectively. Total predicted body clearance significantly correlated with the measured values ($r = 0.868$; $P = 0.001$). The disposition of ceftazidime is dependent on creatinine clearance and is not significantly altered by surgery or acute infectious processes.

The treatment of intra-abdominal infections generally requires surgical intervention and concomitant antimicrobial therapy with agents active against gram-negative enteric bacilli as well as anaerobic bacteria (1, 13). Ceftazidime exhibits extensive antimicrobial activity against gram-negative and gram-positive organisms and has demonstrated efficacy in the treatment of severe infections (4). Thus, ceftazidime plus an antianaerobic agent may be a useful antibiotic combination for the management of intra-abdominal infection.

The disposition of ceftazidime has been significantly correlated with renal function in uninfected subjects with impaired renal function (7, 14, 17). However, the half-life and clearance of ceftazidime derived from these relationships have been reported to correlate poorly with measured values in infected oncology patients (11) and febrile patients with septicemia (3). This phenomenon has also been reported for aztreonam, imipenem, and netilmicin in acutely ill patients (2, 3, 8). This study was designed to characterize the serum-concentration-time profile of ceftazidime at steady state in infected surgical patients receiving ceftazidime and clindamycin. We also assessed the accuracy with which the pharmacokinetic parameters (half-life and clearance) of ceftazidime in these patients could be predicted from the relationships of these parameters to creatinine clearance derived from studies in noninfected volunteers (10, 14).

MATERIALS AND METHODS

This study was approved by the Research Advisory Committee of Hennepin County Medical Center, Minneapolis, Minn. Eleven patients 18 years of age or older with suspected intra-abdominal sepsis and no known hypersensitivity to cephalosporins or clindamycin participated in the study after granting written informed consent. A medical history, physical examination, and hematological and biochemical screening profile were completed for each patient before participation in the study. Patients with renal dysfunction as manifested by a serum creatinine greater than 3 mg/dl were excluded. All patients had surgery for suspected intra-abdominal infection before or within 24 h of starting antimicrobial therapy with 2 g of ceftazidime intravenously (i.v.) every 8 h and 900 mg of clindamycin i.v. every 8 h. The ceftazidime (Glaxo Inc., Research Triangle Park, N.C.) dose was diluted in 20 ml of 0.9% sodium chloride and infused into a forearm vein over a 5-min period.

Blood samples were drawn immediately before and 5 min after the end of infusion of the morning dose on day 2 of therapy. On one occasion between days 3 and 6 of therapy, multiple blood samples (7 ml) were collected via a heparin lock or direct venipuncture from a forearm vein in the arm contralateral to that used for drug administration. These samples were taken immediately before administration of the dose and at 0, 10, and 20 min and 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 h after the end of the i.v. infusion. The blood samples were allowed to clot at room temperature, and serum was separated and stored at −70°C until analysis.

The concentration of ceftazidime in serum was determined by the specific reverse-phase high-performance liquid chromatographic technique modified by Leeder et al. (9). The chromatographic system consisted of a U6K injection port, a 6000 A pump, a Lambda Max 480 UV detector set at 254 nm, and a 730 data module recording integrator (Waters Associates, Inc., Milford, Mass.). The column was a C-18 μBondapak (250 by 4.6 mm; 10-μm particle size). The mobile phase consisted of 880 ml of 0.15 M KH_2PO_4 with pH adjusted to 6.5 and 120 ml methanol. Serum samples (0.2 ml) were mixed with sodium tungstate and sulfuric acid. The samples were then neutralized with sodium acetate. After centrifugation (15 min at 4°C; 1,500 × *g*), the clear supernatant (10 to 20 μl) was injected into the column. The intraday and interday coefficients of variation for ceftazidime concentrations in serum were less than 5% for both low (15.5 mg/liter)- and high (206.1 mg/liter)-quality control samples. The lower and upper detection limits were 1 and 500 mg/liter.

The ceftazidime serum-concentration-versus-time profile

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TABLE 1. Demographic characteristics of patients

Patient	Sex[a]	Age (yr)	Wt (kg)	CL_{CR} (ml/min)
1	M	62	73.0	88
2	M	39	92.6	186
3	M	21	67.3	101
4	F	82	50.1	43
5	M	64	101.8	72
6	M	23	36.3	59
7	M	23	74.1	120
8	M	29	56.6	145
9	F	81	66.1	51
10	M	34	88.1	144
11	M	38	62.0	73
Mean		45.1	69.8	98.4
SD		23.1	19.2	45.5

[a] M, Male; F, female.

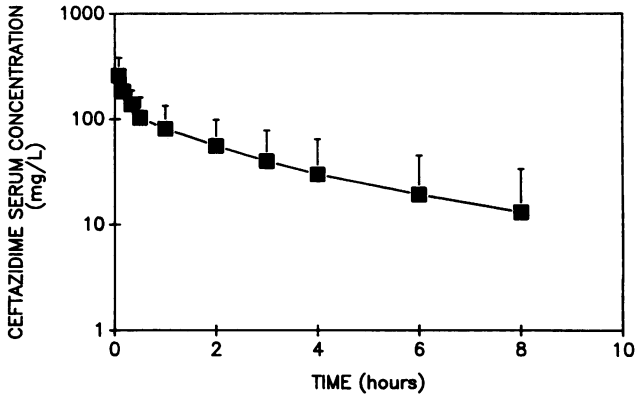

FIG. 1. Serum-concentration-versus-time profile of ceftazidime in patients (n = 11) after i.v. ceftazidime administration. Data are expressed as the mean ± standard deviation (bars).

after i.v. administration was analyzed in terms of the following equation:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_t is the concentration in serum at time t, A and B are the intercepts, and α and β are the hybrid disposition rate constants obtained from the first and second phases, respectively, of the plot of log ceftazidime concentration in serum versus time. Initial estimates of the parameters were obtained by a standard curve-stripping procedure. Nonlinear regression analysis with the program PCNONLIN on a microcomputer was used to obtain final estimates of the pharmacokinetic parameters (15). The coefficients of the biexponential equation were corrected to values reflecting a single i.v. bolus (5, 14). The area under the ceftazidime serum-concentration-versus-time curve during the dosing interval ($AUC_{ss\ 0-\tau}$) was calculated by linear trapezoidal approximation. The terminal elimination half-life ($t_{1/2\beta}$), steady-state volume of distribution (V_{ss}), and total body clearance (TBC) were calculated by standard techniques (5).

We evaluated the accuracy with which ceftazidime $t_{1/2}$ and TBC were predicted from the relationships reported by Norrby et al. (14; log $t_{1/2}$ = 2.23 − 1.03 · log GFR [glomerular filtration rate]) and Leroy et al. (10; TBC = 1.15 CL_{CR} [creatinine clearance] + 10.6).

A paired Student t test was used to compare the observed and predicted values for $t_{1/2\beta}$ and TBC. Orthogonal regression analysis was used to ascertain the relationship between the observed and predicted pharmacokinetic parameters of ceftazidime. Statistical significance was assessed at the $P < 0.05$ level. Data are presented as the mean ± standard deviation.

RESULTS

Eleven patients (nine men and two women aged 21 to 82 years) with various intra-abdominal diagnoses participated in this study. The clinical and relevant demographic characteristics are presented in Table 1.

The ceftazidime serum-concentration-versus-time profile was multiexponential in all patients (Fig. 1). The peak and trough concentrations in serum observed at this time were 257.4 ± 122.0 and 13.1 ± 20.6 mg/liter, respectively. The attainment of steady state was illustrated by the trough concentration on day 2 of therapy, 13.9 ± 23.3 mg/liter.

The disposition of ceftazidime in the patients was highly variable. The $t_{1/2\beta}$ ranged from 1.36 to 5.85 h (mean, 2.52 h), and the V_{ss} ranged from 0.19 to 0.64 liter/kg (mean, 0.31 liter/kg) (Table 2). The degrees of variability in TBC and $AUC_{0-\tau}$ were similar, with ranges of 0.034 to 0.193 liter/h per kg and 178.8 to 1,157.5 mg · h/liter, respectively.

The predicted values of $t_{1/2\beta}$ ranged from 0.78 to 3.53 h (1.85 ± 0.88 h), and the mean predicted $t_{1/2\beta}$ was lower than the observed $t_{1/2\beta}$ (P = 0.033). However, there was a significant relationship between the predicted $t_{1/2\beta}$ and the observed values ($y = 1.80x - 0.80$; r = 0.763; P = 0.007). In contrast, no significant difference was noted between the observed and predicted ceftazidime TBCs of 125.6 ± 43.1 and 123.7 ± 52.3 ml/min, respectively. Furthermore, the relationship between the observed and predicted ceftazidime TBCs was highly significant ($y = 0.80x + 26.5$; r = 0.868; P = 0.001) (Fig. 2).

DISCUSSION

The dispositions of several antibiotics have been demonstrated to be significantly different in infected patients and normal volunteers. In patients with gram-negative infections, the TBC of aztreonam was significantly lower than previously reported in volunteers (58.5 versus 76.8 ml/min

TABLE 2. Ceftazidime pharmacokinetic parameters[a]

Patient	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V_{ss} (liter/kg)	TBC (liter/h per kg)	$AUC_{0-\tau}$ (mg · h/liter)
1	0.21	2.34	0.33	0.120	229.3
2	0.26	1.83	0.25	0.121	178.8
3	0.47	2.08	0.27	0.114	260.3
4	0.49	4.57	0.22	0.034	1,157.5
5	0.10	2.29	0.19	0.061	322.9
6	0.14	1.68	0.37	0.193	291.6
7	0.10	1.65	0.23	0.118	230.0
8	0.18	1.36	0.30	0.180	196.5
9	0.28	5.85	0.64	0.079	377.8
10	0.07	2.00	0.29	0.103	222.9
11	0.13	2.13	0.34	0.116	276.9
Mean	0.22	2.52	0.31	0.113	340.4
SD	0.14	1.39	0.12	0.046	277.0

[a] $t_{1/2\alpha}$, Half-life of the distribution phase; $t_{1/2\beta}$, half-life of the elimination phase; V_{ss}, volume of distribution at steady state; TBC, total body clearance; $AUC_{0-\tau}$, area under the serum-concentration-versus-time curve during the dosing interval.

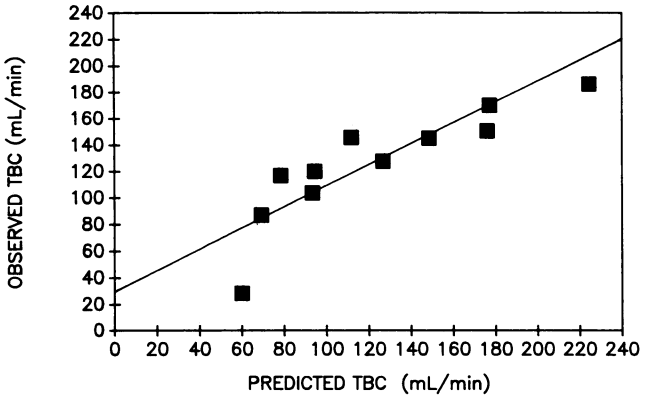

FIG. 2. Observed TBC versus predicted TBC (r = 0.868; y = 0.80x + 26.5).

per 70 kg) (8). Furthermore, protein binding was observed to be lower in infected patients (30 versus 60%) (16). The dispositions of ceftazidime and netilmicin in febrile patients with septicemia have also been reported to be altered (3). Furthermore, imipenem pharmacokinetics were altered in febrile neutropenic cancer patients relative to previous observations in normal volunteers (2). Specifically, imipenem clearance was lower and the AUC was higher. In contrast, no significant difference was observed in the $t_{1/2\beta}$ of ciprofloxacin in elderly patients with pneumonia compared with healthy elderly individuals (6).

The pharmacokinetics of ceftazidime at steady state in these patients with intra-abdominal infection were markedly variable. However, the mean pharmacokinetic parameters of ceftazidime were similar to those of previous reports for noninfected subjects with similar degrees of renal function (9, 10). Thus, the observed variability in ceftazidime disposition may be primarily attributable to variability in renal function rather than to an effect of the infectious process on the disposition of ceftazidime.

The second objective of this investigation was to assess the accuracy with which ceftazidime $t_{1/2\beta}$ and TBC could be predicted from the relationships reported by Norrby et al. (14) and Leroy et al. (10). These relationships have been suggested as a tool to derive estimates of the pharmacokinetic parameters for acutely ill patients (10, 14). Although there was a significant relationship between the predicted and observed values for ceftazidime TBC with the relationship reported by Leroy et al. (10), the mean predicted $t_{1/2\beta}$ was significantly lower than the mean observed $t_{1/2\beta}$.

The relationship of Norrby et al. was previously evaluated with three patients by Narang and Hunter (12). Although there was no significant difference in observed and predicted ceftazidime $t_{1/2\beta}$s in one patient with chronic renal insufficiency, the $t_{1/2\beta}$ of ceftazidime was markedly underestimated in two patients with lymphoma and concurrent granulocytopenia. Our observation of an underestimation of $t_{1/2\beta}$ in these surgical patients with estimated CL_{CR}s ranging from 43 to 186 ml/min supports the premise that this relationship should not be used to project the $t_{1/2\beta}$ of ceftazidime in acutely ill patients.

Drug disposition is often altered in geriatric patients, generally as a result of a decline in renal function rather than as a direct effect of aging itself (11). Although, patients 4 and 9 were elderly and the only females included in this study, they also had the lowest CL_{CR}s, 43 and 51 ml/min. The low CL_{CR}s of these two patients were more likely responsible for the decreased ceftazidime TBCs (0.034 and 0.079 liter/h per kg) and increased ceftazidime $t_{1/2\beta}$s (4.57 and 5.85 h) than were age or sex.

The clearance of ceftazidime in patients with intra-abdominal infection was highly variable and significantly correlated with renal function. The serum-concentration-time profile did not markedly differ in patients with decreased ceftazidime TBC. Thus, no alteration of ceftazidime dosage appears to be necessary for acutely ill surgical patients with intra-abdominal infections, provided that severe impairment of renal function does not exist and that the dosage interval is not shorter than 8 h. This predictable serum-concentration-time profile makes ceftazidime an attractive agent for use in this patient population.

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