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Kinetic Disposition of Intravenous Ceftriaxone in Normal Subjects and Patients with Renal Failure on Hemodialysis or Peritoneal Dialysis

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The kinetic disposition of a single intravenous dose of ceftriaxone (250 to 665 mg) was studied in six normal subjects and nine patients with renal insufficiency and normal hepatic function. In normal subjects, ceftriaxone was eliminated with a $t_{1/2\beta}$ of 5.2 h (range, 4.1 to 5.8). The total body clearance (Q_b) was 13.5 ml/kg per h (range, 8.4 to 23.3), and renal clearance was 8.3 ml/kg per h (range, 5.8 to 13.3). In patients with severe renal insufficiency requiring peritoneal or hemodialysis, the mean $t_{1/2\beta}$ was prolonged to 13.4 h (range, 7.7 to 15.8) and the mean Q_b was reduced to 6.9 ml/kg per h (range, 3.4 to 12.8). The apparent volumes of distribution (V_c and V_{ss}) were not different from those determined in normal subjects. Peritoneal dialysis did not remove ceftriaxone. The dialysate of three patients on continuous peritoneal dialysis did not contain any measurable ceftriaxone, and the kinetic disposition in these patients was similar to the hemodialysis patients between their dialysis treatment. During a 4-h hemodialysis session, the total body clearance of ceftriaxone was reduced, perhaps secondary to a decrease in hepatic blood flow induced by the hemodialysis procedure. After a 12- or 24-h dose regimen, predicted trough concentrations of ceftriaxone in plasma at steady state derived from kinetic data generated from the study and assuming linear pharmacokinetic behavior were well above the minimum inhibitory concentrations of most sensitive bacteria, suggesting the feasibility of a once-a-day dosage regimen especially for patients with severe renal insufficiency.

Ceftriaxone is a new cephalosporin with broad-spectrum antibacterial activity comparable to that of newer agents such as cefotaxime and moxalactam (4). It differs from the other members of the cephalosporin family by having a much longer elimination half-life. In normal subjects, its elimination half-life is reported to be in the range of 6 to 8 h (5, 6, 9, 10). In comparison, cefazolin, cefotaxime, and moxalactam have elimination half-lives of 1.5, 1, and 2 h, respectively. The longer elimination half-life of ceftriaxone may be a clinical advantage in the management of patients, especially if the drug can be administered once a day. Treatment of patients with ceftriaxone on a 12-h regimen has been reported (1, 2). However, further studies are required to provide guidelines for rational dosage schedules in various clinical situations.

We investigated the kinetic disposition of ceftriaxone in normal subjects and patients with renal failure. Since ceftriaxone may be used to treat patients with renal failure who are on chronic peritoneal or hemodialysis, attention must be given to the use of this drug with this group of patients. We therefore studied patients given ceftriaxone while on and off dialysis.

MATERIALS AND METHODS

After providing informed consent, all volunteers were screened with a complete history, physical examination, and laboratory studies consisting of a complete blood count with differential, a 12-channel sequential multiple analyzer study, prothrombin time, partial thromboplastin time, urinalysis, chest X ray, and electrocardiogram. Subjects were included if they had none of the following exclusion criteria: pregnancy, known penicillin or cephalosporin allergy, infection, hepatic or biliary tract disease, normal volunteers who were on any drugs, and renal failure patients who were taking drugs other than those necessary to control symptoms and complications of renal disease. Urinalysis, hematological, and biochemical tests were repeated 24 h after administration of the drug and repeated if necessary.

Six normal volunteers with physical characteristics as shown in Table 1 were studied. On the morning of the study after an overnight 10-h fast, each subject had a baseline blood sample drawn, and 7 mg of ceftriaxone per kg was administered by a constant 10-min infusion with a Harvard Servo-Control pump. Blood samples were drawn through an indwelling intravenous catheter in the opposite arm at the end of the drug infusion (zero time) and then at 5, 15, 30, and 90 min and 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h from zero time. The indwelling intravenous catheter was kept patent with heparinized saline (10 U/ml). Urine was collected at 12-h intervals for 24 h.

Nine patients with chronic renal failure were studied. They were shorter and older than the normal subjects (Table 1) but did not differ in average weight. Three patients were studied while undergoing ambulatory peritoneal dialysis after an overnight fast. Each had the first exchange of the day at the Clinical Pharmacology Unit. Immediately after the instillation of the new dialysate, an indwelling catheter was inserted in an antecubital vein for blood sampling, and 250 mg of ceftriaxone was infused intravenously in the opposite arm over 10 min. The dose was limited to 250 mg in renal

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TABLE 1. Subject characteristics

Subject[a]	Age (yr)	Sex	Height (m)	Weight (kg)
Normal renal function				
1	35	M	1.75	66.0
2	23	M	1.83	95.0
3	21	M	2.00	87.0
4	30	M	1.85	78.5
5	20	M	1.70	72.5
6	21	M	1.84	76.5
Mean	25.2		1.83	79.0
SD	6.4		0.10	10.5
Decreased renal function				
CAPD patients				
7	64	M	1.63	71.5
8	29	F	1.42	47.0
9	52	F	1.49	95.0
Mean	48.3		1.51	71.2
SD	17.8		0.11	24.0
Hemodialysis patients				
10	24	M	1.77	64.7
11	23	F	1.58	59.0
12	61	F	1.50	60.9
13	51	M	1.66	66.0
14	65	M	1.74	68.0
15	24	M	1.80	69.0
Mean	42.6		1.66	68.3
SD	18.5		0.11	10.4

[a] SD, Standard deviation; CAPD, chronic ambulatory peritoneal dialysis.

failure patients in this protocol by the Health Protection Branch of the Department of Health and Welfare of Canada. Blood samples were drawn at the end of the infusion (zero time) and at 10, 20, 30, and 60 min and 3, 5, 7, 9, 24, 36, and 48 h after zero time. A sample of each exchange during the first 24 h was collected for analysis. One patient had three 2-liter exchanges and two patients had four 2-liter exchanges in 24 h. None of the patients with renal failure produced urine during the experimental periods.

Six chronic renal failure patients on hemodialysis, three sessions per week, were studied twice, between hemodialysis (interdialysis) and during hemodialysis. For the interdialysis study, an indwelling venous catheter was inserted in the arm without the arteriovenous fistula for blood sampling on the morning of the study after a 10-h overnight fast. One diabetic patient had her usual breakfast and insulin dose before the study. All patients except one were given 250 mg of ceftriaxone intravenously over 10 min in the arm with the sampling catheter but in a different vein. One patient had only one venous access site through which the drug was given and samples were drawn. For this patient, the first sample (zero time) was drawn 3 min after the end of the infusion and all subsequent samples were taken 3 min later than usual. For the rest of the patients, blood samples were drawn at the end of the infusion (zero time) and at 10, 20, and 30 min and 1, 3, 5, 7, 9, 24, and 36 h from zero time. Again, none of these renal failure patients produced urine during the experimental periods.

The second study, separated from the first by at least 1 week, was performed during hemodialysis in the Hemodialysis Unit. Patients were studied during their regular hemodialysis sessions and were not required to fast before the study. The first patient (no. 10) was given 250 mg of ceftriaxone intravenously over 10 min, and within 30 min of the completion of the infusion, he was put on the hemodialyser and blood samples were drawn as for the others. The other five patients had their hemodialysis set up and 250 mg of ceftriaxone was administered through the venous return tubing over 10 min. Simultaneous arterial and venous samples at 30, 60, 120, 180, and 240 min after the end of the infusion were taken from the tubing entering and leaving the artificial kidney, respectively. The same type of membrane (GAMBRO-GF-120M) was used for all sessions. Artificial kidney blood flow rate and hematocrit from the arterial samples were also recorded at the sampling times. Four patients were on one-needle dialysis and two were on two-needle dialysis.

The ceftriaxone assay was performed as follows: methanol (0.3 ml) containing 100 μg of cefotaxime per ml as the internal standard was added to 0.2 ml of plasma. After vortexing and centrifugation, the supernatant was transferred to the microinjection vials of a Waters Associates WISP for 50-μl injections. Chromatography was performed on a 10-μm octadecylsilane column (25 cm by 4.6 mm) at a flow rate of 1 ml/min. A 1-liter amount of mobile phase was composed of 0.78 g of monopotassium phosphate, 8.66 g of disodium phosphate (anhydrous), 1.75 g of tetrabutylammonium hydrogensulfate, 800 ml of water, and 200 ml of methanol. Detection was by an electrochemical detector, using a glassy carbon electrode at a potential of 1.15 V relative to silver-silver chloride. Under these conditions, ceftriaxone and the internal standard had baseline resolution both from each other and from other peaks, with ceftriaxone eluting at 8.5 min and the internal standard eluting at 11.5 min. Total run time was 18 min. Standard curves were constructed by using plasma containing 6.25, 12.5, 25, 50, and 100 mg/liter of ceftriaxone. Quantitation was by peak height ratios of ceftriaxone and the internal standard with a lower limit of detection of 0.1 mg/liter. The between day coefficient of variation at 100 mg/liter was 3.5%, at 25 mg/liter it was 6.6%, and at 6.25 mg/liter it was 6.9%. The coefficient of variation within the assay for duplicate analyses was 6.4% on day 1, 4.9% on day 8, and 5.0% on day 16, the last day of analytical work.

The kinetic parameters of each subject were estimated from the unweighted time-concentration data by using an iterative nonlinear least squares curve-fitting computer program which combined the Gauss-Newton and Marquardt techniques. A two-compartment open model with first-order transfer constants and elimination from the central compartment adequately described the ceftriaxone time-concentration data. This model was used to fit the data of all of the subjects, and it was also used in the simulation studies. However, in some patients there was a suggestion of a slower third elimination phase, and a three-compartment open model with two peripheral compartments significantly improved the fit in one subject. Therefore, additional fitting to the three-compartment model was performed. Urinary clearance was estimated by the following formula: $Q_u = X_u/AUC$, where Q_u is urinary clearance, X_u is the total amount of ceftriaxone in the urine for the time interval collected, and AUC is the area under the plasma concentration curve obtained by integration of the fitted two-compartment equation over the interval.

The average Q_u over the four intervals (0 to 12, 12 to 24, 24 to 36, 36 to 48 h) was estimated from the slope of linear regression through the origin on four points. For each point

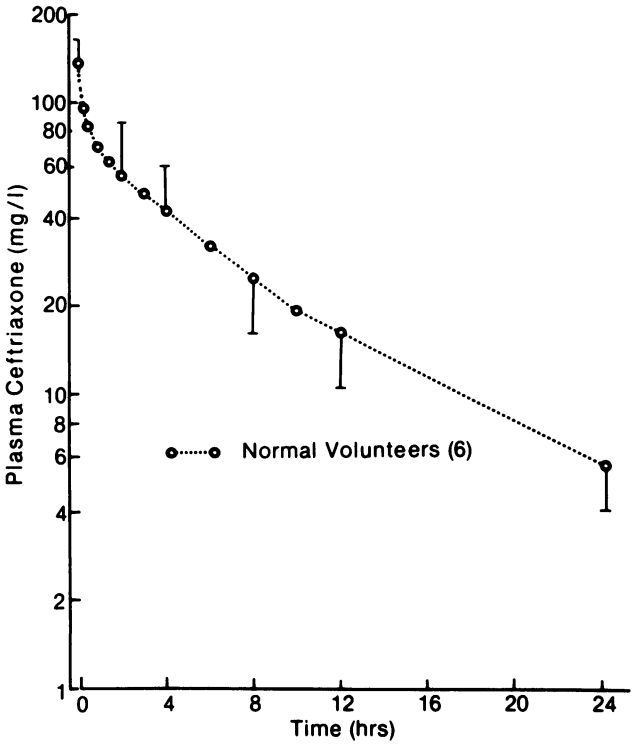

FIG. 1. Mean (± standard deviation) concentrations of drug in plasma for six normal subjects given ceftriaxone at 7 mg/kg intravenously over 10 min.

the independent variable was the area under the curve, and the dependent variable was X_u.

The artificial kidney clearance was calculated from the equation $(C_a - C_v/C_a) \cdot$ (plasma flow rate), where C_a was the drug concentration in plasma entering the membrane system, C_v was the drug concentration in plasma leaving the system, and the plasma flow rate was calculated from the measured hemodialysis blood flow rate and the hematocrit. The hemodialysis blood flow rate was estimated from the average of two bubble transit times. Ultrafiltration was not used during the dialysis studies, and the hematocrits did not change significantly during the study.

All statistical comparisons utilized distribution-free techniques because of the small sample size and the high possibility of abnormally distributed data. We used the Mann-Whitney U test for all two-sample comparisons and the Kruskal-Wallis technique for more than two samples.

RESULTS

The mean drug concentration in plasma-time curves of normal subjects and renal failure patients are shown in Fig. 1 and 2. In normal subjects the mean peak concentration of the drug in plasma after a dose of 7 mg of ceftriaxone per kg was 136.2 mg/liter (range, 107.2 to 175), and the concentration decreased to 5.8 mg/liter (range, 2.6 to 7.6) at 24 h. After a dose of 250 mg of ceftriaxone the mean peak concentration of the drug in plasma in hemodialysis patients (interdialysis period) was 68.8 mg/liter (range, 55.0 to 70.2), and in patients on continuous peritoneal dialysis it was 60 mg/liter (range, 52.4 to 67.5). At 24 h postinfusion the mean concentration of the drug in plasma was 11.9 mg/liter (range, 3.6 to 20.2) in hemodialysis patients and 11.9 mg/liter (range, 5.8 to 15.2) in the peritoneal dialysis patients. A clear, rapid distribution phase was apparent in the normal subjects and both renal failure groups; however, the beginning of the terminal elimination phase was less distinct.

A summary of the estimated kinetic values is shown in Table 2. The mean elimination half-life was prolonged over normal in renal failure; however, the ranges for total body clearance (Q_b) overlapped. Urinary clearance (Q_u) was 63% of total body clearance in the normal subjects. Apparent volumes of distribution (V_c, V_{ss}) did not differ significantly among the groups. By using the three-compartment open model analysis in normal subjects only the terminal half-life was longer than that obtained by the two-compartment analysis. However, in both normal subjects and the renal failure groups the total body ceftriaxone clearance obtained with the three-compartment model was unchanged from that obtained in the two-compartment analysis.

The dialysate of the three patients undergoing ambulatory peritoneal dialysis did not contain measurable drug after the single intravenous dose of 250 mg of ceftriaxone.

Arterial plasma ceftriaxone concentration-time curves of six patients during 4-h hemodialyses are compared to the concentration-time curves during the interdialysis period in Table 3. Concentrations were slightly higher during hemodialysis. A biphasic decline in arterial ceftriaxone concentrations is apparent, and in four of the six patients, the terminal-phase half-life determined by the slope of the log-linear terminal phase exceeded 50 h. We had too few concentration data points to justify computerized curve fitting with a two- or even one-compartment model. The mean artificial kidney plasma flow rate was 149 ml/min (range, 116 to 196), and calculated hemodialysis clearance of ceftriaxone was 31 ml/min (range, 9 to 52) with arteriovenous concentration differences. Flow rates were similar during one- or two-needle dialyses. This clearance rate was clearly incompatible with the time course of the decline in the concentrations of ceftriaxone arterial plasma, which suggests markedly reduced total body clearance during hemodialysis as compared with the interdialysis studies (Table 3). The clearance values calculated by arteriovenous differences were not affected by the number of needles used in hemodialysis.

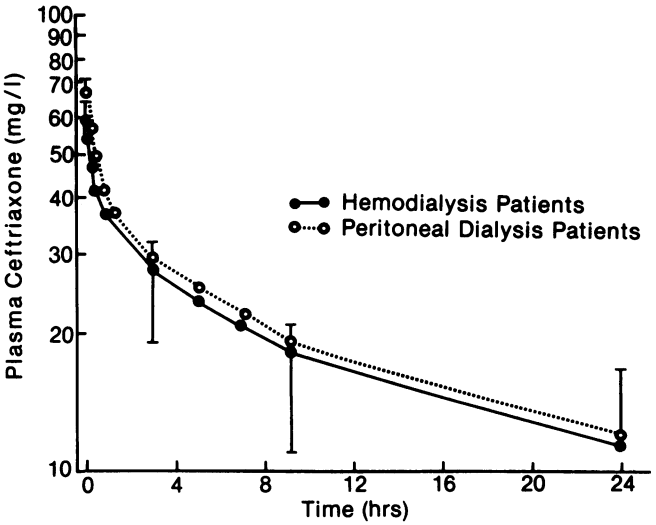

FIG. 2. Mean (± standard deviation) concentrations of drug in plasma for six patients with chronic renal failure between hemodialysis treatments and three patients with chronic renal failure during chronic ambulatory peritoneal dialysis given 250 mg of ceftriaxone intravenously over 10 min.

TABLE 2. Mean computer-estimated kinetic values for intravenous ceftriaxone in normal subjects and patients with chronic renal failure[a]

Renal function	Two-compartment kinetic analysis					Three-compartment kinetic analysis	
	V_c (liters/kg)	V_{ss} (liters/kg)	$t_{1/2\beta}$ (h)	Q_b (ml/kg per h)	Q_u (ml/kg per h)	$t_{1/2\gamma}$ (h)	Q_g (ml/kg per h)
Normal (n = 6)	0.04 (0.04–0.06)	0.09 (0.06–0.17)	5.2 (4.1–5.8)	13.5 (8.4–23.3)	8.3 (5.8–13.3)	8.7 (5.7–12.8)	12.7 (7.9–24.0)
Decreased							
CAPD[b] (n = 3)	0.05 (0.05–0.07)	0.12 (0.08–0.18)	12.2 (7.7–14.4)	7.4 (4.0–12.9)		14.7 (8.8–25.7)	7.5 (3.3–13.7)
HD[c] (n = 6)	0.05 (0.05–0.07)	0.11 (0.08–0.15)	14.6 (8.4–19.8)	6.4 (3.4–12.0)		17.3 (9.6–26.0)	6.0 (3.2–11.9)

[a] Ranges are given in parentheses.
[b] CAPD, Chronic ambulatory peritoneal dialysis patients.
[c] HD, Hemodialysis (interdialysis) patients.

Normal subjects did not develop symptoms after administration of ceftriaxone. Two patients with renal failure had mild abdominal cramps, one complained of a metallic taste, and one patient started sneezing a number of times after drug infusion. The symptoms lasted up to 3 h, were mild, and resolved spontaneously. Three normal subjects, one patient on continuous ambulatory peritoneal dialysis and two patients on hemodialysis, had a 20 to 50% decrease in the percentage of neutrophils from baseline values. However, none of the values were in the neutropenic range, and the change was confirmed to be transient. There were no significant changes in the biochemical tests after drug administration. Two normal subjects had transient, mild proteinuria.

Simulation studies. Simulation studies were performed with two dosing regimens (Table 4). For normal subjects, ceftriaxone, given in a bolus of 1,000 mg intravenously every 24 h or a 500-mg bolus every 12 h, reached steady-state concentrations by day 2. For hemodialysis patients during the interdialysis period, ceftriaxone, 250 mg every 12 h or 500 mg every 24 h, resulted in steady-state concentrations by day 3 (in the absence of intervening dialysis). Trough concentrations in normal subjects given 1,000 mg of ceftriaxone every 24 h averaged 5.8 mg/liter at steady state, and the renal failure groups given half this dose every 24 h had steady-state trough concentrations five times higher than the normal subjects.

DISCUSSION

We studied the kinetic disposition of a single dose of ceftriaxone (250 to 665 mg) in six normal subjects and nine patients with renal insufficiency and normal hepatic function. In normal subjects the elimination half-life of ceftriaxone of 5.2 h was slightly lower than the average $t_{1/2\beta}$ of 6 to 8 h reported by some investigators, but it was within the range of 4.7 to 7.7 found by others (5, 6, 9, 10). Analysis of our results by a three-compartment model instead of a two-compartment model gave an average elimination half-life of 8.7 h (range, 5.7 to 12.8) in normal subjects (Table 2), slightly longer than previously reported values. However, total body clearance with this model did not differ from the clearance obtained with the two-compartment model.

The $t_{1/2\beta}$ of ceftriaxone in patients with severe renal failure was prolonged to 2.5 times that of normal, and the total body clearance (Q_b) was reduced to ca. 50% that of normal subjects. In the normal subjects, renal clearance of ceftriaxone accounted for 63% of the total body clearance, comparable to that found by Findlay et al. (2). Since our patients with renal failure failed to produce urine during the experimental periods, we must conclude that their renal clearance of ceftriaxone was zero. The loss of renal clearance in patients with severe renal failure must be a major cause of the prolonged $t_{1/2\beta}$ and reduction of Q_b. However, in several renal failure patients, the values of Q_b overlapped the lower range of values in normal subjects. We were unable to discern any physical, laboratory, or disease characteristics which might help predict which patients would have a greater reduction of ceftriaxone clearance due to renal failure. In the face of reduced or absent renal function, hepatic clearance of the drug may have been increased in those patients with lesser impairment of total body ceftriaxone clearance.

Renal failure patients on ambulatory peritoneal dialysis and hemodialysis patients during the interdialysis period had similar slow clearance rates of the drug after an intravenous dose of 250 mg. This was not surprising, since the dialysate from the patients on continuous peritoneal dialysis did not contain any measurable ceftriaxone. Arteriovenous concentration differences of ceftriaxone during hemodialysis greatly overestimated drug clearance, since arterial drug concentrations remained high during the procedure. We have no explanation for this observation but suspect that the venous concentrations were spuriously low. Difficulty with this method of calculating hemodialysis clearance was also reported by Pizzella et al. in their report on the dialysis of cimetidine (8). It is possible that the diminished clearance during dialysis reflected decreased hepatic blood flow.

In our simulation studies in normal subjects given 500 mg of ceftriaxone every 12 h, the predicted peak concentration of 165 mg/liter at steady-state was higher than the range of 77 to 117 mg/liter observed by Pollock et al. (9), but we gave a bolus infusion in the simulation study, whereas Pollock et al. administered the drug over 30 min. Our predicted trough concentration of 17 mg/liter was well in the range of 14 to 28 mg/liter observed by the same investigators. When the total

TABLE 3. Concentrations of ceftriaxone in plasma in patients with renal insufficiency during and between hemodialysis periods

Time (h)	Plasma ceftriaxone (mg/liter) in patient:					
	11	12	13	14	15	16
During dialysis						
0.5		57.3	63.5	56.4	48.7	61.7
1.0	62.8	54.7		44.4	44.5	56.2
2.0	51.0	49.7	43.6	31.8	38.2	45.6
3.0	46.8	40.5	34.8	30.3	30.2	40.4
4.0	44.5		29.9	24.0	27.1	35.6
Interdialysis						
0.5	44.3	30.7	24.6	41.8	62.7	49.2
1.0	30.2	28.1	23.5	36.8	58.0	46.1
3.0	24.5	19.7	19.8	30.3	41.5	36.2
5.0	21.8	17.8	16.2	25.2	31.5	33.0

TABLE 4. Predicted plasma concentrations (mean ± standard deviation) of normal subjects and hemodialysis patients (interdialysis period) given repeated bolus doses of ceftriaxone intravenously

Subjects and dose	Day 1		Day 4	
	Peak (mg/liter)	Trough (mg/liter)	Peak (mg/liter)	Trough (mg/liter)
Normal renal function				
500 mg every 12 h	149 ± 37	13.6 ± 5.7	165 ± 41	17.1 ± 7.4
1,000 mg every 24 h	297 ± 74	5.5 ± 2.9	303 ± 74	5.8 ± 3.0
Hemodialysis, (interdialysis)				
250 mg every 12 h	74 ± 9	9.2 ± 2.9	87 ± 41	12.6 ± 4.5
500 mg every 24 h	148 ± 19	18.5 ± 5.8	173 ± 22	25.4 ± 8.9

dose of 1,000 mg was given every 24 h, a higher peak (302 mg/liter) and a lower trough (6 mg/liter) was obtained compared with the 12-h regimen. The peak and trough values for both regimens were well above the minimum inhibitory concentration of 1 mg/liter required for sensitive organisms.

In patients with severe renal failure given one-quarter of the dose recommended for normal subjects once a day, the predicted peak concentration at steady state was one-third that of the normal subjects, but the trough concentration was three times as high. Again both peak and trough concentrations were well above the minimum inhibitory concentrations of susceptible organisms. Theoretically, a once-a-day dosage regimen for ceftriaxone seems reasonable, especially in patients with severe renal failure. The efficacy of such a regimen will have to be tested in clinical trials.

No significant adverse reactions were noted in our study. Patients with severe renal failure were more likely to develop symptoms than normal subjects. The most commonly reported gastrointestinal symptom is diarrhea (2, 7). Although none of our patients developed diarrhea, two had abdominal cramps. Transient proteinuria, which occurred in two patients, was also reported by Pickup et al. (7). It will be important to monitor renal function and hematology when patients are on prolonged treatment with ceftriaxone.

ACKNOWLEDGMENT

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