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Ceftriaxone Pharmacokinetics in Patients with Various Degrees of Renal Impairment

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The effects of renal impairment on the pharmacokinetics of ceftriaxone in humans were examined after intravenous infusion of a 1-g dose over 15 min to 30 renally impaired patients. The study included 12 dialysis patients and 18 patients with severe, moderate, or mild renal impairment. Plasma and, where appropriate, urine and dialysate samples were collected at predetermined times and analyzed for ceftriaxone by high-pressure liquid chromatography. The elimination half-life (group mean ranged from 11.7 to 17.3 h) and plasma clearance (group mean ranged from 529 to 705 ml/h) did not correlate linearly with creatinine clearance. The renal clearance and fraction of dose excreted unchanged in urine were related linearly, however weakly, with creatinine clearance. Ceftriaxone was not removed from plasma to a significant extent during hemodialysis. The half-life was prolonged twofold, the plasma clearance was lowered less than 50%, and the volume of distribution was relatively unchanged in renally impaired patients compared with young or elderly healthy subjects with normal renal function at an equivalent dose. Since these changes are moderate, adjustment in the dosage regimen of ceftriaxone for patients with impaired renal function should not be necessary when ceftriaxone dosage is 2 g or less per day (2 g every 24 h or 1 g every 12 h). It was reported that the elimination half-life of ceftriaxone is substantially prolonged in a small percentage of patients with end-stage renal disease maintained on hemodialysis. Therefore, plasma concentrations of ceftriaxone should be monitored in dialysis patients to determine whether dosage adjustments are necessary.

Patients with renal diseases are at increased risk of developing bacterial infections. Because of rising antibiotic resistance, especially in nosocomially acquired infections, aminoglycoside usage in such patients is common. These patients are extremely susceptible to the nephrotoxicity associated with these agents. On the basis of its antibacterial activity (1, 11), ceftriaxone has the potential of providing an effective antibiotic regimen for the parenteral therapy of systemic bacterial infections in patients with reduced renal function. In recent studies (3, 14), increases in the ceftriaxone elimination half-life were observed in patients with end-stage renal disease (creatinine clearance [CL_{CR}] less than 10 ml/min) maintained on hemodialysis. The present study examined the effects of various degrees of renal insufficiency (CL_{CR} ranging from 73 to <5 ml/min per 1.73 m^2) on the ceftriaxone pharmacokinetics, including removal of ceftriaxone from plasma by the hemodialysis procedure.

MATERIALS AND METHODS

Patient population. Thirty adult male and female patients with various degrees of renal impairment who were otherwise free of clinical illness participated in the study after giving written informed consent. Before entering the study, a history, physical examination, vital signs, and laboratory tests consisting of hemoglobin, hematocrit, leukocyte count (total and differential), quantitative platelet count, blood urea nitrogen, serum creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, serum bilirubin, creatinine clearance, and urinalysis (biochemical and microscopic) were performed on all patients. Patients over 40 years of age had had an electrocardiogram within the year and a chest X-ray within 2 years.

The patients ranged in age from 21 to 75 years (mean ± standard deviation, 52.6 ± 15.3 years) and in body weight from 51.8 to 103 kg (mean ± standard deviation, 65.9 ± 12.0 kg) (Table 1). Based on the CL_{CR}, patients were divided into four groups: (i) 12 dialysis patients, CL_{CR} < 5 ml/min per 1.73 m^2; (ii) 6 patients with severe renal impairment, CL_{CR}, 5 to 15 ml/min per 1.73 m^2; (iii) 6 patients with moderate renal impairment, CL_{CR}, 16 to 30 ml/min per 1.73 m^2; (iv) 6 patients with mild renal impairment, CL_{CR}, 31 to 60 ml/min per 1.73 m^2.

Study design. Ceftriaxone sodium equivalent to 1 g of anhydrous free acid was infused intravenously over 15 min to 12 dialysis patients and 18 nondialysis patients. In the case of dialysis patients, six patients received the drug between two hemodialysis treatments (i.e., during an interdialysis period), and the remaining patients received the drug just before the commencement of the hemodialysis procedure (i.e., hemodialysis was started at the end of drug infusion). The patients were dialyzed with the Gambro Fiber Dialyzer (GF-120-M) and Cuprophan membrane (surface area, 1.2 m^2). The dialysis treatment lasted 3 to 5 h, and the dialysate volume ranged from 104 to 120 liters.

Sample collection. (i) Dialysis patients during hemodialysis. Arterial (inlet of dialyzer) blood, venous (outlet of dialyzer) blood, and dialysate samples were collected at 2 h after the start of drug infusion and then hourly until hemodialysis was complete.

(ii) Dialysis patients during interdialysis period. Venous blood from a peripheral vein was collected before dose (0 h)

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and at 15 min (end of infusion) and 1, 4, 8, 12, and 24 h after the start of drug infusion and also immediately before the next hemodialysis treatment.

(iii) Mondialysis patients. Venous blood was collected before dose (0 h) and at 15 (end of infusion), 20, 25, 30, 45, 60, and 90 min and at 2, 4, 6, 8, 10, 12, and 24 h after the start of drug infusion. Urine was collected before dose (−2 to 0 h) and then between 0 and 4, 4 and 8, 8 and 12, 12 and 24, and 24 and 48 h.

Blood samples were drawn into heparinized Vacutainer tubes (Becton Dickinson and Co.; no. 6527) and centrifuged immediately, and plasma was separated and stored at or below −17°C. Urine voided during each collection interval was refrigerated until the end of the collection interval. After the total volume was recorded, a 15-ml portion was removed and stored at or below −17°C. Dialysate samples were also stored at or below −17°C.

Sample analysis. Plasma, urine, and dialysate samples were analyzed for ceftriaxone by the reverse-phase, ion-pairing high-pressure liquid chromatography procedure described previously (12). The assay procedure for dialysate samples was the same as that for urine samples. The assay sensitivity limits were 5 μg/ml for plasma and 10 μg/ml for urine and dialysate. The interassay precision was 6% or better over a 5 to 400 μg/ml concentration range.

Pharmacokinetic analysis. The following model-independent pharmacokinetic parameters were estimated from the plasma and urine concentration data: (i) the terminal elimination rate constant (β) by fitting 4- to 24-h plasma concentrations to a monoexponential equation using the NONLIN program (9) and the reciprocal of the plasma concentration as a weighting factor; (ii) elimination half-life ($t_{1/2}$) from ln 2/β; (iii) area under the plasma concentration-time curve from time zero to infinity (AUC) using the conventional linear trapezoidal and extrapolation methods; (iv) plasma clearance (CL_P) from the dose to AUC ratio; (v) renal clearance (CL_R) by dividing the amount of drug excreted unchanged in urine in 24 h with the corresponding area under the plasma concentration-time curve; (vi) apparent volume of distribution in β phase (V) by dividing CL_P with β; and (vii) the fraction of dose excreted unchanged in urine (f_e) from the CL_R to CL_P ratio.

RESULTS

Concentrations of ceftriaxone in dialysis patients during hemodialysis. Ceftriaxone was not detected in dialysate samples. Additionally, concentrations of ceftriaxone in plasma collected from the arterial and venous sides of the dialyzer were similar at each sampling time in the six subjects (Fig. 1). These findings suggest that ceftriaxone was not removed significantly from plasma during hemodialysis.

Pharmacokinetics of ceftriaxone in dialysis patients during interdialysis period. The mean plasma concentration-time curve of ceftriaxone is shown in Fig. 2, and the corresponding pharmacokinetic parameters are listed in Table 2. In one patient, β could not be determined accurately because of erratic and shallow fall-off of plasma concentrations over the sample collection interval. However, the plasma concentration data suggested a considerably longer $t_{1/2}$ and smaller clearance rate of ceftriaxone in this patient than observed in the remaining patients. The mean parameter values in this group of patients were 0.040 h^{-1} for β, 17.3 h for $t_{1/2}$, 13.8 liters for V, and 538 ml/h for CL_P (Table 2). Each of these parameters was quite similar to that determined for nondialysis patients with moderate or several renal insufficiency (Table 2).

TABLE 1. Patient characteristics[a]

Patient group	CL_{CR} (ml/min per 1.73 m^2)	Serum creatinine (mg/dl)	No. of males/no. of females	Age (yr)	Body wt (kg)	Serum bilirubin (mg/dl)	Blood urea nitrogen (mg/dl)
Hemodialysis	Anephric	16.3 ± 3.9 (10.4–20.4)	5/1	45 ± 14 (21–58)	67.7 ± 14.6 (51.8–91.4)	0.4 ± 0.1 (0.3–0.4)	87 ± 20 (60–118)
Interdialysis	Anephric	—[b]	4/2	46 ± 14 (24–67)	70.9 ± 19.4 (63.6–103.2)	0.3 ± 0.1 (0.2–0.4)	57 ± 16 (36–81)
Severe renal impairment	10 ± 3 (5–14)	7.7 ± 3.0 (3.3–11.9)	4/2	59 ± 15 (33–73)	61.2 ± 5.7 (54.5–70.9)	0.4 ± 0.3 (0.2–0.9)	74 ± 28 (42–117)
Moderate renal impairment	25 ± 5 (18–30)	3.3 ± 2.3 (1.3–7.1)	5/1	54 ± 19 (29–75)	60.1 ± 7.1 (51.8–71.8)	0.6 ± 0.5 (0.2–1.6)	52 ± 27 (17–91)
Mild renal impairment	52 ± 11 (41–73)	1.9 ± 0.6 (1.3–2.9)	5/1	61 ± 11 (42–74)	69.5 ± 6.7 (60.5–76.8)	0.5 ± 0.1 (0.4–0.7)	29 ± 5 (22–34)

[a] The numbers represent means ± standard deviations. Ranges are in parentheses.
[b] —, Serum creatinine was not determined.

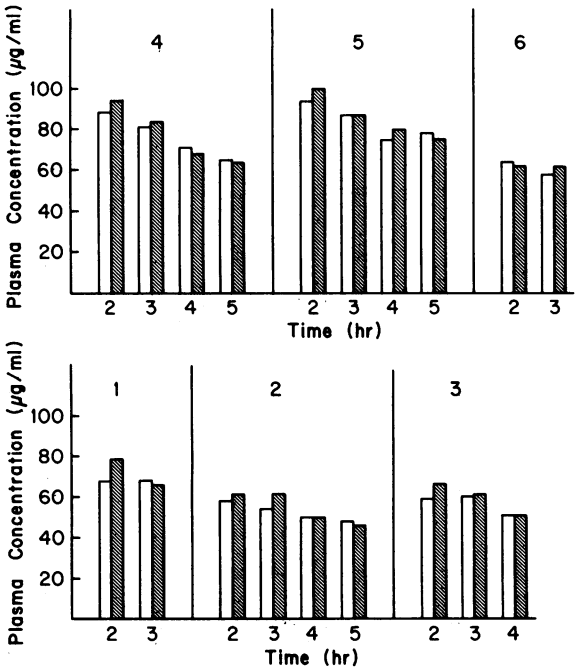

FIG. 1. Concentrations of ceftriaxone in plasma collected from arterial (□) and venous (▨) sides of a dialyzer in six dialysis patients during hemodialysis.

Pharmacokinetics of ceftriaxone in patients with mild, moderate, and severe renal impairment. The mean plasma concentration-time curve (Fig. 2) observed for patients with moderate renal impairment was similar to that observed for patients with severe renal impairment, whereas the mean plasma curve observed for patients with mild renal impairment was only slightly lower than those observed for the other two groups. The mean parameter values in the patients with severe, moderate, and mild renal impairment were 0.048, 0.053, and 0.059 h^{-1}, respectively, for β; 14.4, 13.1, and 11.7 h, respectively, for $t_{1/2}$; 11.5, 10.3 and 12.7 liters, respectively, for V; 603, 529, and 705 ml/h, respectively, for CL_P; 58.7, 142, and 231 ml/h, respectively, for CL_R; and 10.1, 26.9, and 32.0%, respectively, for f_e (Table 2). Linear regression analyses of CL_P as a function of CL_{CR} (Fig. 3) revealed a lack of a linear correlation between β, $t_{1/2}$, V or CL_P and CL_{CR}. As expected, both CL_R and f_e were linearly related to CL_{CR}, although the relationships were weak, as suggested by coefficient of determination (r^2). These findings indicate that the pharmacokinetics of ceftriaxone are not greatly affected by a progressive decrease in the renal function from mild to severe.

DISCUSSION

Since the patients in this study varied considerably in age (21 to 75 years), the pharmacokinetics of ceftriaxone observed in renally impaired patients were compared with those observed in a previous single-dose study (6a) involving intravenous infusion of a 1-g dose to both young and elderly healthy subjects with normal renal function (Table 2). As expected, the CL_R and f_e were considerably smaller in the renally impaired patients than in healthy young and elderly subjects. The V was similar in patients with impaired renal function and in the young and elderly subjects. The $t_{1/2}$ was 1.5- to 2-fold longer, and the CL_P was 15 to 50% smaller in the patients with compromised renal function than in young and elderly subjects with normal renal function. The lack of a more pronounced effect of renal impairment on $t_{1/2}$ and CL_P can usually be anticipated for a drug like ceftriaxone, which is excreted unchanged in the urine of human volunteers to 40 to 67% (8, 12, 13).

Ceftriaxone was not dialyzed from the plasma during hemodialysis, and therefore supplemental dosages should not be necessary for patients maintained on hemodialysis. Because ceftriaxone is 85 to 95% bound to plasma proteins (13, 14), the lack of dialyzability of ceftriaxone was expected even though its V is relatively small.

The pharmacokinetics of ceftriaxone observed in five dialysis patients in this study are reasonably consistent with

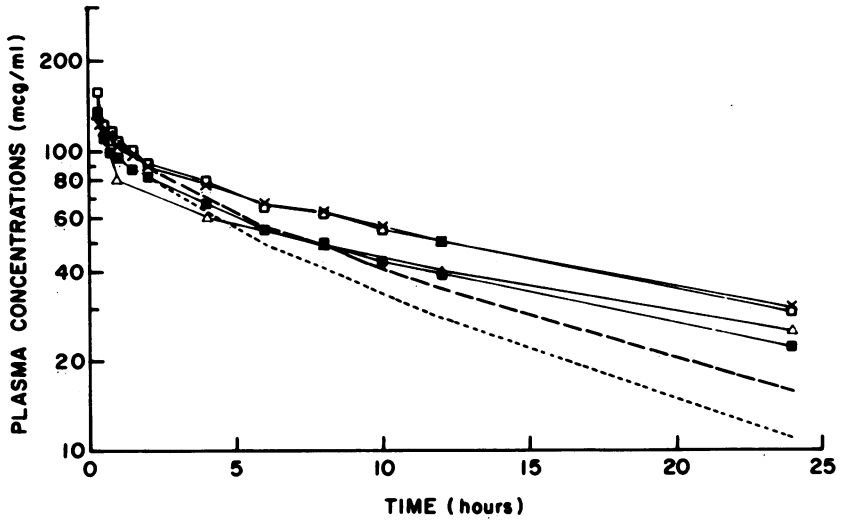

FIG. 2. Average concentration-time profiles of ceftriaxone in plasma after intravenous infusion of a 1-g dose to dialysis patients during an interdialysis period (△; n = 5) and to patients with severe (X; n = 5), moderate (□; n = 6), and mild (■; n = 6) renal impairment. The broken lines represent the average concentration-time profiles of ceftriaxone in plasma after intravenous infusion of a 1-g dose for healthy young (-----; n = 8) and elderly (——; n = 8) subjects with normal renal function.

those of Cohen et al. (3) and Stoeckel et al. (14). These investigators concluded from their data that no changes in the dosage regimen of ceftriaxone would be required for end-stage renal disease patients with normal hepatic function.

The pharmacokinetics of ceftriaxone in patients with renal impairment differ markedly from those of other newer cephalosporins. Compared to values in healthy subjects with normal renal function, the $t_{1/2}$ of moxalactam (2), cefsulodin (4), and ceforanide (5) is six- to eightfold higher in patients with severe end-stage renal disease. Renal impairment results in about a two- to threefold increase in the $t_{1/2}$ of cefoperazone (10). Although the $t_{1/2}$ of cefotaxime is only slightly prolonged (from 1 h to 2 to 3 h), the $t_{1/2}$ of its active desacetyl metabolite is prolonged 10-fold, from 1 h to 10 h (7). The package inserts for cefotaxime and moxalactam recommend that dosage adjustments based on CL_{CR} be made for patients with renal insufficiency.

In one dialysis patient reported here, the elimination half-life of ceftriaxone appeared to be markedly prolonged. A substantially prolonged half-life of ceftriaxone in a small percentage of dialysis patients was also observed by Cohen et al. (3), Stoeckel et al. (11), and Wright and Wise (N. Wright and R. Wise, 12th International Congress of Chemotherapy, Florence, Italy, July 19–24, p. 221, 1981). The markedly reduced elimination of ceftriaxone in some dialysis patients could not be explained by the prestudy biochemical parameters (blood urea nitrogen, serum creatinine, etc.) and

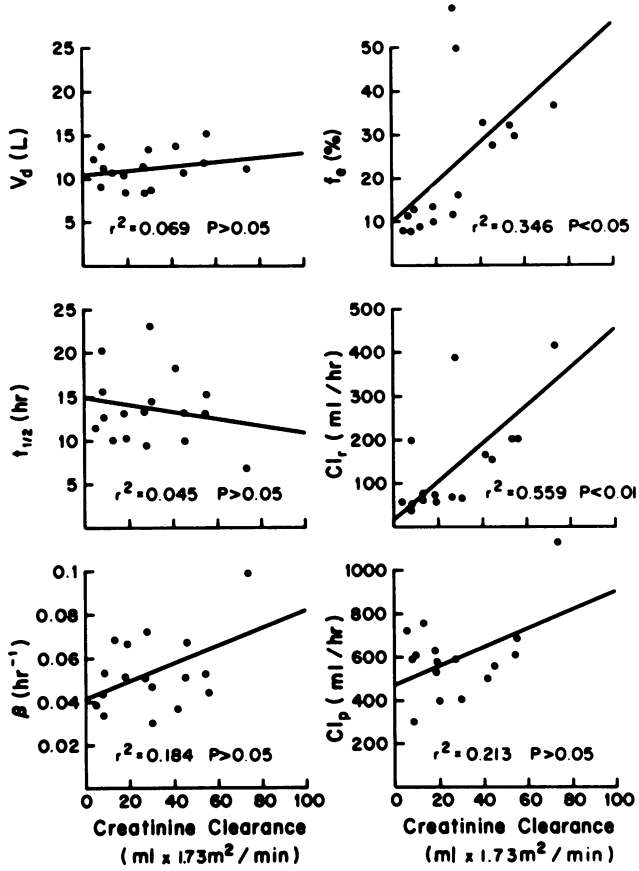

FIG. 3. Relationships between each of the calculated pharmacokinetic parameters of ceftriaxone and CL_{CR} in patients with severe, moderate, and mild renal impairment.

TABLE 2. Comparison of pharmacokinetic parameters of ceftriaxone in patients with impaired renal function to those in healthy young and elderly subjects[a]

Renal function (no. of patients)	Age (yr)	Body wt (kg)	CL_{CR} (ml/min per 1.73 m²)	β (h^{-1})	$t_{1/2}$ (h)	V (liters)	CL_P (ml/h)	CL_R (ml/h)	f_e (%)
Dialysis (4)[b]	44.3 ± 17.7	67.2 ± 12.6		0.040 ± 0.008	17.3	13.8 ± 3.2	538 ± 69		
Impaired									
Severe (5)[b]	63.6 ± 8.6	62.5 ± 5.3	8.6 ± 2.9	0.048 ± 0.014	14.4	11.5 ± 1.7	603 ± 177	58.7 ± 16.0	10.1 ± 2.4
Moderate (6)	53.8 ± 18.6	60.1 ± 7.1	25.3 ± 5.4	0.053 ± 0.015	13.1	10.3 ± 2.0	529 ± 97	142 ± 127	26.9 ± 21.6
Mild (6)	60.7 ± 10.5	69.5 ± 6.7	52.3 ± 11.5	0.059 ± 0.023	11.7	12.7 ± 1.8	705 ± 251	231 ± 108	32.0 ± 3.4
Normal[c]									
Young subjects (8)	28.9 ± 4.6	73.3 ± 12.7	114 ± 26	0.093 ± 0.014	7.5	11.0 ± 1.7	1,203 ± 189	416 ± 69	41.4 ± 4.0
Elderly subjects (8)	70.5 ± 4.5	71.5 ± 9.3	92 ± 14	0.078 ± 0.019	8.9	10.7 ± 2.1	833 ± 250	318 ± 66	39.6 ± 8.0

[a] Values are means ± standard deviations. Harmonic mean values are reported for $t_{1/2}$.
[b] In one patient, plasma concentrations could not be determined because of an interfering peak at the retention time of ceftriaxone.
[c] From reference 6a.

may be due to an impaired biliary excretion process, which is the alternate pathway of elimination for ceftriaxone in humans (12–14). It is suggested, therefore, that ceftriaxone concentrations in plasma should be monitored in the patients with end-stage renal disease to determine whether dosage adjustments are necessary. Maximum ceftriaxone plasma concentrations in all other patients generally do not exceed 300 μg/ml when the dose is 2 g/day. A clinical efficacy trial in patients with end-stage renal disease will be necessary to obtain more safety data.

In summary, the elimination of ceftriaxone is reduced moderately in patients with CL_{CR} above 5 ml/min, and therefore dosage adjustments should not be necessary as long as the ceftriaxone dosage is 2 g or less per day. In dialysis patients maintained on hemodialysis, plasma concentrations should be monitored to determine whether dosage adjustments are warranted. Since ceftriaxone is not removed from plasma by hemodialysis, supplemental doses should not be necessary for dialysis patients on hemodialysis.

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