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Cefmenoxime Pharmacokinetics in Healthy Volunteers and Subjects with Renal Insufficiency and on Hemodialysis

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The pharmacokinetics of cefmenoxime were characterized in five healthy volunteers and in 15 subjects with various degrees of renal insufficiency after a single 10-mg/kg, 5-min intravenous infusion. Five of these subjects were studied both on hemodialysis and during an interdialytic period. Plasma, urine and dialysate were assayed for cefmenoxime by a specific high-pressure liquid chromatographic assay. Peak plasma concentrations of cefmenoxime were ca. 94 μg/ml after completion of the infusion. The mean plasma and renal clearances in the healthy volunteers were 281 ± 66 and 228 ± 52 ml/min, respectively. Plasma clearance declined in patients with renal insufficiency and correlated significantly with creatinine clearance. The mean apparent volume of distribution at steady state in the healthy volunteers was 0.23 liters/kg and was not found to be significantly different in subjects with renal insufficiency. The mean cumulative 24-h urinary recovery of cefmenoxime in healthy volunteers was 81% of the administered dose and decreased with reduced renal function. Cefmenoxine dosage should be reduced in proportion to the decline in creatinine clearance. A simple nomogram for dose selection is provided.

Cefmenoxime, a new semisynthetic cephalosporin antibiotic, possesses broad-spectrum antibacterial activity against both gram-positive and gram-negative bacteria (4, 9). The in vitro activity of cefmenoxime is considerably greater than that of cefazolin, cefamandole, and cefoxitin against most *Enterobacteriaceae* species and *Pseudomonas aeruginosa* but slightly less active than cefazolin and cefamandole against *Staphylococcus aureus*.

Studies in subjects with normal renal function have shown the drug to be primarily eliminated unchanged in the urine, with a plasma half-life of ca. 1 h (5). Renal clearance is responsible for 80% of the total plasma clearance, and renal insufficiency would be expected to prolong its elimination.

The purpose of this investigation was to examine the pharmacokinetic disposition of cefmenoxime in subjects with normal kidney function and with various degrees of renal impairment and to determine the influence of hemodialysis on its removal.

MATERIALS AND METHODS

Twenty subjects (15 male, 5 female) agreed to participate in the study after informed written consent was obtained. Demographic data are shown in Table 1. Five healthy volunteers had normal renal function, and 15 subjects had various degrees of renal function. The renal function of each individual was stable throughout the course of the study. Endogenous creatinine clearances determined from two separate 24-h urine collections (pre- and poststudy) were used as the measure of renal function. Estimations of creatinine clearance were also calculated by the method of Cockcroft and Gault (1), using total and ideal body weight (2). The body surface area for each subject was estimated by the formula of DuBois and DuBois (3).

Five subjects with measured creatinine clearances of less than 2 ml/min and who were receiving intermittent hemodialysis were studied both during hemodialysis and during an interdialytic period.

A complete medical history, a physical examination, and a laboratory profile were obtained for all subjects before and after the study period. The subjects received no other antibiotics during the study, and all other medications were administered as prescribed.

Cefmenoxime (Abbott Laboratories, North Chicago, Ill.) was administered in a dose of 10 mg/kg of body weight dissolved in 50 ml of 5% glucose in water and infused over a 5-min period with a constant-rate Harvard infusion pump. Blood samples (5 ml each) were collected before the dose and then at 0.08, 0.17, 0.25, 0.33, 0.50, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8, 12, and 24 h. Additional samples were taken at 36 and 48 h from the patients with some degree of renal dysfunction. Samples were immediately placed in ice and centrifuged, and the plasma was removed and frozen at −20°C until assayed. Urine samples (when available) were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 24, 36, and 48 h. Urine samples were refrigerated during the collection period. All plasma and urine samples were usually assayed within 24 to 48 h of the study period.

Subjects studied during a hemodialysis period received a single 10-mg/kg dose given intravenously at least 1.5 h before the beginning of dialysis. Hemodialysis was performed with Centry II dialyzer units (Cobe Laboratories Inc., Lakewood, Colo.) with single-pass dialysate flow and hollow-fiber cuprophane membrane artificial kidneys (Gambro Inc., Lund, Sweden). Blood flow rates were maintained constant and measured for each subject by bubble transit time. Dialysate was sampled and flow rates were determined by collecting and measuring total hourly dialysate volumes. Total membrane pressure was recorded, and negative membrane pressure was minimized to prevent excessive ultrafiltration. The hemodialysis characteristics are listed in Table 2. Blood samples were collected from the arterial and venous dialysis tubing at 30-min intervals during hemodialysis. Blood and dialysate samples were processed as above.

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TABLE 1. Subject characteristics[a]

Subject	Age (yr)	Sex	Weight (kg)	Body surface area (m^2)[b]	Serum creatinine (mg/dl)[c]	CL_{CR} (ml/min)[c]
Healthy						
1	26	M	85	1.99	1.2	118
2	33	M	90	2.04	1.4	110
3	26	M	82	1.94	1.2	108
4	30	M	82	1.94	1.2	98
5	26	M	88	2.04	1.1	99
Renal impairment						
6	58	M	96	2.18	1.7	99
7	75	M	70	1.73	1.0	93
8	66	M	72	1.77	1.0	78
9	68	M	71	1.75	1.6	68
10	39	F	47	1.29	1.7	49
11	50	F	70	1.73	2.0	27
12	57	F	70	1.73	2.6	20
13	61	M	83	1.96	6.3	18
14	44	M	75	1.82	3.7	18
15	58	F	89	2.06	5.3	6
16	58	M	89[d]	2.07	13.8	2
17	38	M	71[d]	1.74	23.8	0
18	75	M	74[d]	1.80	12.6	0
19	52	M	78[d]	1.86	18.3	0
20	73	F	47[d]	1.30	4.8	0

[a] Healthy subject means ± standard deviations: age, 28 ± 3 years; weight, 85 ± 4 kg; body surface area, 1.99 ± 0.05 m^2; serum creatinine, 1.2 ± 0.1 mg/dl; CL_{CR}, 106 ± 9 ml/min. Renal impairment subject means ± standard deviations: age, 58 ± 12 years; weight, 73 ± 14; body surface area, 1.78 ± 0.28 m^2.

[b] From the formula of DuBois and DuBois (3).

[c] Serum creatinine and CL_{CR} are an average of two measured determinations.

[d] Weight during an interdialytic period.

After an appropriate washout period of at least 2 weeks, each hemodialysis subject was given the same dose of cefmenoxime shortly after the completion of a hemodialysis period. Venous blood samples were collected before, at 0.08, 0.5, 0.75, 1, 1.5, 2, 3, 6, 8, 12, 18, 24 h, and just before beginning the next hemodialysis period.

Analysis of cefmenoxime in reconstituted vials revealed that the concentration averaged 96.2% of the expected concentrations. Thus, the doses administered to all subjects were corrected before pharmacokinetic analyses.

Analytical. Plasma, urine, and dialysate samples were assayed for cefmenoxime by a high-pressure liquid chromatographic assay developed in our laboratory (8). Reproducibility measurements yielded a coefficient of variation for plasma and urine of less than 5%. The lowest concentrations detectable without extraction were 0.2 μg/ml for plasma and 5 μg/ml for urine.

Pharmacokinetic analysis. A two-compartment model with constant-rate input was used to describe plasma concentrations. The pharmacokinetic parameters were estimated by nonlinear least-squares regression with the PROPHET computer resource (6). Observed concentrations were weighted by the reciprocal of the value squared. Half-life was calculated by dividing the terminal disposition rate constant estimated from the pharmacokinetic model into the natural logarithm of 2 (6). Estimates of plasma clearance (CL) and volume of distribution at steady-state (V_{ss}) were determined by using the noncompartmental equations CL = Dose/AUC and V_{ss} = Dose (AUMC)/$(AUC)^2$, where AUC is the area under the plasma concentration-time curve from time zero to infinity and AUMC is the area under the first moment of the plasma concentration-time curve (7). Since the use of the equation for V_{ss} is appropriate only after intravenous bolus dosing, correction was made for infusion administration by subtracting (t/2) (Dose/AUC) from the V_{ss} values obtained, where t is the infusion time. The estimate of the apparent volume of distribution after distribution equilibrium (V_β) was calculated as the administered dose divided by the area under the concentration-time curve times the terminal disposition rate constant. The areas under the plasma concentration-time curve were calculated by the log-trapezoidal rule, and the remaining area, from the last time point to infinity, was determined by dividing the last plasma concentration-time point by the terminal disposition rate constant.

Renal clearance (CL_R) was calculated by $CL_R = A_e/AUC$, where A_e is the total amount of cefmenoxime recovered in the urine over time divided by the area under the concentration time curve from time zero to infinity.

Clearance by hemodialysis (CL_D) was calculated from the equation $CL_D = (Q_D{}^t \times C_D{}^t)/(C_p \text{ mid})^t$, where Q_D is the dialysate flow rate, C_D is the concentration of the drug in the dialysate during the collection period (t), and C_p mid is the arterial plasma concentration at the midpoint of the collection period.

Statistical analysis. Relationships between parameters and renal function were assessed by linear regression analysis. The 0.05 level, with a two-tailed determination, was chosen as the level of significance.

RESULTS

Plasma concentration-time curves representative of the healthy subjects and subjects with various degrees of renal

TABLE 2. Hemodialyzability of cefmenoxime

Subject	Duration of dialysis (h)	Hct (%)[a]	Dialysis membrane surface area (m^2)	Blood flow (ml/min)[b]	Dialysate flow (ml/min)[c]	Mean plasma extraction ratio (%)	Mean dialysis clearance (ml/min)[d]	Fraction of dose recovered in dialysate
16	3.5	24	1.8	250	520	27.0 ± 20.0	59.1 ± 5.1	0.32
17	3.5	29	1.8	260	500	14.5 ± 10.8	67.8 ± 33.4	0.38
18	3.0	29	0.41	166	490	24.1 ± 13.1	43.0 ± 18.1	0.16
19	4.0	19	2.5	200	520	14.2 ± 5.0	47.0 ± 9.0	0.51
20	4.0	29	0.80	190	530	14.2 ± 9.3	30.7 ± 4.7	0.32

[a] Average hematocrit (Hct) value from pre- and postdialysis samples.

[b] Measured by bubble transit time.

[c] Measured from total hourly dialysate collections.

[d] Determined from the amount of drug recovered in the dialysate.

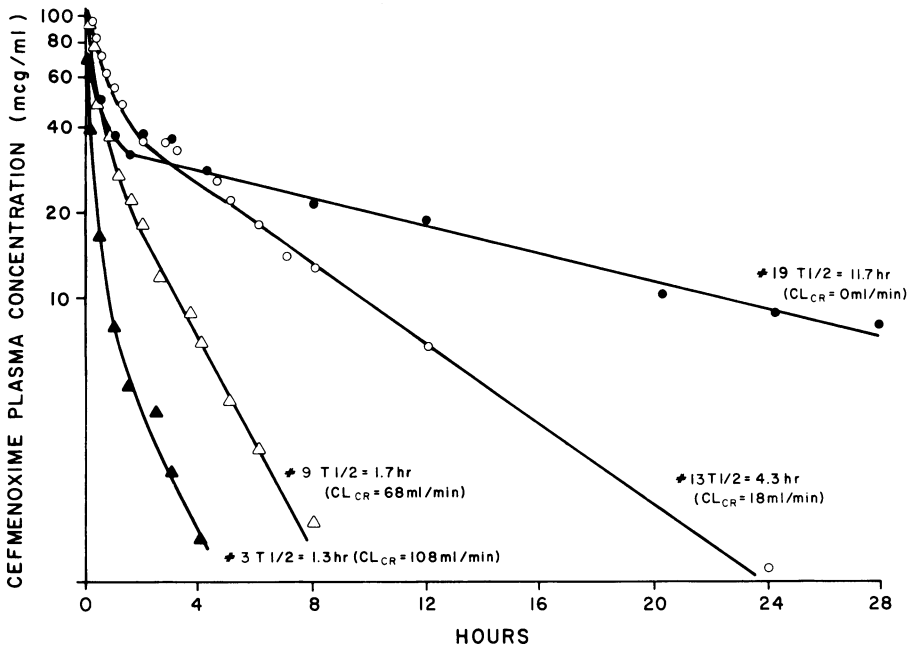

FIG. 1. Cefmenoxime plasma concentrations versus time for individual subjects representative of various degrees of renal function.

function are shown in Fig. 1. The biexponential decay of cefmenoxime in plasma was evident in each case, and the terminal half-life increased with decreasing renal function. In the five healthy subjects, the maximum plasma concentration attained after a 10 mg/kg intravenous dose over 5 min was 88.3 ± 21.2 μg/ml (mean ± standard deviation). In the 15 subjects with renal insufficiency, the maximum concentration was 95.5 ± 65.5 μg/ml.

The pharmacokinetic parameters of cefmenoxime are listed in Table 3. The plasma clearance and renal clearance of cefmenoxime were 281 ± 66 and 228 ± 52 ml/min, respectively, in the healthy subjects and were decreased in subjects with renal insufficiency. A significant correlation was found between plasma clearance and measured creatinine clearance ($P < 0.0001$) (Fig. 2). In addition, a significant correlation was also found between plasma clearance and estimated creatinine clearance calculated with total body weight ($P < 0.0001$). Furthermore, the use of ideal body weight in the calculation of creatinine clearance only slightly improved the fit of the line. In the five subjects on hemodialysis, (creatinine clearance less than 2 ml/min), plasma clearance represented nonrenal clearance (30 ± 25 ml/min). Nonrenal clearance in the healthy subjects was determined by subtracting renal clearance from plasma clearance. This value was found to be 53 ± 25 ml/min, which was not significantly different ($P > 0.05$, unpaired t test) from that found in the five subjects on hemodialysis.

The V_{ss} for the normal subjects was 0.23 ± 0.07 liters/kg (range, 0.14 to 0.33 liters/kg). In subjects with renal insufficiency, the V_{ss} ranged from 0.06 to 0.75 liters/kg. When regression analysis of V_{ss} versus measured creatinine clearance for all subjects was performed, no significant trend was found among the healthy subjects and those with renal dysfunction. The V_β was 0.37 ± 0.11 liters/kg (range, 0.20 to 0.48 liters/kg) for the normal subjects and 0.10 to 1.54 liters/kg in subjects with renal insufficiency.

High urinary concentrations of cefmenoxime were achieved in the healthy subjects since the majority of the drug is excreted unchanged into the urine (average 81 ± 6% of the dose in 24 h). In the subjects with normal renal function, 40% of the dose was excreted in 0.5 h, 70% by 2 h, and 80% by 4 h. Only 3% of the administered dose was excreted after the first 4 h. Thus, urine concentrations were as high as 750 to 4,300 μg/ml in 0.5 h and averaged 50 μg/ml

TABLE 3. Pharmacokinetic parameters[a]

Subject	CL (ml/min)	CL_R (ml/min)	$t_{1/2}$ (h)[b]	V_{ss} (liters/kg)	V_β (liters/kg)
Healthy					
1	294	218	1.2	0.19	0.42
2	185	154	1.1	0.14	0.20
3	310	277	1.3	0.24	0.34
4	256	213	1.6	0.23	0.43
5	362	279	1.4	0.33	0.48
Renal impairment					
6	130	111	1.5	0.13	0.18
7	180	129	1.4	0.30	0.32
8	217	198	1.4	0.24	0.36
9	130	76	1.7	0.16	0.20
10	176	140	1.6	0.43	0.51
11	28	16	2.9	0.06	0.10
12	106	75	4.6	0.57	0.60
13	39	11	4.3	0.16	0.18
14	148	107	9.0	0.75	1.54
15	30	9	17.5	0.52	0.51
16	59	4	10.6	0.54	0.61
17	54	0	6.3	0.38	0.41
18	14	0	21.2	0.33	0.33
19	5	0	26.4	0.25	0.25
20	20	0	11.7	0.26	0.26

[a] Healthy subject means ± standard deviation: CL, 281 ± 66 ml/min; CL_R, 228 ± 52 ml/min; $t_{1/2}$, 1.3 ± 0.2 h; V_{ss}, 0.23 ± 0.07 liters/kg; V_β, 0.37 ± 0.11 liters/kg. Means for subjects with renal impairment are not given since they did not represent a homogeneous population.

[b] Terminal elimination half-life.

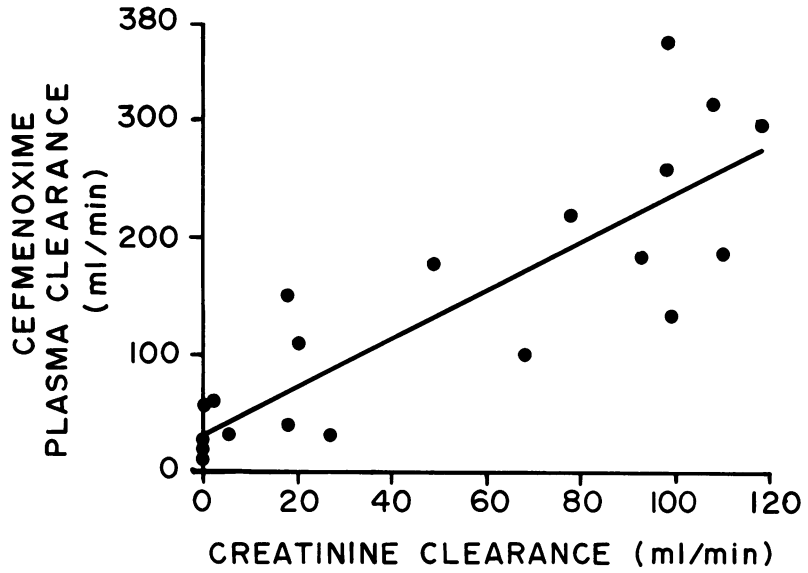

FIG. 2. Cefmenoxime plasma clearance versus measured creatinine clearance. $r^2 = 0.73$. Cefmenoxime clearance = $(2.05 \times CL_{CR}) + 31.8$ ($P < 0.0001$).

(range, 26 to 82 μg/ml) at 4 h. At 6 h, urine levels ranged from 3 to 98 μg/ml. Renal clearance averaged 228 ± 52 ml/min and represented 81 ± 6% of total plasma clearance in subjects with normal renal function. Eleven of the 15 subjects with renal insufficiency were able to make urine. Eight of 11 had measurable urine concentrations at 24 h ranging from 19 to 290 μg/ml. Renal clearance and cumulative percentage of the dose excreted in the urine at 24 h in subjects with various degrees of renal impairment ranged from 4 to 198 ml/min and 3 to 91%, respectively.

The dialysis clearance and the fraction of the dose removed by a dialysis period are detailed in Table 2. The dialysis clearance ranged from 30.7 to 67.8 ml/min, with 16 to 51% of the administered dose recovered in the dialysate. The plasma extraction ratio across the dialyzer membrane averaged 19 ± 6% calculated from arterial and venous concentrations. A graph of the arterial and venous plasma concentrations of subject 19 is shown in Fig. 3.

DISCUSSION

The results of our investigation of the pharmacokinetic disposition of cefmenoxime were similar to those reported by Granneman et al. (5) and Leroy et al. (A. Leroy, G. Humbert, J. P. Fillastre, F. Borsa, and M. Godin, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami Fla., abstr. no. 108, 1982). When cefmenoxime (10 mg/kg) was given by a 5-min infusion to all subjects, a maximum concentration of 93.5 ± 56.7 μg/ml resulted. Similar to other cephalosporins, cefmenoxime distributes primarily in body water. We found the V_{ss} (0.23 liters/kg) to be slightly larger than that reported by Leroy et al. (22nd ICAAC, abstr. no. 108), 0.16 to 0.20 liters/kg in healthy volunteers. This may be related to differences in methods of determining this parameter.

Cefmenoxime is eliminated primarily by renal mechanisms. Mean urinary recovery was 81% over 24 h in healthy subjects, similar to that found by Leroy et al. (81 to 88%) (22nd ICAAC, abstr. no.. 108) and greater than that reported by Granneman et al. (60.6 to 78.5%) (5). Renal clearance of cefmenoxime exceeded creatinine clearance in the healthy volunteers and demonstrated that net tubular secretion of the antibiotic contributes to the overall renal elimination.

Our mean value for plasma clearance in healthy subjects, 281 ml/min (245 ml/min/1.73 m^2) was similar to those re-

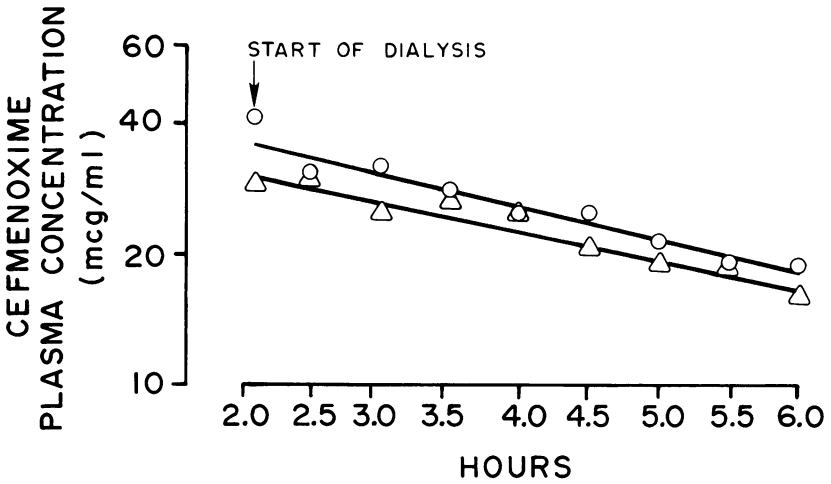

FIG. 3. Arterial (○) and venous (△) plasma concentration-time curve of subject 19 while on hemodialysis.

ported by Granneman et al. (5) and Leroy et al. (22nd ICAAC, abstr. no. 108), 245 ml/min and 151.2 to 242.6 ml/min/1.73 m^2, respectively.

The elimination of cefmenoxime was reduced in relation to the degree of renal insufficiency; the half-life of cefmenoxime was 1.4 ± 0.2, 5.2 ± 2.6, and 15.6 ± 7.5 h in subjects with creatinine clearances of ca. 50 to 120 ml/min, 20 to 50 ml/min, and 0 to 6 ml/min, respectively. Leroy et al. (22nd ICAAC, abstr. no. 108) also found prolongation of the elimination half-life in subjects with decreasing renal function, 2.0, 3.2, and 7.9 h in subjects with creatinine clearances of 40 to 80 ml/min, 15 to 40 ml/min, and less than 15 ml/min, respectively. Our mean value for renal clearance in healthy subjects, 228 ± 52 ml/min (199 ± 45 ml/min/1.73 m^2), was similar to those reported by Granneman et al. (5) and Leroy et al. (22nd ICAAC, abstr. no. 108) of 182 ml/min and 117 to 198 ml/min per 1.73 m^2, respectively. Renal clearance of cefmenoxime decreased with decreasing renal function. Variability in the cause of the primary renal lesion, infrequent voiding, incomplete bladder emptying, and the requirement of long collection periods make the calculation of renal clearance in moderate-to-severe renal impairment difficult. Therefore, the renal clearance values reported in Table 3 for moderate-to-severe renal impairment subjects should be interpreted with caution.

The contribution of nonrenal elimination to plasma drug clearance in healthy volunteers is relatively small but becomes an important route of elimination in severe renal impairment. The values we report are not significantly different from those calculated (24 to 39 ml/min) from the data of Leroy et al. (22nd ICAAC, abstr. no. 108).

Cefmenoxime is removed by hemodialysis as might be expected from its low molecular weight (molecular weight, 530), intermediate degree of protein binding (77%), and small volume of distribution (5). The amount of drug removed, 16 to 51% of the administered dose, was dependent on the surface area of the dialysis membrane, blood flow rate, and the duration of the hemodialysis period. Therefore, a supplemental dose of cefmenoxime should be given after each dialysis period to maintain an average effective plasma concentration. This dose is dependent upon the characteristics of the dialysis prescription.

A dosing nomogram was formulated based on the average steady-state plasma concentration, the creatinine clearance of the patient, and the defined microbiological breakpoints for in vitro susceptibility testing. The average steady-state plasma concentrations were chosen to exceed the microbiological breakpoints (4) (susceptible, 8 μg/ml; intermediate, 16 μg/ml) by twofold. A linear correlation existed between cefmenoxime plasma clearance and measured creatinine clearance (Fig. 2) or calculated creatinine clearance. Therefore, the amount of drug to be administered per day to maintain the average plasma concentration desired can be determined (Table 4). The dosing intervals were chosen relative to the decrease in kidney function and the cefmenoxime plasma clearance. The dosing interval and size of the dose must be determined by the site of the infection and the susceptibility of the pathogen.

TABLE 4. Dosage nomogram for cefmenoxime

CL_{CR} (ml/min)[a]	Dosage (mg/kg per day) for:		Recommended interval (h)
	Mild to moderate infection	Serious infection	
80–120	70–100	140–200	4 to 6
50–79	45–65	95–135	6 to 8
10–49	20–45	40–85	8
<10	10–20	20–35	12
0 (hemodialysis)	7.5	15	24[b]

[a] Creatinine clearance was measured by 24-h collection or calculated by the Cockcroft and Gault equation (1).

[b] A supplemental dose of 3.5 to 7.5 mg/kg should be given after each hemodialysis period.

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