Pharmacokinetics of Cefuroxime in Normal and Impaired Renal Function: Comparison of High-Pressure Liquid Chromatography and Microbiological Assays

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The pharmacokinetics of cefuroxime were studied after a single dose of 750 mg was given intravenously to each of 21 male volunteers grouped according to their creatinine clearances; these clearances were 60 to 120, 20 to 59, and <20 ml/min per 1.73 m,^{2} respectively, for groups 1 (12 subjects), 2 (4 subjects), and 3 (5 subjects). Cefuroxime obeyed two-compartment model kinetics in all three groups. Initial serum levels of cefuroxime were approximately 130 μg/ml in group 1 and 2 and 80 μg/ml in group 3. The levels then declined rapidly for 0.5 to 1 h after injection. After that time, cefuroxime levels declined more slowly, and the elimination rate became monoexponential. The mean serum half-lives for cefuroxime in groups 1, 2, and 3 were 1.7, 2.4, and 17.6 h, respectively. Mean cefuroxime levels in serum were greater than 8 μg/ml for 3 h in group 1, for 6 h in group 2, and for 30 h in group 3. Cumulative 24-h urinary excretion accounted for essentially 100% of the dose in group 1 and 2, and for 40% in group 3. Urine levels exceeded the minimal inhibitory concentration for susceptible organisms for more than 12 h in all groups. Cefuroxime distribution characteristics were independent of renal function. In patients with creatinine clearances less than 20 ml/min per 1.73 m^2, doses of cefuroxime needs to be reduced. A microbiological disk diffusion assay and a high-pressure liquid chromatography assay for cefuroxime yielded statistically identical results, except for serum levels in uremic patients (group 3).

Cefuroxime, a new cephalosporin antibiotic, has a broad spectrum of antimicrobial activity that includes many gram-positive and gram-negative bacteria which are resistant to some other cephalosporins (2, 6, 9, 10, 12, 13). Cefuroxime is resistant to many of the β-lactamases produced by gram-negative organisms (9, 12).

Cefuroxime pharmacokinetics have been examined in normal persons, in patients with infections, and in subjects with renal failure (3–5, 7, 11, 14). It has a biological half-life of 1.4 to 1.8 h in normal persons, which increases to approximately 20 h in anuric patients. The volume of distribution is 12 to 18 liters, and 33% of it is bound to serum proteins at therapeutic concentrations.

We have examined the pharmacokinetics of cefuroxime in detail in normal subjects and also in subjects who had renal failure or anuria. All serum and urine drug levels were determined with a standard microbiological cefuroxime assay and a high-pressure liquid chromatography (HPLC) assay, and the results obtained by the two methods were compared.

MATERIALS AND METHODS

Subjects. Subjects were 21 male patients in the medical and surgical wards at the William S. Middleton Memorial Veterans Hospital. All subjects gave informed consent to participation in the study, and all showed negative skin responses for penicillin allergy. Subjects were ambulatory but had a variety of medical conditions, none of which were severe. None of the subjects had liver disease or infection, or were receiving antibiotics.

Procedures. The subjects were divided into three groups according to their normalized creatinine clearances. Groups 1 (12 subjects, ages 46 to 91, weighing 62 to 135 kg), 2 (4 subjects, ages 72 to 84, weighing 58 to 77 kg), and 3 (5 subjects, ages 47 to 75, weighing 60 to 80 kg) had creatinine clearances of ≥60, 20 to 59, and <20 ml/min per 1.73 m^2, respectively. Shortly after breakfast, each subject received 750 mg of cefuroxime, (Glaxo Research Division, Mayer Laboratories, Fort Lauderdale, Fla) dissolved in 20 ml of physiological saline, by infusion into a forearm vein over a 2-min period. Blood samples (5 ml) were obtained from the contralateral forearm vein immediately before and serially after the cefuroxime was administered. The blood was allowed to clot; serum was obtained after centrifugation and frozen until assayed.

Urine samples were collected immediately before dosing and quantitatively at intervals of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h thereafter, and were frozen until assayed. Some patients in group 3 were unable to produce urine.

Cefuroxime assay. The concentrations of cefuroxime in serum and urine were determined by both HPLC and microbiological assays. Serum and urine were examined in triplicate by a modified microbiological disk diffusion method previously described (8). Antibiotic medium no. 2 (Oxoid Ltd., London, England) in phosphate buffer at pH 7.0 was used, and the indicator organism was *Bacillus subtilus* ATCC 6633. Dilution of serum and urine samples into phosphate buffer at pH 7.0 was necessary for some samples due to high concentrations of cefuroxime. Serum and urine standards were prepared in normal pooled serum and phosphate buffer at pH 7.0. The relationship between the diameters of the zone of inhibition of bacterial growth and the logarithm of drug concentration was linear over the concentration range of 1.5 to 50 µg/ml. Assay reproducibility was ±10%.

Plasma and urine samples were also analyzed by a modification of the HPLC method of Aziz et al. (1) for cefamandole. Equal portions of plasma and 60% methanol–0.2 M sodium acetate (pH 5.2) were mixed by blending in a Vortex mixer, and incubated for 2 min at 60°C. Samples were centrifuged 10 min at 3,000 rpm, and 25 µl of supernatant were injected into an HPLC system consisting of a Waters model U6K injection valve, model 6000 A solvent pump and a model 450 variable wavelength detector set at 270 nm. The column was C_{18} µ-Bondapak, and the mobile phase was 20% methanol–0.01 M sodium acetate, which had been passed through an HA 0.45-µm membrane filter (Millipore Corp., Bedford, Mass.) and degassed. The flow rate of the mobile phase through the HPLC system was 1.5 ml/min.

Urine samples were diluted 1:1 to 1:10 with water, depending on concentration of cefuroxime, and 25-µl samples were injected directly into the HPLC. All plasma and urine samples and standard solutions were prefiltered with an HA 0.45-µm membrane filter (Millipore Corp.) Plasma and urine standards were prepared by serially diluting to final concentrations of 160, 80, 40, 20, 10, and 5 µg of cefuroxime per ml.

Data analysis. The individual serum profiles of cefuroxime by both assay procedures were fitted to a biexponential function of the form of equation 1 (15),

$$C = Ae^{-\alpha t} + Be^{-\beta t} \qquad (1)$$

in which C is the concentration of antibiotic in serum at time *t* postdosing, A and B are concentration coefficients, and α and β are rate constants governing the fast and slow phases of drug loss from serum.

Initial estimates of the function in equation 1 were obtained by standard curve-stripping procedures. Improved estimates were obtained by nonlinear regression analysis with the program NREG on a Univac digital computer (MAAC Nonlinear Regression Routines, Academic Computer Center, University of Wisconsin). All cefuroxime concentrations were weighted according to their reciprocals during the computer analysis.

Because the observed pattern of cefuroxime loss

from serum after intravenous dosing is frequently identified with the pharmacokinetic two-compartment open model, the computer estimates were further analyzed in terms of the specific constants associated with this model by means of equations 2 and 3, with the data obtained by the HPLC assay (15).

$$C = \frac{D}{V_1(\alpha - \beta)}[(k_{21} - \beta)e^{-\beta t} - (k_{21} - \alpha)e^{-\alpha t}] \qquad (2)$$

in which

$$\begin{aligned}\alpha \\ \beta\end{aligned} = 0.5\left[(k_{12} + k_{21} + k_{el}) \pm ((k_{12} + k_{21} \\ + k_{el})^2 - 4k_{21}k_{el})^{1/2}\right] \qquad (3)$$

Serum and urine levels of cefuroxime, and also the parameter values obtained after fitting the cefuroxime data to equation 1, were compared by assay and patient group by analysis of variance. The pharmacokinetic values subsequently obtained from the HPLC assay values were also compared by group by analysis of variance. In any instance where a significant effect was shown by analysis of variance, differences between assays and between particular groups were further examined by paired and unpaired *t* tests, respectively.

RESULTS

Comparison of assays. The mean serum and urine levels of cefuroxime at each sampling interval, as measured by the two assay procedures, are given in Tables 1 and 2. Also given in Table 1 are the results of statistical comparison of drug concentrations in serum obtained by the two assay methods. In groups 1 and 2, the two assay methods generally gave statistically indistinguishable results. In group 1, the HPLC method yielded values significantly higher than those obtained with the microbiological method at 3 and 8 h. In group 2, the HPLC method yielded values significantly higher than those obtained with the microbiological method at 1 h, but lower values at 2 h. The two methods gave statistically indistinguishable cefuroxime values in both groups 1 and 2 at all other sampling times. In group 3, however, the HPLC method yielded serum values significantly higher than those obtained with the microbiological method at all sampling time except those at 0, 0.08, and 0.25 h postdosing.

To explain these assay differences, known amounts of cefuroxime were added to drug-free sera from two patients each in group 1 and group 3 HPLC assays of all four sera and microbiological assays of the two sera from group 1 patients gave values that were within 6% of the expected concentration. In contrast, microbiological assays of sera from group 3 patients yielded values that were 22 and 34% less than the added amount. This difference disappeared when the sera were reassayed after a 1:5 dilution in buffer.

TABLE 1. *Mean serum concentrations of cefuroxime and standard deviations, as measured by HPLC and microbiological methods*

Group	Test	Concn of cefuroxime in serum (µg/ml) at time (h):													
		0	0.08	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24
1	HPLC	144±46	72±13	47±15	37±6	30±6	25±5	20±5	16±5	11.3±4.5[a]	7.8±3.7	5.6[b]	2±1.6	0.4±0.7	ND[c]
	Microbiological	149±42	77±17	54±14	39±13	31±9	24±7	18±6	15±6	9.6±4.5	7.5±4.7	4.3±7.5	1.7±1.7	0.1±0.3	ND
2	HPLC	121±54	92±51	55±9	44±7	41±8	36±10[a]	30±10[a]	25±9	18±8	15±8	11.2±8.8	6.1±4.0	2.4±2.2	0.5±1.0
	Microbiological	105±34	99±43	55±9	42±14	38±11	33±9	23±8	22±10	18±9	7.9±3.5	14[b]	6.5±5.7	2.9±3.0	ND
3	HPLC	81±44	66±15	55±9	51±6[a]	48±6[a]	48±6[a]	45±7[a]	41±7[a]	39±7[a]	36±8[a]	40[b]	31±8[a]	24±8[a]	17±7[a]
	Microbiological	82±52	62±18	44±14	39±11	33±4	32±1	26±5	25±5	23±4	21±4	25[b]	16±8	15±6	11±3

[a] Values obtained from the two different assays are significantly different ($P < 0.05$).
[b] Average of two samples.
[c] ND, None detected.

Contrary to the results obtained with serum, the two assays gave statistically indistinguishable results at all sampling intervals in urine (Table 2).

Serum levels and urinary excretion of cefuroxime. Mean serum levels of cefuroxime obtained by HPLC analysis are shown on a semilogarithmic scale in Fig. 1. In all groups the decline in drug levels was biphasic. The rapid phase of cefuroxime loss from serum lasted 0.5 to 1.0 hours postdosing. Cefuroxime levels were similar in both groups 1 and 2 during this period, with maximum values of approximately 130 µg/ml occurring immediately postdosing. In group 3, initial mean serum levels of cefuroxime were somewhat lower at 80 µg/ml.

After the rapid phase of drug loss, serum cefuroxime levels declined at a slower, monoexponential rate. This latter phase was clearly related to renal function. Mean cefuroxime concentrations in serum were greater than 8 µg/ml for 3 h in group 1, for 6 h in group 2 and for 30 h in group 3.

Urinary levels of antibiotic were uniformly high in group 1 and group 2 subjects (Table 2), but by the 12 to 24 h interval collection, levels had declined to 24 and 44 µg/ml, respectively. Drug levels were lower in group 3, but excretion was more prolonged. Two patients in group 3 had levels of 58 and 85 µg/ml during the 24 to 36 h urine collections.

The cumulative percentage of the cefuroxime dose recovered unchanged in the urine, as determined by the HPLC method, is shown in Table 2. Subjects in group 1 and 2 excreted 96% of the dose within 24 h whereas the mean recovery from group 3 was 40%. For some individuals in group 3, however, urine collections were not collected for a sufficiently long period to ensure complete recovery of drug. Two subjects with creatinine clearances of 1 to 2 ml/min per 1.73 m^2 excreted only 0.6 and 2.9% of the dose during 0 to 12 h postdosing.

Description of serum data by using a biexponential function. The mean values (obtained by fitting individual data sets from the two assay methods to equation 1) together with statistical comparisons of the results obtained between assay methods and between groups, are summarized in Table 3. From the table it can be seen that the values of all four parameters A, B, α, and β are independent of the assay procedure. The overall postdistributive elimination rate constant, β, is group dependent and increases in the order of group 3 < 2 < 1. Similarly, the area under the serum level versus time curve (AUC) is group dependent, increasing in the order group 1 < 2 < 3. The AUC value is also assay dependent in group 3, because the HPLC method

TABLE 2. *Mean urine concentrations of cefuroxime and standard deviations, as measured by HPLC and microbiological methods*

| Group	Assay	Concn of cefuroxime in urine (µg/ml) at time (h):					% of dose recovered in urine
		0-2	2-4	4-8	8-12	12-24	
1	HPLC	2133 ± 1470	982 ± 1056	240 ± 203	81 ± 81	24 ± 20	96 ± 10'
	Microbiological	2024 ± 1221	920 ± 768	224 ± 181	89 ± 75	22 ± 28	
2	HPLC	1831 ± 1995	944 ± 446	393 ± 90	173 ± 115	44 ± 23	98 ± 1
	Microbiological	1504 ± 1377	586 ± 383	558 ± 349	190 ± 172	58 ± 48	
3	HPLC	236 ± 183	301[a]	351	285 ± 152	161 ± 97	45 ± 9
	Microbiological	257 ± 209	225	527	208 ± 40	126 ± 62	

[a] Average of two samples.
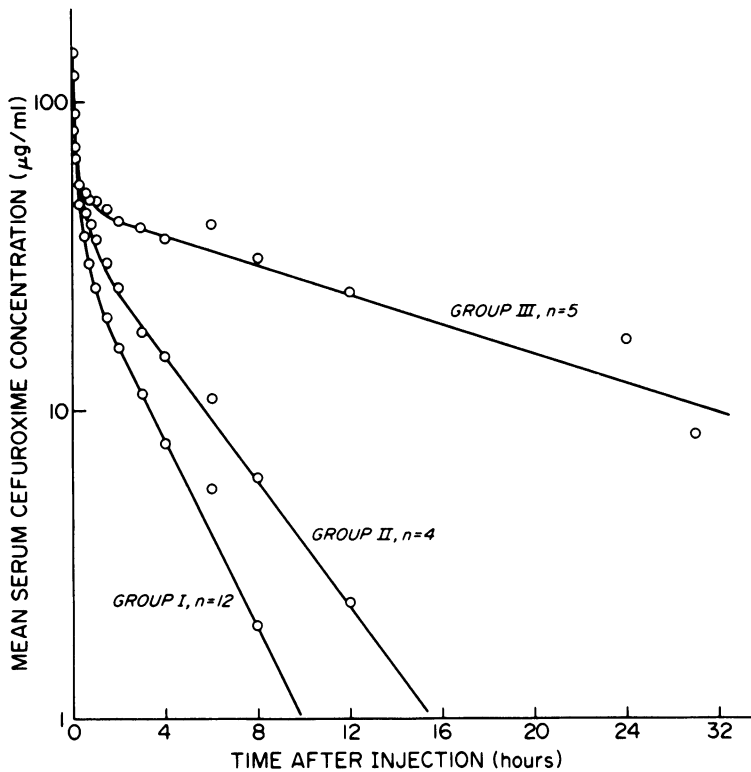
FIG. 1. *Mean serum levels of cefuroxime as measured by the HPLC assay in groups 1 (Cl_{cr} = 60 to 120 ml/ min per 1.73 m^2), 2 (Cl_{cr} = 20 to 59 ml/min per 1.73 m^2), and 3 (Cl_{cr} < 20 ml/min per 1.73 m^2). Each subject received 750 mg of cefuroxime during 2 min intravenously. Standard deviations of these data are given in Table 2.*

yielded significantly higher values than the microbiological method in this group. The coefficients of determination (r^2) in Table 3 were not significantly different between assays.

Pharmacokinetic analysis of serum data. The pharmacokinetic analysis of the data from the HPLC assay, according to the kinetic two-compartment model, is summarized in Table 4.

The distribution rate constant (α), distribution constants (k_{12}, k_{21}), and also the volume terms (V_l, Vd_{ss}) are independent of renal function in these patients. The overall elimination of half-life ($t_{1/2\beta}$) and the intrinsic elimination rate (k_{el}) constants and both the renal and serum clearances (Cl_r, Cl_s) are renal function dependent. However, Cl_s was not reduced to the same extent

TABLE 3. Mean values of the pharmacokinetic parameters A, B, α, β[a]

Variable	Group 1		Group 2		Group 3		ANOVA[b]	t-test
	HPLC	Microbiological	HPLC	Microbiological	HPLC	Microbiological		
A (μg/ml)	114 (68)	102 (48)	105 (64)	106 (68)	46 (27)	57 (42)	NS[c]	NC[d]
α (h⁻¹)	9.4 (4.7)	10.1 (9.6)	11.2 (7.9)	8.4 (6.8)	11.3 (9.8)	4.6 (3.7)	NS	NC
B (μg/ml)	42 (8)	43 (16)	47 (10)	37 (11)	43 (14)	26 (7)	NS	NC
β (h⁻¹)	0.46 (0.16)	0.52 (0.20)	0.31 (0.09)	0.26 (0.07)	0.046 (0.021)	0.046 (0.024)	P < 0.001 (group)	Group 1 > 2 > 3
r²	0.997 (0.003)	0.996 (0.004)	0.997 (0.003)	0.984 (0.019)	0.992 (0.015)	0.998 (0.009)	NC	NC
AUC[e] (μg·h per ml)	109 (31)	105 (39)	180 (87)	179 (102)	1070 (398)	644 (253)	P < 0.001 (group) / P < 0.025 (assay)	Group 1 < 2 < 3 / HPLC > microbiological in group 3

[a] Parameters are from the equation $C = Ae^{-\alpha t} + Be^{-\beta t}$, in which C is the concentration of cefuroxime in serum at time t after dosing of the coefficients of determination (r^2), indicating the accuracy with which the equation describes the data, and also of the areas under the cefuroxime curves in serum obtained with the HPLC and microbiological methods of analysis in the three patient groups. Standard deviations are within parentheses.
[b] ANOVA, Analysis of variance.
[c] NS, Not significant.
[d] NC, Not calculated.
[e] AUC, Area under cefuroxime serum profile, as calculated by trapezoidal rule.

as Cl_r in severe renal impairment, indicating a nonrenal contribution to cefuroxime elimination in these patients. The value of $t_{1/2\beta}$ was 1.7 h in group 1, 2.4 h in group 2, and 17.6 h in group 3. These values are similar to those reported by others (3–5, 7, 11, 14).

Regressions of cefuroxime pharmacokinetic values against creatinine clearance. Regressions of β, Cl_s, Cl_r, 1/AUC, and AUC (k_{el}) against creatinine clearance in all patients are shown in Table 5. The linear relationship between β and creatinine clearance (Cl_{cr}) for all 21 patients is shown in Fig. 2. The regression is highly significant and provides a basic for cefuroxime dosage adjustment in uremic patients. Other regressions are also significant ($P < 0.001$), with the exception of the regression of normalized AUC [AUC (k_{el})] against creatinine clearance. This regression yielded a value of only +0.418, reflecting the negligible effect that renal impairment has on the distribution characteristics of cefuroxime.

DISCUSSION

This study has examined in detail the pharmacokinetic parameters of cefuroxime in persons with various degrees of renal insufficiency and also compared the results of two different cefuroxime assay methods.

The pharmacokinetics of cefuroxime are similar to other penicillins and cephalosporins in that, after intravenous administration, circulating drug levels may be described by a biexponential function utilizing two first-order rate constants. The overall equilibrium distribution volume was approximately 0.22 liter/kg and was not affected by renal insufficiency. Equilibrium of cefuroxime between serum and tissues was achieved within 0.5 to 1.0 h, and thereafter serum levels decline monoexponentially at a rate that was closely related to renal function. The mean β-phase elimination half-life increased from 1.7 h in subjects with normal renal function to 2.4 h in subjects with moderate renal impairment, and to 17.6 h in individuals with severe renal impairment.

The two assay methods examined gave statistically indistinguishable results, except in the serum levels of subjects with severe renal impairment, where significantly higher serum drug levels were obtained by the HPLC assay compared with the microbiological methods. It appears that some substance in the serum of these individuals either interferes with the diffusion of cefuroxime in the disk diffusion method or alters the sensitivity of the assay organism to cefuroxime. This inhibitory effect in serum from uremic individuals was lost when the sera were diluted 1:5 in phosphate buffer.

TABLE 4. *Mean pharmacokinetic values obtained from analysis of individual data sets obtained by HPLC assay[a]*

Parameter	Mean value (standard deviation)			ANOVA[b]	t-test
	Group 1	Group 2	Group 3		
$t_{1/2\alpha}$[c] (h)	0.10 (0.6)	0.15 (0.19)	0.09 (0.18)	NS[d]	NC[e]
$t_{1/2\beta}$[f] (h)	1.7 (0.6)	2.4 (0.8)	17.6 (6.1)	$P < 0.001$	$1, 2 < 3$
k_{el}[g] (h^{-1})	1.4 (0.9)	0.9 (0.4)	0.10 (0.07)	$P < 0.01$	1, 2 3
k_{12}[g] (h^{-1})	5.2 (2.9)	7.0 (5.4)	4.9 (3.8)	NS	NC
k_{21}[g] (h^{-1})	3.4 (1.6)	3.6 (2.3)	6.4 (6.3)	NS	NC
V_l[h] (liters·kg^{-1})	0.072 (0.31)	0.089 (0.059)	0.14 (0.07)	NS	NC
Vd_{ss}[i] (liters·kg^{-1})	0.19 (0.04)	0.20 (0.04)	0.27 (0.09)	NS	NC
CL_{cr}[j] (ml·min·$^{-1}$·1.73 m^2)	96 (38)	50 (7)	13 (7)	$P < 0.001$	$1 > 2 > 3$
CL_s[k] (ml·min·$^{-1}$·1.73 m^2)	123 (34)	79 (28)	13 (7)	$P < 0.001$	$1, 2 > 3$
Cl_r[l] (ml·min·$^{-1}$·1.73 m^2)	128 (43)	82 (29)	5.5 (5.0)	$P < 0.001$	$1, 2 > 3$
Number of patients	12	4	5		

[a] All values were calculated assuming the two-compartment open model (15) in which serum levels of cefuroxime are described by equations (2) and (3) (see the text).

[b] ANOVA, Analysis of variance.

[c] Half-life of the rapid, distribution component of cefuroxime serum levels, $t_{1/2\alpha} = ln\ 2/\alpha$.

[d] NS, Not significant ($P \geq 0.05$).

[e] NC, Not calculated.

[f] Half-life of the terminal, postdistribution component of cefuroxime serum levels, $t_{1/2\beta} = ln\ 2/\beta$.

[g] First-order rate constant governing transfer of drug from the central compartment to the peripheral compartment (k_{12}), from the peripheral compartment to the central compartment (k_{21}), and for loss of drug from the central compartment due to elimination (k_{el}).

[h] Apparent value of the central body compartment of the two-compartment open model, expressed as liters per kg of body weight.

[i] Apparent overall equilibrium distribution volume of cefuroxime, calculated from $Vd_{ss} = V_l(1 + k_{12}/k_{21})$.

[j] Cl_{cr}, Creatinine clearance.

[k] Serum clearance of cefuroxime, calculated from $Cl_s = V_l k_{el}$.

[l] Renal clearance of cefuroxime, calculated from Cl_r = (amount of drug voided in urine) ÷ (the cefuroxime concentration in serum at the midpoint of the urine collection interval). Each recorded clearance value is the average of two to four determinations in each subject. All clearance values are normalized to a body surface area of 1.73 m^2.

TABLE 5. *Regressions of cefuroxime elimination rate constants, renal and serum clearances, reciprocals of the area under the cefuroxime serum profile and of the normalized area under the cefuroxime serum profile, against creatinine clearance*

Regression	Equation	n	r	P
β vs. Cl_{cr}	$Y_2 = 0.004Y_1 + 0.056$[a]	21	+0.897	<0.001
k_{el} vs. Cl_{cr}	$Y_2 = 0.015Y_1 - 0.012$	21	+0.791	<0.001
Cl_s vs. Cl_{cr}	$Y_2 = 0.940Y_1 + 19.63$	21	+0.877	<0.001
Cl_r vs. Cl_{cr}	$Y_2 = 1.03Y_1 + 22.30$	21	+0.758	<0.001
(l/AUC) (10^4) vs. Cl_{cr}	$Y_2 = 0.85Y_1 + 14.82$	21	+0.895	<0.001
(AUC) (k_{el}) vs. Cl_{cr}	$Y_2 = 0.57Y_1 + 91.95$	21	+0.418	<0.05

[a] Y_1 = parameter being regressed against Cl_{cr}, $Y_2 = Cl_{cr}$.

The levels of cefuroxime in urine were adequate to treat most urinary tract pathogens regardless of renal impairment. However, due to the marked dependency of cefuroxime elimination on renal function, the dosage of this compound should be reduced in severely uremic patients.

The relationship between β and creatinine clearance (Table 5, Fig. 2) predicts a 12-fold increase in the cefuroxime biological half-life in severely uremic patients, compared with normal individuals (16). The observed β values in patients with creatinine clearance values less than 40 ml/min fell below the overall regression line in Fig. 2. However, the differences between the observed and calculated values for β in these individuals would influence dosage reduction by only 5 to 17%. This difference is unlikely to be clinically significant. Further information from severely uremic patients, with serum sampling extended beyond the 24 h of this study, is needed to resolve this.

Our data suggest that, if cefuroxime is administered at 4-h intervals, no drug accumulation
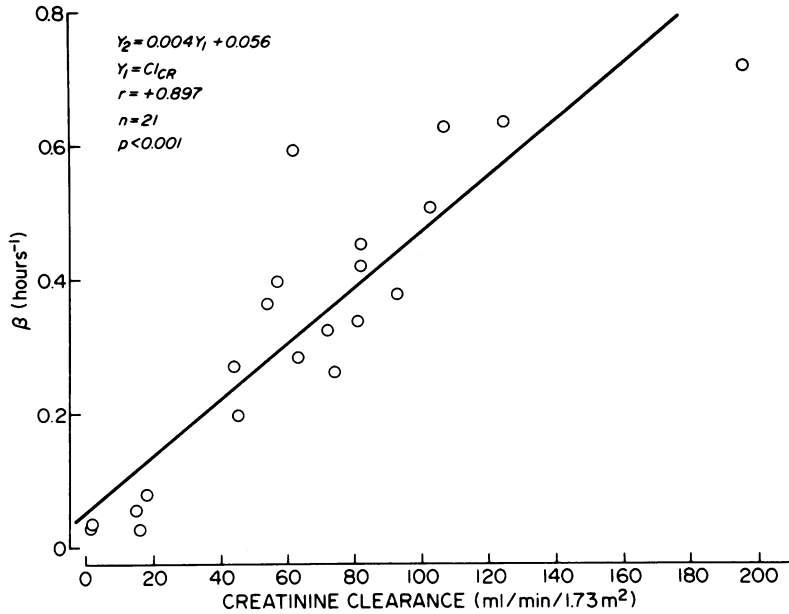
$$Y_2 = 0.004 Y_1 + 0.056$$
$$Y_1 = Cl_{CR}$$
$$r = +0.897$$
$$n = 21$$
$$p < 0.001$$

FIG. 2. *Regression of the elimination rate constant, β, against creatinine clearance in all patients.*

will occur in patients with normal or mildly impaired renal function. However, in severe uremia drug levels are likely to accumulate in serum to reach levels six to seven times the initial values after 3 days of repeated dosing. In such patients the dosage interval should be extended to 24 h.

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