

Moxalactam and Cefazolin: Comparative Pharmacokinetics in Normal Subjects

W. MICHAEL SCHELD,* DANIEL A. SPYKER, GERALD R. DONOWITZ, W. KLINE BOLTON, AND MERLE A. SANDE

Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Virginia 22908

Received 17 October 1980/Accepted 29 January 1981

Moxalactam, a new β -lactam antibiotic with a wide in vitro spectrum of activity, was compared with cefazolin after intravenous and intramuscular administration of 1.0 g in a double-blind crossover design in 21 adult male subjects with normal renal function. Serum samples were obtained at 0.5, 1, 2, 3, 4, 6, 8, and 12 h, and urine was collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 12 h after dosing. Intravenous kinetics were described by a linear two-compartment model. For moxalactam, the drug clearance and volume of distribution were larger (115.2 versus 75.9 ml/min per 70 kg, $P = 0.001$, and 0.44 versus 0.19 liter/kg, $P < 0.001$, respectively), and the $t_{1/2\beta}$ was longer (3.47 versus 2.18 h, $P = 0.01$), with correspondingly smaller area under the curve (151 versus 236 h \cdot μ g/ml, $P = 0.003$) and lower serum concentration at 30 min (62 versus 106 μ g/ml, $P = 0.003$) than cefazolin. Intramuscular kinetics were similar and were well described by a single-compartment model. Urinary recovery was essentially identical for both drugs: 55 to 75% in 8 h. Consistent departures from the two-compartment model for moxalactam (not noted for cefazolin) suggested enterohepatic recirculation of moxalactam. Both drugs were well tolerated, and no adverse reactions were noted.

Moxalactam (1-oxa- β -lactam, LY127935, Shionogi 6059-S) is a new bactericidal semisynthetic β -lactam antibiotic. This compound is the first of a new type of β -lactam with the substitution of a dihydrooxazine ring for the dihydrothiazine ring common to cephalosporins and cephamycins (13), and it is described in the literature as an oxa- β -lactam or as a 1-oxacephalosporin. The antibacterial activity in vitro covers a wide spectrum which includes gram-positive aerobic cocci (with the exception of *Streptococcus faecalis*), *Neisseria gonorrhoeae* (including penicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), the *Enterobacteriaceae* (with susceptibilities comparable to those of cefoperazone and cefotaxime against *Escherichia coli*, *Klebsiella* sp., *Proteus* sp., *Serratia marcescens*, *Providencia* sp., *Enterobacter* sp., and *Citrobacter* sp.), *Pseudomonas aeruginosa*, and *Bacteroides fragilis* (2-4, 7, 13, 22). In addition, the drug is highly active against many multiply drug-resistant gram-negative bacilli (9, 22).

Preliminary toxicological studies in animals and humans have been encouraging (S. Matsuura, T. Yoshida, K. Sugeno, Y. Harada, M. Harada, and S. Kuwahara, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 152, 1978; Robert Kammer, personal communication). This inves-

tigation compares the pharmacokinetics and safety of moxalactam with those of an established cephalosporin, cefazolin, after intravenous (i.v.) and intramuscular (i.m.) administration in healthy adult male volunteers.

(This work was presented in part at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., September, 1980 [W. M. Scheld, D. A. Spyker, G. R. Donowitz, W. K. Bolton, and M. A. Sande, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother 20th, abstr. no. 238, 1980].)

MATERIALS AND METHODS

Description of subjects. Informed consent (approved by the Human Experimentation Committee, University of Virginia) was obtained from 21 healthy adult male volunteers before entry into the study. Their ages ranged between 21 and 40 years, and weights ranged between 63.2 and 91.0 kg. A complete medical history excluded patients with cardiovascular, hepatic, renal, or hematological disease. No subject reported allergies to any antibiotic, and all had completely normal physical examinations. Antibiotics were not ingested in the 48 h prior to drug administration in this study.

Laboratory measurements. A number of tests, including 24-h urine creatinine clearance, urinalysis, complete blood count, platelet count, Coombs test, and a blood chemistry screen (including levels of sodium, potassium, CO₂, chloride, glucose, calcium, phos-

phorus, creatinine, blood urea nitrogen, uric acid, total protein, albumin, total bilirubin, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and lactic dehydrogenase), were performed immediately before and 24 h after the administration of each dose of antibiotic. All laboratory values were within normal limits. Subjects were ambulatory and were evaluated hourly by a physician for evidence of side effects or symptoms. Blood pressure and pulse were recorded hourly.

Administration of antibiotics. Moxalactam and cefazolin were provided by Lilly Research Laboratories (Indianapolis, Ind.). Vials containing 1 g of sterile powder were stored at 4°C before use.

The drugs were reconstituted, according to the instructions on package inserts, in 3 ml of sterile 0.9% NaCl. In the first experiment, both drugs were administered i.v. in a dose of 1 g; 11 subjects received moxalactam, and 10 received cefazolin. An uncoagulated blood sample was obtained before drug administration, and blood was collected to test for drug levels at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h after the drug was slowly infused over 3 min. Urine samples were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 12 h after the drug administration. One month later the drugs were given i.m. (volume, 3 ml). Those subjects who initially received moxalactam were given cefazolin, and vice versa. Blood and urine samples were obtained as described above after the i.v. dose. All samples were allowed to clot for 1 h at room temperature and then placed immediately in a refrigerated centrifuge (4°C), and the serum was stored at -70°C until the antibiotic assay was performed (within 2 weeks). This period of storage did not affect the assay results.

Antibiotic assay. Agar well diffusion methods were used for the bioassay of both drugs. All urine and serum samples were thawed simultaneously immediately before assay, and all samples obtained from each experiment were analyzed on the same day. The assay for moxalactam employed *E. coli* ATCC 10536 as the indicator organism. This strain was grown in antibiotic medium no. 3 (Difco) for 18 h at 37°C; 2.5 ml of this culture was added to 1 liter of antibiotic medium no. 1 (Difco), and 30 ml of this mixture was poured evenly into 105-mm petri dishes. Wells were cut, 6 mm in diameter (12 per plate), and all standards were diluted in pooled human serum. Urine or serum alone did not produce a zone of inhibition in this assay. The sensitivity was $\leq 0.3 \mu\text{g/ml}$. All determinations were done in triplicate.

Cefazolin levels were determined by a similar procedure employing 0.1 ml of *Bacillus subtilis* spore suspension (Difco) per 100 ml of antibiotic medium no. 1 agar. This assay detected $\leq 0.3 \mu\text{g}$ of cefazolin per ml and was also done in triplicate.

Pharmacokinetic analysis. Data for each subject were entered via a computer terminal, stored directly on disk files, and verified. Thereafter the data were manipulated only by pharmacokinetic and statistical computer programs.

Since the drug was administered over 3 min and the first drug level was measured at 30 min, the levels were analyzed in terms of an i.v. bolus at time zero.

A linear two-compartment model (equation 1) pro-

vided a good description of the measured blood levels:

$$C = A_e^{-\alpha t} + B_e^{-\beta t} \quad (1)$$

An iterative least-squares method was used to find the four parameters, α , β , A , and B , which best described the observed serum levels for each subject (19). The symbols α and β represent the distribution and elimination constants; A and B represent the zero-time intercepts for the concentration curves. As an initial step in the analysis, individual computer-generated plots were examined by the authors (D.A.S. and W.M.S.). The two-compartment model gives rise to several definitions of volume of distribution (V_d). The volume calculated from area under the curve (AUC) seems most relevant for single i.v. doses (21): V_d (area) = dose/ $(\beta \text{ AUC})$, where area under the curve $\text{AUC} = A/\alpha + B/\beta$.

Statistical analysis. For the i.m. serum levels, the single-compartment model provided as good a fit as the two-compartment model. Thus the one-compartment representation of k_a , V_d , and k_e provided the kinetic analysis of the i.m. data:

$$C = \frac{\text{Dose}}{V_d} \times \frac{k_a}{k_a \cdot k_e} \times (e^{-k_a t} - e^{-k_e t}) \quad (2)$$

A fourth parameter, time lag until the appearance of blood levels, was included.

The V_d was examined for each drug as a function of measured weight, body surface area (6), and lean body weight (LBW) by using least-squares linear regression. LBW was defined as the lesser of measured or expected weight (5). Linear regression analysis was performed, and scatter plots were examined for V_d versus height, measured weight, expected weight, and LBW (20). We likewise examined the relation between serum creatinine and elimination half-life.

RESULTS

All of the experimental subjects were male, aged from 21 to 40, and weighing from 63 to 91 kg (Table 1). Renal function was normal, with mean serum creatinine of 1.0 mg/100 ml and a weight-corrected creatinine clearance of 108/ml/min per 70 kg. We found no statistically significant differences between experimental groups with respect to age, weight, height, LBW, body surface area, or parameters of renal function (Table 1).

Table 2 summarizes the relations between volumes of distribution (V_d) and patient height, weight, LBW, and surface area. Overall, weight correlated most consistently with the V_d parameters. None of the patient parameters, including serum creatinine, showed any consistent relation to drug half-life.

Table 3 summarizes the pharmacokinetic analysis of blood level data after i.v. injection of both drugs. Moxalactam exhibited a V_d about twice that of cefazolin (0.44 versus 0.19 liter/kg)

TABLE 1. Description of subjects

Group (n)	Drug (route)	Patient no.	Age (yr)	Ht (cm)	Wt (kg)	LBW ^a (kg)	Body surface area (m ²) ^b	Serum creatinine (mg/dl)	Creatinine clearance ^c (ml/min)
A(10)	Cefazolin (i.v.) + moxalactam (i.m.)	1	22.0	187.0	77.2	77.2	2.02	1.0	118
		2	31.0	177.0	77.5	75.7	1.95	1.3	83
		3	32.0	182.0	83.0	79.8	2.04	1.2	89
		4	25.0	181.0	75.5	75.5	1.96	1.0	115
		5	24.0	182.0	71.0	71.0	1.91	0.9	129
		6	21.0	171.0	91.0	65.8	2.03	1.0	119
		7	24.0	175.0	65.8	65.8	1.80	1.0	116
		8	34.0	175.0	79.0	75.5	1.95	1.0	106
		9	22.0	173.0	65.5	65.5	1.78	1.0	118
		10	32.0	171.0	74.3	71.8	1.86	1.0	108
Mean			26.7	177.4	76.0	72.4	1.93	1.0	110
SD ^d			5.0	5.4	7.7	5.2	0.09	0.1	14
B (11)	Cefazolin (i.m.) + moxalactam (i.v.)	11	29.0	180.0	87.5	77.0	2.07	1.2	92
		12	25.0	180.2	79.5	75.0	1.99	1.2	95
		13	27.0	181.0	76.0	76.0	1.96	1.1	102
		14	21.0	176.0	85.2	69.5	2.02	1.1	108
		15	24.0	180.2	79.5	74.5	1.99	0.9	129
		16	40.0	175.0	68.2	68.2	1.83	0.8	125
		17	25.0	160.0	65.5	60.3	1.68	1.0	115
		18	25.0	171.0	63.2	63.2	1.74	1.4	104
		19	30.0	192.9	79.5	79.5	2.09	1.1	99
		20	30.0	173.0	64.0	64.0	1.76	1.0	110
		21	27.0	195.4	85.0	85.0	2.17	1.1	102
Mean			27.5	178.6	75.7	72.0	1.94	1.1	107
SD			4.9	9.8	9.0	7.6	0.16	0.1	12
<i>t</i> value ^e			0.39	0.35	0.07	0.12	0.14	0.28	0.45
<i>P</i> value ^f			0.702	0.732	0.946	0.899	0.887	0.780	0.659

^a LBW from height, age, and sex (5).

^b Body surface area, from DuBois formula (6).

^c Corrected creatinine clearance per 70 kg, based on 24-h urine collection.

^d SD, Standard deviation.

^e *t* value, Value of Student's *t* test for above two groups.

^f *P* value, Probability of the null hypothesis for *t*.

TABLE 2. Volume of distribution versus weight, height, LBW, and body surface area (correlation coefficients)^a

Route	Drug	Correlation coefficient of V_d versus:			
		Wt	Ht	LBW	BSA
i.v.	Cefazolin	0.186	-0.794	-0.432	-0.216
i.v.	Moxalactam	0.784	0.637	0.738	0.782
i.m.	Cefazolin	0.553	0.216	0.312	0.439
i.m.	Moxalactam	0.688	0.376	0.303	0.780

^a LBW and body surface area (BSA) as in Table 1. Coefficient >0.632 has associated $P < 0.05$.

and a correspondingly smaller area under the curve ($P = 0.003$). Half-life was 3.5 h for moxalactam compared to 2.2 h for cefazolin ($P = 0.01$). Drug clearance, however, was slightly

larger for moxalactam (115 versus 76 ml/min), which approximates the expected creatinine clearance (107 and 110 ml/min per 70 kg) corrected for measured weight (10, 18). Urine recovery was essentially the same for the two drugs, about 70% in 8 h.

Figure 1 shows the mean and standard error of the mean serum concentrations for the 10 subjects receiving i.v. cefazolin. The two-compartment model provides accurate description of the observed means. The kinetic parameters for the curve-fit means (Fig. 1) are similar to the average parameters from individual curves (Table 3).

The difference between the serum levels and best least-squares fit for moxalactam is remarkable (Fig. 2). Every patient receiving i.v. moxalactam exhibited 2-h and 8-h levels above the

TABLE 3. Comparison of kinetics after i.v. administration.

Drug	Patient no.	Parameter								
		A ^a ($\mu\text{g/ml}$)	B ^a ($\mu\text{g/ml}$)	t_{α} (h) ^b	t_{β} (h) ^b	Drug clearance (ml/min)	V_{area}^c (liters)	V_d (liters) per kg	AUC (h· $\mu\text{g/ml}$)	Urine recovery ^d (mg)
Cefazolin	1	286.6	51.9	0.30	2.15	58.3	10.8	0.140	285.7	703
	2	333.3	55.5	0.26	1.96	59.2	10.1	0.130	281.4	767
	3	96.5	47.7	0.51	2.28	73.1	14.4	0.174	228.1	571
	4	156.2	44.4	0.49	2.03	69.6	12.2	0.162	239.6	999
	5	1,001.9	70.3	0.16	1.79	40.3	6.2	0.088	414.1	869
	6	0.0	49.7	0.00	2.33	99.6	20.1	0.221	167.4	629
	7	145.8	26.4	0.56	2.21	82.7	15.8	0.240	201.6	850
	8	150.6	18.3	0.62	2.41	84.6	17.6	0.223	197.1	763
	9	87.8	23.9	0.78	2.25	94.8	18.5	0.282	175.8	1,082
	10	112.1	18.8	0.66	2.39	97.2	20.1	0.270	171.6	788
Mean		237.1	40.7	0.43	2.18	75.9	14.6	0.193	236.2	802
SD ^e		285.4	17.8	0.24	0.20	19.4	4.7	0.064	75.6	156
Moxalactam	11	91.2	6.8	0.75	7.16	99.0	61.3	0.701	168.4	758
	12	73.8	17.4	0.64	3.22	112.1	31.2	0.393	148.7	665
	13	72.2	19.0	0.65	2.83	114.6	28.0	0.369	145.5	803
	14	50.8	17.8	0.60	2.53	152.7	33.4	0.392	109.2	604
	15	76.1	17.6	0.59	2.95	118.9	30.3	0.382	140.2	887
	16	85.3	12.1	0.60	2.91	133.8	33.7	0.494	124.6	737
	17	60.7	29.3	0.85	2.50	92.4	20.0	0.305	180.5	611
	18	93.3	20.4	0.57	2.57	109.1	24.3	0.384	152.8	987
	19	63.5	10.4	0.69	3.09	152.1	40.7	0.512	109.6	682
	20	176.4	19.2	0.55	3.35	71.6	20.8	0.325	232.8	887
	21	69.7	11.2	0.67	5.09	110.9	48.8	0.575	150.3	736
Mean		83.0	16.5	0.65	3.47	115.2	33.9	0.439	151.1	760
SD		33.5	6.1	0.09	1.42	24.2	12.4	0.119	34.9	122
<i>t</i> value		1.78	4.26	2.80	2.85	4.07	4.62	5.80	3.361	0.70
<i>P</i> value		0.088	0.001	0.011	0.010	0.001	<0.001	<0.001	0.003	0.502

^a A,B, Zero-time intercepts for alpha and beta phase.

^b t_{α} , t_{β} , Alpha, beta half-life.

^c V_{area} , Volume of distribution from area under the curve (AUC).

^d Corrected to $t = \infty$.

^e SD, Standard deviation.

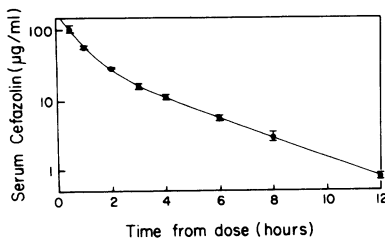


FIG. 1. Serum cefazolin concentration versus time after 1.0 g i.v. Bars on all figures indicate standard error of the mean.

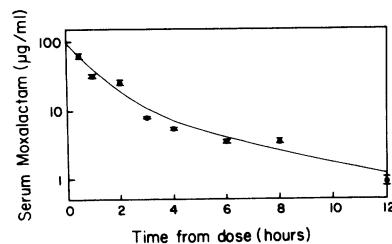


FIG. 2. Serum moxalactam concentration versus time after 1.0 g i.v.

best least-squares two-compartment model, whereas levels at 3, 6, and 12 h were all below the individual curves.

Table 4 presents the pharmacokinetic descrip-

tion of moxalactam and cefazolin after i.m. administration. The volumes of distribution show the same relation and similar absolute values for i.v. results (0.19 and 0.45 liter/kg for cefazolin

TABLE 4. Comparison of kinetics after i.m. injection

Drug	Patient no.	Parameter								Urine recovery (mg)	
		t_{abs}^a (h)	Lag ^b (h)	C_{pk}^c ($\mu\text{g}/\text{ml}$)	$C_{pk}/70^d$	t_{peak}^e (h)	t_{elim}^f (h)	V_d (liters)	V_d (liters) per kg of body wt		AUC ($\text{h} \cdot \mu\text{g}/\text{ml}$)
Cefazolin	11	0.939	0.411	31.0	24.8	2.57	2.59	18.11	0.207	206.6	473.6
	12	0.841	0.014	44.9	39.5	1.94	2.30	12.48	0.157	266.2	642.4
	13	0.921	0.000	43.4	40.0	1.82	1.79	11.40	0.150	227.0	651.7
	14	0.382	0.000	38.3	31.5	1.32	3.15	19.51	0.229	232.7	336.5
	15	0.024	0.000	33.7	29.7	0.16	2.48	28.38	0.357	126.2	408.7
	16	0.835	0.019	37.5	38.5	1.68	1.66	13.30	0.195	180.0	576.6
	17	1.045	0.237	41.2	44.0	2.03	1.49	10.55	0.161	203.5	663.7
	18	0.665	0.000	63.7	70.6	1.40	1.50	8.22	0.130	263.9	857.7
	19	0.510	0.000	52.1	45.8	1.33	1.94	11.93	0.150	234.6	608.1
	20	0.579	0.000	47.3	51.7	1.52	2.24	13.18	0.206	244.6	666.4
	21	1.043	0.418	33.6	27.6	2.61	2.34	15.56	0.183	216.7	657.7
Mean		0.707	0.100	42.4	40.3	1.67	2.13	14.78	0.193	218.4	594.8
SD ^g		0.315	0.170	9.5	13.0	0.67	0.51	5.57	0.062	39.9	143.2
Moxalactam	1	0.136	0.385	22.6	20.5	1.03	3.09	38.37	0.497	116.3	670.0
	2	0.270	0.000	25.4	23.0	0.98	2.56	30.15	0.389	122.7	474.0
	3	0.404	0.000	20.1	16.9	1.33	2.89	36.19	0.436	115.3	474.8
	4	0.065	0.405	23.2	21.5	0.76	2.48	39.03	0.517	91.8	436.0
	5	0.068	0.414	23.2	22.9	0.77	2.35	38.84	0.547	87.5	470.5
	6	0.548	0.262	16.3	12.6	1.93	3.11	42.22	0.464	106.3	508.8
	7	0.662	0.120	23.2	24.7	1.60	1.70	23.62	0.359	103.7	657.4
	8	0.999	0.217	16.5	14.6	2.37	2.36	32.23	0.408	105.7	567.2
	9	0.065	0.437	31.1	33.3	0.76	1.76	28.30	0.432	89.6	498.7
	10	0.065	0.420	27.8	26.2	0.77	2.37	32.47	0.437	105.1	542.1
Mean		0.328	0.266	23.0	21.6	1.23	2.47	34.14	0.449	104.4	530.0
SD		0.322	0.174	4.6	6.0	0.57	0.49	5.78	0.058	11.9	79.8
t value		2.73	2.21	5.87	4.17	1.63	1.53	7.82	9.67	8.67	1.26
P value		0.013	0.038	<0.001	0.001	0.117	0.140	<0.001	<0.001	<0.001	0.220

^a t_{abs} , Absorption half-life.^b Lag, Absorption delay.^c C_{pk} , Peak drug concentration.^d $C_{pk}/70$, Peak C corrected to 70 kg of body weight.^e t_{peak} , Time of peak.^f t_{elim} , Elimination half-life.^g SD, Standard deviation.

and moxalactam, respectively). The area under the curve reflects these results, being 52% less for moxalactam ($P < 0.001$). Mean peak serum levels were 42 $\mu\text{g}/\text{ml}$ for cefazolin compared to 23 $\mu\text{g}/\text{ml}$ for moxalactam. Time to peak serum level (1.67 versus 1.23 h) was not statistically different ($P = 0.12$). The cefazolin half-life of 2.1 h compared closely with the 2.2 h after the i.v. route and was slightly (though not statistically) shorter than the 2.47 h for moxalactam ($P = 0.14$). Recovery in the urine was slightly less after i.m. administration: 59% for cefazolin and 53% for moxalactam.

The mean serum levels from the 11 subjects

receiving i.m. cefazolin were well described by the biexponential single-compartment model. Levels from the 10 subjects receiving i.m. moxalactam showed consistent departure from the model curve, as did those from patients receiving the drug i.v. (Fig. 3 and 4).

Moxalactam was well tolerated by all subjects after i.v. or i.m. administration. Two volunteers, one in each group, developed self-limited diarrhea after i.m. administration of antibiotic. No skin rashes were noted. No adverse reactions were found in any of the laboratory parameters obtained, including estimates of renal, hepatic, or hematological dysfunction.

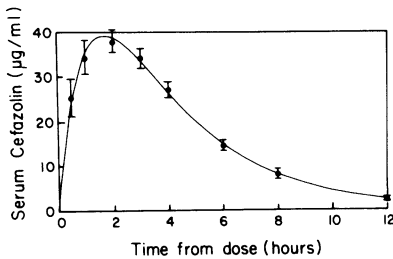


FIG. 3. Serum cefazolin concentration versus time after 1.0 g i.m.

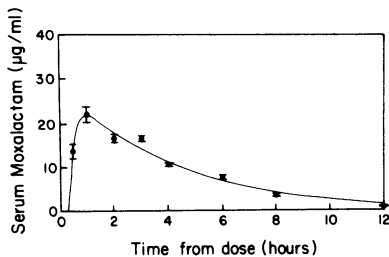


FIG. 4. Serum moxalactam concentration versus time after 1.0 g i.m.

DISCUSSION

This study compares the pharmacokinetics of moxalactam, a new β -lactam antibiotic, with those of an established cephalosporin (cefazolin) after i.v. and i.m. administration in 21 normal adult male volunteers. Major differences in pharmacokinetic parameters were found between the two compounds. Both were tolerated well with no significant reactions noted by the subjects.

After i.v. administration, moxalactam demonstrated a larger drug clearance and volume of distribution than cefazolin. These properties led correspondingly to lower "peak" serum levels (62 versus 106 $\mu\text{g/ml}$ at 30 min), a longer β half-life (3.5 versus 2.2 h), and a smaller area under the curve for the new agent. Urinary recovery was approximately 70% in 8 h for each agent after i.v. administration.

Similar results were seen after i.m. administration. Peak serum levels were higher for cefazolin (42 versus 23 $\mu\text{g/ml}$), whereas moxalactam again displayed a larger volume of distribution and smaller area under the curve. The lag period of absorption and time to peak serum concentration were similar for both agents; the elimination half-life was slightly longer for moxalactam (2.5 versus 2.1 h, $P = 0.14$). Urinary recovery was 77 to 83% of that observed after the i.v. route, again similar for both agents.

The results of this study are similar to those of other studies of moxalactam and cefazolin (11,

14-16). Mean peak moxalactam serum levels of 70.7 $\mu\text{g/ml}$ were obtained after 1 g i.v. (15), similar to the levels of 62.1 $\mu\text{g/ml}$ reported here. Because of a larger clearance and V_d , the β half-life was longer than cefazolin. Consistent departures from the two-compartment model by moxalactam after i.v. administration were found. Our patients fasted before drug administration and then ate breakfast. The 2-h serum concentration was above the best least-squares fit in every subject. We also noted this after the i.m. injection in a separate group of volunteers. These departures from the model seem most consistent with enterohepatic recirculation of this compound. Parsons et al. (15) show similar departures from expected kinetic data.

Similar serum levels with a prolonged β half-life have been commented on recently (R. Wise, S. Baker, and J. M. Andrews, 20th ICAAC, abstr. no. 240, 1980; S. Srinivasan, E. L. Francke, and H. C. Neu, 20th ICAAC, abstr. no. 241, 1980). All investigators have found a prolonged β half-life for moxalactam, with similar urinary recoveries after the i.v. or i.m. route. The total recovery in the urine is slower than that for the cephalosporins, however, perhaps reflecting the large V_d , long β half-life, lower protein binding (50% versus 85% for cefazolin; Kammer, personal communication), and possibly enterohepatic recirculation of drug. Multiple-dose studies have demonstrated no accumulation of moxalactam within the serum and high patient acceptance without major adverse effects (E. Estey, S. Weaver, D. Ho, and G. P. Bodey, 20th ICAAC, abstr. no. 237, 1980; R. Lüthy, R. Wise, A. Bonetti, and J. Blaser, 20th ICAAC, abstr. no. 239, 1980).

The wide in vitro spectrum of moxalactam (1-4, 7, 9, 13, 22) suggests that this agent will be active in a variety of infections. Indeed, favorable clinical reports are beginning to appear (8). In addition, the efficient penetration of moxalactam across inflamed meninges in both experimental animals (17) and humans (12) suggests a role for this agent in gram-negative meningitis. In these and other infections, the pharmacokinetic data suggest that 2 g i.v. every 8 h (or even every 12 h) will be adequate if renal function is normal. The therapeutic efficacies of these regimens are being investigated at the present time.

ACKNOWLEDGMENT

Partial support was provided by Public Health Service grant 21484 from the National Institute of Arthritis, Metabolism and Digestive Diseases to W.K.B.

LITERATURE CITED

1. Baker, C. N., C. Thornsberry, and R. N. Jones. 1980. In vitro antimicrobial activity of cefoperazone, cefotaxime, moxalactam (LY127935), azlocillin, mezlocillin, and

- other β -lactam antibiotics against *Neisseria gonorrhoeae* and *Haemophilus influenzae*, including β -lactamase-producing strains. *Antimicrob. Agents Chemother.* 17:757-761.
2. Barza, M., F. P. Tally, N. V. Jacobus, and S. L. Gorbach. 1979. In vitro activity of LY127935. *Antimicrob. Agents Chemother.* 16:287-292.
 3. Borobio, M. V., J. Aznar, R. Jimenez, F. Garcia, and E. J. Perea. 1980. Comparative in vitro activity of 1-oxa- β -lactam (LY127935) and cefoperazone with other β -lactam antibiotics against anaerobic bacteria. *Antimicrob. Agents Chemother.* 17:129-131.
 4. Delgado, D. G., C. J. Brau, C. G. Cobbs, and W. E. Dismukes. 1979. In vitro activity of LY127935, a new 1-oxa cephalosporin, against aerobic gram-negative bacilli. *Antimicrob. Agents Chemother.* 16:864-868.
 5. Diem, K., and C. Lentner. 1970. *Documenta Geigy*. Scientific tables, 7th ed., p. 711. J. R. Geigy, Basel.
 6. Dubois, D., and E. F. Dubois. 1916. A formula to estimate the approximate surface area if height and weight be known. *Arch. Intern. Med.* 17:863-871.
 7. Fass, R. J. 1979. In vitro activity of LY127935. *Antimicrob. Agents Chemother.* 16:503-509.
 8. Gibbs, R. S., J. D. Blanco, Y. S. Castaneda, and P. J. St. Clair. 1980. Therapy of obstetrical infections with moxalactam. *Antimicrob. Agents Chemother.* 17:1004-1007.
 9. Hall, W. H., B. J. Opfer, and D. N. Gerding. 1980. Comparative activities of the oxa- β -lactam LY127935, cefotaxime, cefoperazone, cefamandole, and ticarcillin against multiply resistant gram-negative bacilli. *Antimicrob. Agents Chemother.* 17:273-279.
 10. Hull, J. H., and F. A. Sarubbi. 1976. Gentamicin serum concentrations: pharmacokinetic predictions. *Ann. Intern. Med.* 85:183-189.
 11. Kirby, W. M. M., and C. Regamey. 1973. Pharmacokinetics of cefazolin compared with four other cephalosporins. *J. Infect. Dis.* 128(Suppl.):S341-S346.
 12. Landesman, S. H., M. L. Corrado, C. C. Cherubin, M. Gombert, and D. Cleri. 1980. Diffusion of a new beta-lactam (LY127935) into cerebrospinal fluid. Implications for therapy of gram-negative bacillary meningitis. *Am. J. Med.* 69:92-98.
 13. Neu, H. C., N. Aswapokee, K. P. Fu, and P. Aswapokee. 1979. Antibacterial activity of a new 1-oxa cephalosporin compared with that of other β -lactam compounds. *Antimicrob. Agents Chemother.* 16:141-149.
 14. Nightingale, C. H., D. S. Greene, and R. Quintilliani. 1975. Pharmacokinetics and clinical use of cephalosporin antibiotics. *J. Pharm. Sci.* 64:1899-1927.
 15. Parsons, J. N., J. M. Romano, and M. E. Levison. 1980. Pharmacology of a new 1-oxa- β -lactam (LY127935) in normal volunteers. *Antimicrob. Agents Chemother.* 17:226-228.
 16. Ries, K., M. E. Levison, and D. Kaye. 1973. Clinical and in vitro evaluation of cefazolin, a new cephalosporin antibiotic. *Antimicrob. Agents Chemother.* 3:168-174.
 17. Schaad, U. B., G. H. McCracken, Jr., C. A. Looock, and M. L. Thomas. 1980. Pharmacokinetics and bacteriological efficacy of moxalactam (LY127935), netilmicin, and ampicillin in experimental gram-negative enteric bacillary meningitis. *Antimicrob. Agents Chemother.* 17:406-411.
 18. Spyker, D. A. and R. L. Guerrant. 1977. Gentamicin dosage. *Ann. Intern. Med.* 86:357.
 19. Spyker, D. A., R. J. Rugloski, R. L. Vann, and W. M. O'Brien. 1977. Pharmacokinetics of amoxicillin: dose dependence after intravenous, oral, and intramuscular administration. *Antimicrob. Agents Chemother.* 11:132-141.
 20. Spyker, D. A., and J. M. Spyker. 1977. Response model analysis for cross-fostering studies: prenatal versus postnatal effects on offspring exposed to methylmercury. *Toxicol. Appl. Pharmacol.* 40:511-527.
 21. Wagner, J. G. 1975. *Fundamentals of clinical pharmacokinetics*, p. 461. Drug Intelligence Publications, Hamilton, Ill.
 22. Wise, R., J. M. Andrews, and K. A. Bedford. 1979. LY127935, a novel oxa- β -lactam: an in vitro comparison with other β -lactam antibiotics. *Antimicrob. Agents Chemother.* 16:341-345.