Clinical Pharmacology of Moxalactam in Patients with Malignant Disease

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Pharmacological studies of moxalactam were conducted with 37 cancer patients. Intramuscular administration of 500 mg of moxalactam to 10 patients produced a mean peak serum concentration of 12.4 $\mu\text{g/ml}$. The serum terminal-phase half-life was 3.9 h. Intravenous administration of 500 mg of moxalactam over 5 min to the same 10 patients produced a mean serum concentration of 42.0 $\mu\text{g/ml}$ at 15 min, which decreased to 3.3 $\mu\text{g/ml}$ at 6 h. A dose of 1 g of moxalactam was given in an identical manner to the same 10 patients. The mean serum concentration was 69.6 $\mu\text{g/ml}$ at 15 min and 7.4 $\mu\text{g/ml}$ at 6 h. The mean proportions of drug recovered in the urine by 12 h after administration were 59% after the intramuscular dose and 61 and 55% after the single intravenous doses. Multiple-dose intravenous studies were also conducted. The serum terminal-phase half-life varied from 2.0 to 3.2 h. Continuous infusion studies were performed for up to 9 days by using a loading dose of 1 g over 0.5 h, followed by 2 g every 6 h. Serum concentrations were maintained at about 30.0 $\mu\text{g/ml}$ during the study period.

Moxalactam is a semisynthetic β -lactam antibiotic with a spectrum of activity which includes most gram-positive cocci, the *Enterobacteriaceae*, and *Pseudomonas aeruginosa*. Although several substituent groups in combination are thought to contribute to these properties, the replacement of sulfur with oxygen in the six-member ring of the conventional cephem nucleus is believed to be especially important. When the activity of moxalactam was compared with the activities of cephalothin, cefamandole, cefoxitin, carbenicillin, mezlocillin, and piperacillin against gram-negative organisms (11), moxalactam demonstrated the greatest potency and broadest spectrum, inhibiting a majority of isolates of all organisms except *P. aeruginosa* at concentrations below 6.25 $\mu\text{g/ml}$. It was the most active antibiotic against the *Enterobacteriaceae* and was also active against *P. aeruginosa*, inhibiting 50% of these organisms at a concentration of 25.0 $\mu\text{g/ml}$. Others have reported very similar results (1, 3, 4, 10, 12). Preliminary data for animals and humans have indicated very little toxicity. Because of these properties, moxalactam is of potential clinical utility in cancer patients since these patients have significant mortality and morbidity from bacterial infections, especially infections caused by gram-negative bacilli (5). Accordingly, we conducted pharmacological studies of moxalactam in a group of patients with malignant diseases.

MATERIALS AND METHODS

We conducted a total of 41 studies with 37 cancer patients who ranged in age from 19 to 71 years (median, 46 years). The body surface area of these patients varied from 1.4 to 2.4 m^2 (median, 1.9 m^2), and their weight varied from 40 to 111 kg (median, 70 kg). All patients but one had normal serum creatinine levels. The exception was a male with an initial serum creatinine level of 1.6 mg/dl, in whom the level decreased to 1.1 mg/dl by the second study day; thereafter, this patient continued to have normal values. There was no substantial difference between the day 1 results for this patient and the results for the other patients; hence, his results were combined with the results for the other patients. With three exceptions, all patients had normal serum bilirubin levels. Two of the three exceptions had initial serum bilirubin levels of 1.3 mg/dl, which returned to normal by the second day; the third patient had an initial level of 1.5 mg/dl, which rose to 2.1 mg/dl by completion of the study. In none of these cases were results substantially different from the results for patients with normal serum bilirubin levels, and, therefore, the results were combined.

Single-dose moxalactam studies were performed with 10 patient volunteers. The drug was administered intramuscularly (i.m.) at a dose of 500 mg and intravenously (i.v.) at doses of 500 mg and 2 g. The i.v. doses were given in 50 ml of 5% dextrose over a period of 5 min. Patients were assigned randomly to three different sequences of drug administration. The interval between studies was at least 2 days for each patient. Blood samples were collected 0, 0.25, 0.5, 1, 2, 4, and 6 h after drug administration. Urine samples were collected before drug administration, and all urine was

saved for 12 h after drug administration in three separate collections (0 to 3 h, 3 to 6 h and 6 to 12 h).

A total of 31 multiple-dose studies were conducted with 27 patients. Most of these patients were receiving antibiotic prophylaxis in a laminar airflow room and volunteered to substitute moxalactam for other prophylactic regimens. Seven patients received moxalactam as treatment for presumed (four patients) or proven (three patients) infections after conventional antibiotic regimens failed; these regimens were discontinued 24 h before moxalactam treatment was begun. A total of 10 patients received 1 g of moxalactam i.v. in 50 ml of 5% dextrose over a period of 15 min every 6 h for 7 or 8 days, whereas another 10 patients received 2 g of moxalactam i.v. in 50 ml of 5% dextrose over a period of 15 min every 8 h for 7 or 8 days. In both groups of patients, pharmacological studies were conducted on day 1, 3, or 4 and on day 7 or 8 of treatment. Blood samples were collected 0, 0.25, 1, 2, 4, and 6 h after drug administration from both groups of patients. In addition, a specimen was collected 8 h after drug administration from those patients receiving the drug every 8 h. In the remaining 11 studies, each patient received a 1-g i.v. loading dose of moxalactam in 50 ml of 5% dextrose over a period of 30 min, followed immediately thereafter by a continuous i.v. infusion of 2 g of moxalactam over a period of 6 h. When possible, an infusion pump was used for the continuous infusion studies. Blood samples were collected 0, 0.25, 0.5, 1, 2, 4, and 6 h after drug administration on day 1 and thereafter twice daily (at 10 a.m. and 2 p.m.) until cessation of therapy. Urine specimens were collected 6 h after drug administration on day 3 or 4.

The concentrations of moxalactam in blood and urine were determined by an agar well method, using *Escherichia coli* ATCC 10536 as the test organism. This organism was incubated in antibiotic broth 3 (Difco Laboratories, Detroit, Mich.) for 18 h at 37°C. A 0.5-ml sample of the overnight broth culture was added to 500 ml of antibiotic agar 1 (Penassay Seed Agar; Difco Laboratories). Petri dishes were filled with 15-ml portions of this preparation, and wells (diameter, 0.75 mm; depth, 0.4 mm) were cut into the agar; each well was filled with 0.05 ml of specimen. The plates were incubated at 37°C for 18 h. Zones of inhibition were measured and compared with standard curves. Assays were performed in triplicate. The lower limit of resolution for the agar well dilution assay was 2.5 µg/ml; below this level the presence of drug could be detected but not quantitated. The assay was found to be reproducible with less than 10% error when repeated determinations on the same specimen were performed.

For every treatment schedule, the mean serum concentration was calculated at each time point on each study day. The standard error of the mean was calculated, and 95% confidence limits were defined as twice the standard error of the mean. Values for the serum terminal-phase half-life (elimination half-life), serum concentration at zero time, volume of distribution of the β phase ($V_{d\beta}$), and area under the curve of concentration versus time were calculated by the methods of Ritschel (8), using an open two-compartment model and the mean for each i.v. treatment

schedule. The volume of distribution for the β phase was determined from the following equation: $V_{d\beta} = D\alpha/B\alpha + A\beta$, where D is the dose of drug administered, α is the distribution slope, β is the overall elimination slope, A is the intercept of the distribution slope α with the ordinate, and B is the intercept of the back-extrapolated monoexponential elimination slope β with the ordinate.

The area under the curve (AUC) of concentration versus time was determined from the following formula: $AUC(e \rightarrow \infty) = B/\beta + A/\alpha$. Serum concentration at zero time was determined by taking the sum of A plus B .

RESULTS

Seven patients received moxalactam as treatment for a proven or presumed infection. Three patients had documented infections. One patient had an inguinal cellulitis from which no organisms were recovered and responded promptly to treatment with 1 g of moxalactam every 6 h. Two patients who were granulocytopenic received moxalactam by continuous infusion; one, who had an enterococcal bacteremia (minimal inhibitory concentration for moxalactam, 1.56 µg/ml), responded, whereas the other, who had a perianal infection from which a predominant organism was not grown, did not respond. In addition, four patients with fever and granulocytopenia but without an identified source of infection received moxalactam by continuous infusion. Two of the four defervesced.

Figure 1 shows the mean serum concentrations of moxalactam during the single-dose studies with 10 patients. After the i.v. administration of 500 mg of moxalactam over a 5-min period, the mean serum concentration was 42.0 µg/ml at 15 min; this concentration declined to 7.0 µg/ml at 4 h and 3.3 µg/ml at 6 h. The i.v. administration of 1 g of moxalactam over a 5-min period produced a mean serum concentration of 69.6 µg/ml at 15 min; this concentration fell to 10.9 µg/ml at 4 h and 7.4 µg/ml at 6 h. A 500-mg i.m. dose of moxalactam resulted in a mean peak serum concentration of only 12.4 µg/ml 2 h after drug administration; however, at 2 and 4 h, the mean serum concentrations were similar to the mean serum concentrations obtained with the same dose given i.v., and at 6 h they were greater.

Table 1 shows the mean serum concentrations in the 10 patients who received 1 g of moxalactam i.v. over a period of 15 min every 6 h, and Table 2 shows the mean serum concentrations in the 10 patients who received 2 g of this drug i.v. over a period of 15 min every 8 h.

We conducted studies with 11 patients who received continuous infusions consisting of a loading dose of 1 g of moxalactam given i.v. over a 30-min period, followed immediately by 2 g every 6 h over a 6-h period by continuous infu-

FIG. 1. Mean serum concentrations after single doses of 500 mg of moxalactam given i.m. and 500 mg and 1 g given i.v. over 5 min. The same 10 patients participated in all three studies. Bars indicate standard errors of the means.

TABLE 1. Mean serum concentrations after multiple doses of 1 g of moxalactam given i.v. over a 15-min period every 6 h to 10 patients

Time (h)	Serum concn (µg/ml) on:		
	Day 1	Day 3 or 4	Day 7 or 8
0	0	9.8 ± 1.5 ^a	7.8 ± 1.0
0.25	63.9 ± 8.9	64.4 ± 10.5	61.8 ± 9.3
0.5	49.9 ± 5.6	50.9 ± 3.9	53.6 ± 5.2
1.0	38.4 ± 3.9	42.1 ± 3.7	38.9 ± 2.5
2.0	22.2 ± 2.5	24.1 ± 3.0	24.0 ± 1.7
4.0	10.7 ± 1.4	12.0 ± 1.5	11.9 ± 1.2
6.0	7.9 ± 1.2	10.0 ± 1.2	7.1 ± 1.1

^a Mean ± standard error of the mean.

sion (Fig. 2 and 3). The mean serum concentration was 37.1 µg/ml at the end of the loading dose, and the mean serum concentration remained above 31.0 µg/ml during the initial 6-h infusion. Mean 10 a.m. serum concentrations varied between 33.8 and 42.1 µg/ml, whereas mean 4 p.m. levels varied between 32.2 and 41.5 µg/ml during days 2 through 9 of the study. There was little variation in the serum concentrations obtained for any given patient on different days of the study. The standard error of the

TABLE 2. Mean serum concentrations after multiple doses of 2 g of moxalactam given i.v. over a 15-min period every 8 h to 10 patients

Time (h)	Serum concn (µg/ml) on:		
	Day 1	Day 3 or 4	Day 7 or 8
0	0	7.2 ± 1.5 ^a	6.5 ± 1.2
0.25	125.1 ± 16.5	129.3 ± 19.8	132.9 ± 19.6
0.5	87.6 ± 7.0	92.7 ± 9.8	108.8 ± 12.1
1.0	66.3 ± 6.4	71.6 ± 7.5	80.0 ± 5.2
2.0	35.3 ± 3.0	40.8 ± 5.4	50.3 ± 5.8
4.0	16.2 ± 1.3	18.9 ± 2.8	19.4 ± 2.5
6.0	8.7 ± 1.1	10.4 ± 2.1	10.4 ± 1.3
8.0	6.8 ± 1.6	5.8 ± 1.4	6.0 ± 1.3

^a Mean ± standard error of the mean.

FIG. 2. Mean serum concentrations of moxalactam during the initial 6 h after a 1-g i.v. loading dose over 30 min, followed immediately by continuous i.v. infusion of 2 g over 6 h every 6 h in 11 patients. Bars indicate standard errors of the means.

mean serum concentration for each patient varied only between 1.3 and 2.0 µg/ml. There was no evidence of significant drug accumulation during this continuous infusion study.

Table 3 presents data on the urinary excretion of moxalactam. A mean of 19.7% of a single 500-mg i.m. dose was recovered in the urine in the first 3 h after drug administration, whereas a mean of 58.7% of the administered dose was recovered in the urine by 12 h. Corresponding figures were 35.0 and 61.2% for a single 500-mg i.v. dose, and similar results were obtained after a single 1-g i.v. dose. When 2 g of the drug was given every 6 h as a continuous infusion, a mean of 60.0% of the dose was recovered in the urine during the 6-h period. Urinary concentrations

were still quite high between 6 and 12 h after a single dose of moxalactam, whether it was given i.m. or i.v.; these concentrations ranged from 48.0 to 663.0 $\mu\text{g/ml}$ between 6 and 12 h after a single i.m. dose, from 65.0 to 173.0 $\mu\text{g/ml}$ between 6 and 12 h after a single 500-mg i.v. dose, and from 58.0 to 414.0 $\mu\text{g/ml}$ between 6 and 12 h after a single 1-g i.v. dose. The lowest urinary concentration obtained in a patient receiving a continuous infusion was 770.0 $\mu\text{g/ml}$.

The serum terminal half-life with the i.m.

FIG. 3. Mean morning and afternoon serum concentrations of moxalactam obtained with continuous i.v. infusion of 2 g over 6 h every 6 h after a 1-g loading dose in 11 patients. Bars indicate standard errors of the means.

schedule of moxalactam treatment was 3.9 h. Table 4 shows some pharmacokinetic parameters obtained with the various i.v. treatment schedules. The serum terminal-phase half-life ranged from 2.0 to 3.2 h. Assuming that volumes of distribution of between 10 and 20 liters indicated extravascular, extracellular distribution of the drug (8) and that volumes of distribution of between 25 and 30 liters indicated intracellular as well as extravascular distribution (8), the volumes of distribution for the β phase observed in this study indicated that some drug may have been distributed intracellularly in addition to extravascularly. Although the areas under the curve of concentration versus time on day 1, 3, or 4 and on day 7 or 8 did not indicate any drug accumulation when 1 g of moxalactam was given every 6 h, the increase in the area under the curve of concentration versus time from day 1 to day 7 or 8 when 2 g of moxalactam was given every 8 h indicated slightly less than 20% accumulation of the drug with this treatment schedule.

One patient developed a mild skin rash on the abdomen and legs. The rash was erythematous, maculopopular, and quite typical of skin reactions caused by drugs. The rash resolved in 1 week. No other toxicity was observed during the study in any of the other 36 patients.

DISCUSSION

Because of its broad range of activity against many gram-negative bacilli (1, 3, 4, 10-12), including the *Enterobacteriaceae* and *Pseudomonas*, the new β -lactam antibiotic moxalactam is of considerable interest. Parsons et al. (7)

TABLE 3. Urinary excretion of moxalactam

Dose	Route	Schedule	Collection time (h)	Urinary excretion		Mean urinary concn ($\mu\text{g/ml}$)
				Amt (mg)	%	
500 mg	i.m.	Single dose	0-3	98.3 $\pm$ 14.5 ^a	19.7 $\pm$ 2.9 ^a	464 (87-1,320) ^b
			3-6	113.4 $\pm$ 14.8	22.5 $\pm$ 3.0	826.6 (110-2,625)
			6-12	81.0 $\pm$ 17.1	16.3 $\pm$ 3.4	203.3 (48-663)
			Cumulative	293.3 $\pm$ 35.2	58.7 $\pm$ 7.0	
500 mg	i.v.	Single dose	0-3	175.2 $\pm$ 34.6	35.0 $\pm$ 6.9	523 (100-880)
			3-6	71.7 $\pm$ 11.7	14.3 $\pm$ 2.3	357.8 (110-660)
			6-12	59.1 $\pm$ 7.5	11.8 $\pm$ 1.5	108.3 (65-173)
			Cumulative	306.0 $\pm$ 29.9	61.2 $\pm$ 6.0	
1 g	i.v.	Single dose	0-3	280.5 $\pm$ 66.0	28.1 $\pm$ 6.6	2,063 (630-4,500)
			3-6	137.5 $\pm$ 48.1	13.8 $\pm$ 4.8	451 (155-684)
			6-12	130.0 $\pm$ 17.1	13.0 $\pm$ 1.7	191.8 (58-414)
			Cumulative	548 $\pm$ 111.4	54.8 $\pm$ 11.1	
2 g	i.v.	Every 6 h, continuous infusion	0-6	1,199.0 $\pm$ 223.6	60.0 $\pm$ 11.2	1,748 (770-3,500)

^a Mean $\pm$ standard error of the mean.

^b The numbers in parentheses are the ranges of urinary concentrations observed.

TABLE 4. *Pharmacokinetic data with moxalactam administered i.v.*

Dose (g)	Schedule	Mean serum $t_{1/2\beta}$ (h) ^a	Mean Cp_0 ($\mu\text{g/ml}$) ^b	Mean $V_{d\beta}$ (liters/ 1.73 m^2) ^c	Mean Cxt ($\mu\text{g/ml} \cdot \text{h}$) ^d
0.5	Single i.v. dose over 5 min	2.3	99	19.6	80
1.0	Single i.v. dose over 5 min	2.7	110	24.8	157
1.0	Multiple i.v. doses over 15 min (day 1)	2.7	62	26.0	149
1.0	Multiple i.v. doses over 15 min (day 3 or 4)	3.2	62	25.6	177
1.0	Multiple i.v. doses over 15 min (day 7 or 8)	2.3	63	22.6	146
2.0	Multiple i.v. doses over 15 min (day 1)	2.5	118	31.1	231
2.0	Multiple i.v. doses over 15 min (day 3 or 4)	2.2	122	25.2	246
2.0	Multiple i.v. doses over 15 min (day 7 or 8)	2.0	132	21.5	274

^a $t_{1/2\beta}$, Elimination half-life.^b Cp_0 , Serum concentration at zero time.^c $V_{d\beta}$, Volume of distribution of the β phase.^d Cxt , Area under the curve of concentration versus time.

conducted a pharmacological study of this drug with four normal subjects as volunteers; these workers performed single-dose studies with 1 g administered i.v. over a 20-min period and with 1 g given i.m. The highest mean serum concentrations obtained were 52.3 $\mu\text{g/ml}$ after the i.m. dose and 70.7 $\mu\text{g/ml}$ after the i.v. dose. These values declined at 8 h to 4.8 and 2.8 $\mu\text{g/ml}$, respectively. Using normal volunteers, Israel et al. (R. S. Israel, M. R. Black, R. S. Greffeth, G. L. Bruer, and J. D. Wolney, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, abstr. no. 169, 1979) conducted single- and multiple-dose i.v. studies and found mean peak serum concentrations of 28.4, 68.9, and 152.2 $\mu\text{g/ml}$ after single doses of 500 mg, 1 g, and 2 g, respectively. However, in their multiple-dose studies these workers obtained peak mean serum concentrations ranging from 94 to 150 $\mu\text{g/ml}$ with a 1-g treatment every 8 or 12 h and from 201 to 246 $\mu\text{g/ml}$ with a 2-g treatment every 8 or 12 h. In the work described here, we conducted single-dose i.m. studies with a dose of 500 mg in 10 patients with malignant diseases. The mean peak serum concentration obtained was only 12.4 $\mu\text{g/ml}$, compared with 52.3 $\mu\text{g/ml}$ after a 1-g i.m. dose in the study of Parsons et al. The reasons for this discrepancy are not clear, but this difference may indicate variable absorption after moxalactam is administered i.m. We also conducted single-dose i.v. studies in 10 patients with malignant diseases. Mean serum concentrations after a single 500-mg i.v. dose and after a single 1-g i.v. dose were similar to those obtained by Israel et al. (19th ICAAC, abstr. no. 169) and Parsons et al. (7), respectively.

When we conducted multiple-dose studies

with 1 g of moxalactam administered every 6 h or 2 g administered every 8 h (10 patients each), serum levels exceeding twice the minimal inhibitory concentration for most gram-negative bacteria resulted. These levels could be maintained for about 4 h after antibiotic administration. No evidence of toxicity was observed, although there was some slight accumulation of drug when 2 g was administered every 8 h i.v.

In patients with impaired host defense mechanisms, the continued maintenance of serum levels of antibiotic above the minimal inhibitory concentration for the organism causing an infection may be important (2). This study demonstrates that a schedule of 2 g of moxalactam administered continuously every 6 h can maintain serum levels above 30 $\mu\text{g/ml}$ for more than 1 week. Such levels exceed by more than two times the minimal bactericidal concentrations for 90% of all isolates tested in our laboratory, with the exception of *Enterobacter* spp. and *P. aeruginosa*. Higher doses of moxalactam may be required for optimal therapy of some infections caused by these organisms; the absence of either drug accumulation or toxicity with a continuous infusion schedule indicates that higher doses might be given safely with such a schedule.

Our study confirms the finding of Parsons et al. (7) and Israel et al. (19th ICAAC, abstr. no. 169) that the kidneys are the major route of excretion for moxalactam; 55 to 70% of an administered dose of moxalactam was recovered in the urine by 12 h after a single i.m. or i.v. dose. Because of the high concentrations of moxalactam attainable in the urine after an i.m. or i.v. dose, this drug should be useful in the treatment of urinary tract infections, even when given i.m.

The peak serum concentrations after i.m. administration of 500 mg of moxalactam are similar to those reported after administration of the same dose of either cephalothin or cefoxitin and considerably lower than those obtained after i.m. injections of cefazolin (6, 9). The peak serum levels after a 1-g i.v. dose of moxalactam also closely resemble those reported after i.v. administration of the same dose of cephalothin, cefoxitin, or cefamandole and again are distinctly lower than those obtained after cefazolin injections (6). However, we found that the serum terminal-phase half-life of moxalactam (2.0 to 3.2 h) is longer than the serum terminal-phase half-lives reported for cephalothin (0.6 h), cefoxitin (0.8 h), and cefamandole (0.9 h) and more closely resembles the serum terminal-phase half-life of cefazolin (1.9 h) (6). Parsons et al. (7) and Israel et al. (19th ICAAC, abstr. 169) also found a comparatively longer serum terminal-phase half-life for moxalactam (2.3 and 1.8 to 2.0 h, respectively). The prolongation in the serum terminal-phase half-life of moxalactam may be related to the fact that only about 30% of the dose is recovered in the urine in the initial 3 h after i.v. administration, compared with 68 and 66% for cephalothin and cefamandole, respectively. Parsons et al. (7) also found a comparatively low recovery of drug in the urine soon after i.v. administration (32% in the first 2 h). The large volume of distribution of the drug may also contribute to the comparatively long serum terminal-phase half-life. The prolongation in the half-life observed with moxalactam is of uncertain clinical significance. Certainly, despite some evidence of slight drug accumulation when 2 g of moxalactam was administered every 8 h i.v., no toxicity was observed.

Based on this study and previous *in vitro* susceptibility studies, a dose of 1 to 2 g of moxalactam every 6 to 8 h seems appropriate for the treatment of most infections. The possibility of drug accumulation exists with higher doses ad-

ministered more frequently, although the clinical importance of this is not known. Therapeutic studies with moxalactam are in progress at this institution.

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