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Pharmacokinetics of Moxalactam and Cefazolin Compared in Normal Volunteers

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The pharmacokinetics of moxalactam, a new β-lactam antibiotic with an unusually broad spectrum of activity, were studied in normal volunteers and compared with the pharmacokinetics of cefazolin. After a 1,000-mg intramuscular injection of moxalactam, a mean peak serum level of 49 ± 10 μg/ml was achieved at 30 to 60 min which was equivalent to the level achieved with 0.5 g of cefazolin. Serum levels of 4.57 ± 0.63 μg/ml, above the inhibitory levels for most organisms, were present at 8 h. The half-life of moxalactam was 2.3 h. After a 30-min intravenous infusion of 1 g, the serum level of moxalactam was 60 ± 18.8 μg/ml. This compares with a serum level of 70 μg/ml obtained with an infusion of 0.5 g of cefazolin. At 6 h, 3.59 ± 0.68 μg/ml of moxalactam was present. The half-life of moxalactam was 2.3 h, similar to that of cefazolin. By 1 h after administration, serum levels of moxalactam were higher after intramuscular administration than after intravenous delivery. Urinary recovery of the drug was 76% after intramuscular injection and 74% after intravenous infusion, with the majority of the drug having been excreted in the first 4 h after administration. Urinary recovery of cefazolin was 85%. The pharmacokinetics of moxalactam are similar to those of cefazolin.

Moxalactam has been shown to have activity against most of the *Enterobacteriaceae* (7), inhibiting isolates resistant to cefamandole, cefoxitin, and aminoglycosides at concentrations below 1 μg/ml. It also inhibits anaerobic species such as *Bacteroides fragilis* and *Pseudomonas aeruginosa* at concentrations below 25 μg/ml. Thus, moxalactam markedly extends the in vitro antibacterial activity of the previous cephalosporins.

We wished to compare the pharmacokinetics of moxalactam with those of cefazolin in normal human volunteers after intramuscular (i.m.) and intravenous (i.v.) administration of these agents. Cefazolin was chosen for comparison since it is well tolerated by both i.m. and i.v. routes and has become one of the most widely used cephalosporins in clinical practice, particularly in community hospitals.

MATERIALS AND METHODS

Cefazolin and moxalactam were supplied by Eli Lilly Research Laboratories, Indianapolis, Ind. The antibiotics were reconstituted in 5% dextrose in water for administration.

Six normal males between the ages of 19 and 42 (mean, 32 years) were used in this study. They ranged from 160 to 183 mm (mean, 173 mm) in height and from 62 to 75 kg (mean 68.5 kg) in weight. Mean body surface area was 1.81 m^2. All were judged healthy on the basis of normal physical examination, complete hematological evaluation, urinalysis, and chemistry profiles. All had creatinine clearances above 100 ml/min. None had a history of penicillin allergy. Informed, written consent was obtained in accordance with the guidelines of the Institutional Committee on Human Investigation.

i.m. injection study. The subjects received either 500 mg of cefazolin or 1,000 mg of moxalactam by random allotment, followed 1 week later by the alternate agents. All injections were in the gluteal area. Blood samples were obtained at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after i.m. injection. Urine samples were collected immediately before injection at 0 to 2, 2 to 4, 4 to 8, and 8 to 24 h after the drug was administered. Blood samples were allowed to clot at room temperature and were centrifuged, and the serum was removed 30 min after being drawn. Each serum and urine sample was divided into aliquots which were immediately frozen and stored at −20°C until assay.

i.v. infusion study. Each of the six subjects received by random assignment either 500 mg of cefazolin or 1,000 mg of moxalactam infused intravenously through a small-bore needle over a 30-min period, followed 1 week later by the alternate drug infused in the same manner. Blood samples were drawn before infusion and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3.5, 4.5, and 6.5 h after infusion began. Urine samples were collected before infusion and at intervals of 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h. Serum and urine samples were processed as described for the i.m. study.

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Assays. Moxalactam and cefazolin were assayed by the agar well diffusion technique, using antibiotic medium no. 2 (Difco Laboratories, Detroit, Mich.) as previously described (2, 7). Antibiotic standards for assay of serum samples were prepared in pooled normal human serum from the subjects which had been shown to lack antibacterial activity against the assay organisms. Urine samples were diluted in 0.05 M potassium phosphate buffer (pH 7). The assay organism for moxalactam was *Escherichia coli* 3989 from our collection and that for cefazolin was *Staphylococcus aureus* ATCC 3472. In both instances levels of 0.5 μg/ml could be detected. Serum and urine samples were assayed in quadruplicate, and five standards were used on each plate. Concentrations of drug were calculated by using a linear semilogarithmic plot with use of a computer.

The assay for moxalactam could detect 0.3 μg/ml and was linear from 0.3 to 80 μg/ml. The assay for cefazolin could detect 0.2 μg/ml and was linear from 0.2 to 80 μg/ml. Samples which gave results outside the linear part of the curve were diluted in normal human serum from the volunteers. Samples were thawed only once since duplicates of all samples were kept. Both moxalactam and cefazolin are stable under the conditions of assay (information from Eli Lilly & Co.). Furthermore, samples were prepared at the time of injection and infusion and stored in a similar manner as were samples from the subjects to detect decay. No decay was detected.

Pharmacokinetic and statistical methods. The semilogarithmic plot of the serum concentrations of both agents, when plotted as time after i.v. infusion, conformed to a biexponential curve with an initial distribution and subsequent elimination phase. Thus, two-compartment kinetics were used to define the i.v. study data (4). Regression lines were determined by the method of least squares with a computer. The basic equation was $C = A_e^{-\alpha t} + B_e^{-\beta t}$, with volume of distribution expressed as V_d = dose/$[\beta(A + B/\alpha + \beta)]$ and the rate constants expressed as $k_{10} = (\alpha\beta)/k_2)$, $k_{21} = (A\beta = B\alpha)/(A + B)$, and $k_{12} = \alpha + \beta - k_{21} - k_{10}$. The area under the curve was determined by utilizing Simpson's rule (2). Serum clearance was expressed in milliliters per minute per 1.73 m^2, utilizing the relationship of C = [dose/(AUC × 60)] × (1.73/BSA), where the dose is in micrograms, BSA is the body surface area, and AUC is the area under the curve. The effect of infusion was considered (5).

A one-compartment open model was used to calculate the parameters after i.m. injection (4). Least-squares analysis was performed with a computer.

RESULTS

i.m. study. The mean serum concentrations after administration of 1,000 mg of moxalactam are shown in Fig. 1. The pharmacokinetic parameters for i.m. administration of moxalactam and cefazolin are shown in Table 1. The mean peak serum concentration of moxalactam was 49 ± 10 μg/ml (Fig. 1). The peak serum concentration was reached within 45 min. At the end of 6 h, the mean serum level was 7.5 ± 0.85 μg/ml. At the end of 8 h, the mean serum level was 4.5 ± 2 μg/ml. In contrast, the mean peak serum level after 500 mg of cefazolin, 49 μg/ml, was reached at 1 h, with mean serum levels of 28 μg/ml at 2 h, 16 μg/ml at 4 h, and 5.6 μg/ml at 8 h. There was a modest amount of intrasubject variation in serum concentrations of both drugs which could not be correlated with weight, body

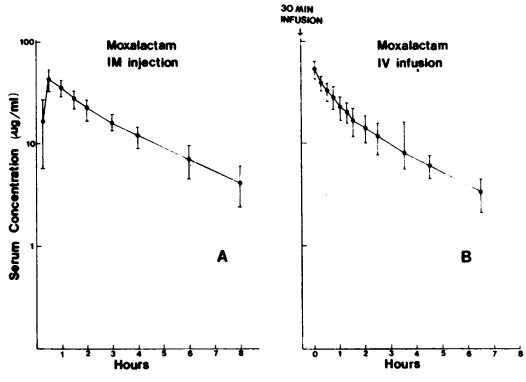

FIG. 1. *Mean serum levels ± standard error of moxalactam after i.m. injection of 1,000 mg (A) and after a 30-min i.v. infusion of 1,000 mg (B).*

TABLE 1. *Pharmacokinetic parameters of moxalactam and cefazolin after i.m. administration*

Parameter	Result	
	Moxalactam	Cefazolin
Dose (mg)	1,000	500
Mean peak serum level (μg/ml)	49 ± 10	49 ± 12
Serum level (μg/ml) at h:		
6	7.5	9.1
8	4.5	5.6
Half-life (h)	2.3	2.2
Vol of distribution (liter/1.73 m^2)	28.3	9.2
Serum clearance (liter/1.73 m^2)	61	78
Renal clearance (liter/1.73 m^2)	51	63
Urinary levels, 0–8 h (μg/ml)	392–3,515	25–3,300
Urinary excretion, 0–24 h (%)	76	78

surface area, or creatinine clearance. The area under the curve was 99 μg/ml·h for moxalactam.

The mean half-life of moxalactam was 2.3 h and that of cefazolin was 2.2 h. The apparent volume of distribution was 28.3 liters per 1.73 m^2 for moxalactam and 9.2 liters per 1.73 m^2 for cefazolin. The mean serum clearance was 61 ml/1.73 m^2 for moxalactam and 78 ml/min for cefazolin. The mean renal clearance was 51 ml/min per 1.73 m^2 for moxalactam and 63 ml/min per 1.73 m^2 for cefazolin. Approximately 40% of a dose was excreted in the first 2 h, with 76% of the 1,000-mg dose having been recovered within 24 h. Urine concentrations in the first 2 h obviously depend upon the volume of urine and ranged from 392 to 3,515 μg/ml for the 1,000-mg dose. In contrast, urine concentrations of cefazolin in the first 2 h ranged from 31 to 211 mg for the 500-mg dose. Approximately 78% of the cefazolin was recovered within 24 h. Moxalactam was present in urine as the parent compound. Breakdown products were not noted on chromatography.

i.v. study. The mean serum levels of moxalactam after a 30-min i.v. infusion of 1,000 mg are shown in Fig. 1. The pharmacokinetic parameters of cefazolin and moxalactam are shown in Table 2. The mean serum concentration at the end of infusion was 60 ± 18.8 μg/ml. At 3 h after start of infusion the mean serum level was 7.5 ± 0.9 μg/ml, and at 6.5 h the mean serum level was 3.6 ± 0.7 μg/ml. The variation in serum levels did not correlate with differences in body size of the subjects or with creatinine clearances. In contrast, the 500 mg of cefazolin administered by i.v. infusion yielded a serum level of 70 ± 7.5 μg/ml at the end of infusion and a mean level of 2.1 μg/ml at 6.5 h. The mean half-life for moxalactam was 2.23 h compared with the cefazolin half-life of 1.97 h. The apparent volume of distribution was 15.6 liters per 1.73 m^2 compared with the cefazolin volume of distribution of 13.9 liters per 1.73 m^2. The mean serum and renal clearances for moxalactam were 77 ml/min per 1.73 m^2 and 55 ml/min per 1.73 m^2, respectively, whereas those for cefazolin were 59 ml/min per 1.73 m^2 and 51 ml/min per 1.73 m^2, respectively.

The urinary recovery of moxalactam ranged from 70 to 92%, with a mean urinary recovery of 74% of the administered dose compared with the cefazolin recovery of 85%. Urine concentrations of moxalactam in the first 2 h after the i.v. dose depended upon the volume and ranged from 594 to 2,090 mg/ml.

Moxalactam and cefazolin were equally well tolerated by both the i.m. and i.v. routes. There was minimal discomfort, and phlebitis was not encountered. Hematological and chemical parameters were not altered by this single-dose administration.

DISCUSSION

Moxalactam differs from the commercially available cephalosporins, such as cephalothin, cefazolin, and cefamandole by its extended antibacterial spectrum and greater in vitro activity against many of the clinically important members of the *Enterobacteriaceae* which are resistant to other cephalosporins and aminoglycosides (7, 8). It inhibits most hospital isolates of *Enterobacteriaceae* at concentrations below 0.5 μg/ml and those of *S. aureus*, *B. fragilis*, and *P. aeruginosa* at concentrations below 25 μg/ml.

The pharmacokinetics of moxalactam, as exhibited in this study, indicate that either an i.m. or i.v. dose of 1,000 mg would provide serum and urine levels which would readily inhibit members of the *Enterobacteriaceae* and, most important, gram-positive species for 8 h. The urine concentration of this compound would also inhibit most bacteria resistant to older cephalosporins and to aminoglycosides.

The pharmacokinetic parameters of moxalactam are similar to those of cefazolin, except for

TABLE 2. *Pharmacokinetic parameters of moxalactam and cefazolin after i.v. infusion over 30 min*

Parameter	Result	
	Moxalactam	Cefazolin
Dose (mg)	1,000	500
Mean serum level at end of infusion (μg/ml)	60 ± 18.8	70 ± 7.5
Mean serum level at h:		
4.5	6.5 ± 1.6	6.7 ± 1.4
6.5	3.6 ± 1.4	1.8 ± 1
Half-life (h)	2.23	1.97
Vol of distribution (liter/1.73 m^2)	15.6	13.9
Serum clearance (ml/1.73 m^2)	77	59
Renal clearance (ml/1.73 m^2)	55	51
Urinary levels, 0–8 h (μg/ml)	594–2,094	40–1,568
Renal recovery (%)	74	85

the height of the serum levels. Thus, 1 g of moxalactam and 500 mg of cefazolin produced comparable serum levels. Unlike cephalothin, cefamandole, cefoxitin, and cefotaxime (1, 3, 6) which have half-lives of 0.7 to 1 h, the half-life of moxalactam is relatively long so that inhibitory serum concentrations are present up to 12 h after i.m. or i.v. injection.

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