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Pharmacokinetics of Mecillinam in Healthy Subjects

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Mecillinam is an amidino penicillinate derivative with a broad spectrum of activity against many gram-negative bacilli. Moreover, marked in vitro synergy against these organisms occurs when mecillinam is combined with other β-lactam antibiotics. The purpose of this study was to determine the pharmacokinetic disposition of this antibiotic. A single dose of 10 mg/kg was administered to 12 healthy volunteers as a 15-min intravenous infusion. Multiple plasma and urine samples were collected at frequent intervals for 8 and 24 h, respectively. Plasma samples were assayed for mecillinam by using a specific high-pressure liquid chromatographic assay developed in our laboratory. Peak plasma levels ranged from 34 to 80 μg/ml, and after 4 h, plasma levels were 0.7 to 1.9 μg/ml. The mean terminal plasma half-life was 51.1 ± 8.6 min. The mean steady-state volume of distribution was calculated to be 0.23 ± 0.04 liter/kg. The mean plasma and renal clearances were 3.5 ± 0.4 and 2.5 ± 0.4 ml/min per kg, respectively. The mean percentage of the dose excreted unchanged in the urine at 4 h was 67 ± 5%; 71 ± 6% was recovered in 24 h. Urine concentrations at 4 h were far above the minimum inhibitory concentration for susceptible gram-negative organisms.

Mecillinam is a new semisynthetic β-lactam antibiotic. It is a 6-amidinopenicillanic acid, whereas other β-lactam antibiotics are 6-acylaminopenicillanic acids. This altered structure has resulted in differences in microbiological activity. Mecillinam is generally more active against gram-negative than gram-positive organisms. The minimum inhibitory concentration of mecillinam for most susceptible strains of gram-negative bacteria is ≤1 to 2 μg/ml (9). Additionally, this antibiotic exhibits synergistic effects in vitro when combined with other β-lactam antibiotics such as ampicillin, carbenicillin, or cephalothin (2).

The objectives of this study were to determine the pharmacokinetic parameters and excretion characteristics of mecillinam after intravenous administration in healthy subjects. This was accomplished by using a newly developed high-pressure liquid chromatographic assay developed by our group for determination of mecillinam in plasma and urine.

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MATERIALS AND METHODS

Experimental procedure. Twelve healthy adult volunteers participated in this study. Informed consent was obtained from each subject, and guidelines for human experimentation of the U.S. Department of Health, Education, and Welfare and those of our institution were followed in the conduct of this clinical research. A panel of laboratory tests, consisting of an SMA 12, complete blood cell count, differential blood cell count, urinalysis, and creatinine clearance, as well as a complete medical history and physical examination were performed before and after drug administration. Table 1 shows individual subject characteristics. Mecillinam (1-g vial) was reconstituted with 8.8 ml of water for injection USP so that each milliliter of solution contained 100 mg of mecillinam. The appropriate dose was then diluted to 50 ml with 5% dextrose solution USP before infusion. A dose of 10 mg of mecillinam per kg of body weight (actual dose, 11.5 mg/kg [see below]) was infused over a 15-min period into a peripheral arm vein by using a constant-rate Harvard infusion pump. Blood samples (10 ml each) were collected before the dose and at 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300, 360, and 480 min. Samples were placed in ice and quickly centrifuged, and the plasma was harvested for assay. Urine specimens were collected half-hourly for the first 3 h and hourly up to 6 h and were pooled from 6 to 24 h. Urine samples were placed in ice before analysis, and the pooled samples were kept under refrigeration during the collection period. Adequate water intake was encouraged to promote urine flow. Both plasma and urine were assayed for mecillinam within 24 h of sample collection.

Analytical methods. Plasma and urine samples were analyzed using a sensitive and specific high-pressure liquid chromatographic (HPLC) method developed in our laboratory (E. T. Lin, J. G. Gambertoglio, S. L. Barriese, and L. Z. Benet, Abstr. Natl. Meet. APHA Acad. Pharm. Sci. 1980, abstr. no. 15, p. 124). Plasma samples (0.2 ml) were deproteinated with 0.4 ml of CH_3CN containing the internal standard desacetylcephalothin. The mixture was blended in a Vortex

TABLE 1. *Subject characteristics*

Subject	Sex	Age (yr)	Wt (kg)	Creatinine clearance[a] (ml/min)
1	F	27	57	88
2	M	32	95	99
3	F	26	66	98
4	M	28	68	99
5	F	28	64	82
6	M	29	68	120
7	F	25	59	91
8	F	26	75	95
9	M	24	80	123
10	M	32	71	106
11	M	27	73	93
12	M	26	70	88

[a] Average of two 24-h determinations.

mixer for 1 min and centrifuged for 10 min, the supernatant was evaporated to 0.1 ml under nitrogen, and 20 to 50 μl was injected into the column. Urine samples were diluted and injected directly onto the column after the addition of desacetylcephalothin. A Perkin-Elmer Series 3 liquid chromatograph with a LC-65T spectrometer was used. The assay was carried out on a μBondapak phenyl column (Waters Associates) with a solvent system of 15% CH_3CN–0.02% H_3PO_4 and a solvent flow rate of 2 ml/min. The ultraviolet detection wavelength was 220 nm. The lowest concentration detectable without extraction was 0.38 μg/ml for plasma and 20 μg/ml for urine. No interference from plasma or urine was noted. Reproducibility measurements yielded a coefficient of variation of 2 to 6%. Mecillinam is unstable in frozen plasma stored at −20°C. However, when an equal volume of CH_3CN was added to plasma, more than 90% of spiked concentrations was retained for 3 weeks in plasma stored at −20°C. The results from the HPLC assay were comparable to that found by using a microbiological assay (J. G. Christenson, Hoffmann-La Roche, personal communication).

Pharmacokinetic analysis. Compartment-independent methods were used for the determination of pharmacokinetic parameters. After graphical analysis of the mecillinam plasma level-time curves on a semilogarithmic plot, a least-squares fit of the terminal linear portion of the curve was used for determination of the slope or disposition rate constant, β. The half-life was then calculated by dividing β into the natural logarithm of 2.

The volume of distribution at steady-state (Vd_{ss}) was calculated by using the compartment-independent equation of Benet and Galeazzi (3):

$$Vd_{ss} = \frac{\text{dose (AUMC)}}{(\text{AUC})^2} \quad (1)$$

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. The areas were calculated by using the trapezoidal rule, and terminal areas were calculated by dividing the last plasma concentration value by β. Since the use of this equation is appropriate only after intravenous bolus dosing, correction was made for infusion administraton by subtracting $(t/2)(\text{Dose/AUC})$ from the Vd_{ss} values obtained, where t is the infusion time (L. Z. Benet, personal communication).

Total plasma clearance (CL_P) was determined by the equation

$$CL_P = \frac{\text{dose}}{\text{AUC}} \quad (2)$$

and renal clearance (CL_R) was calculated by two methods:

$$CL_{R1} = \text{fe } CL_P \quad (3)$$

$$CL_{R2} = \frac{(\text{Ae})_{t_1}^{t_2}}{(\text{AUC})_{t_1}^{t_2}} \quad (4)$$

where fe is the fraction of the dose excreted unchanged in the urine and Ae is the amount of drug excreted in the urine over the time interval t_1 to t_2.

RESULTS

Figure 1 shows a semilogarithmic plot of mecillinam plasma concentrations versus time after a single 10-mg/kg dose given as a 15-min intravenous infusion to subject six. Similar curves were found for each of the 12 subjects studied. Figure 1 also shows an excretion rate-versus-time curve for the same subject, demonstrating a similar half-life. A plot of the mean plasma concentration-time curve for all subjects is shown in Fig. 2. Peak plasma levels achieved

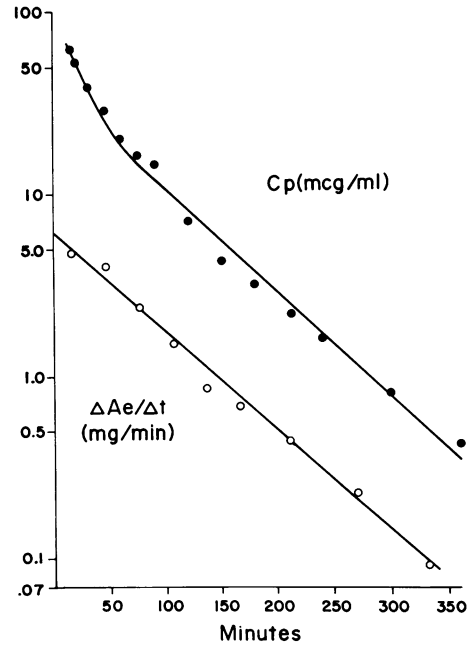

FIG. 1. *Semilogarithmic plot of plasma concentration (●) and urinary excretion (○) versus time after a 10-mg/kg dose of mecillinam given as a 15-min infusion to subject six.*

immediately after the infusion varied considerably among the subjects from 34 to 80 μg/ml, with a mean of 61 μg/ml, although the dose was normalized according to body weight. Plasma concentrations rapidly fell to about 20 μg/ml (range, 13 to 25 μg/ml) after 1 h. At 2 h, the average level was 7.6 μg/ml (6 to 10 μg/ml), and at 4 h, the mean concentration was 1.4 μg/ml (0.7 to 1.9 μg/ml). At 6 h after the dose, levels were unmeasurable in four subjects, and the highest level observed was 0.8 μg/ml.

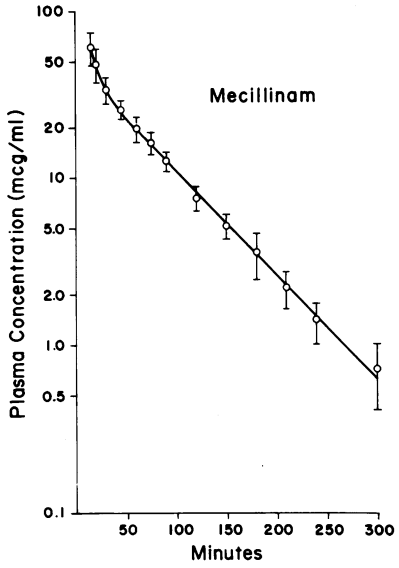

FIG. 2. *Semilogarithmic plot of mean (± standard deviation [vertical bars]) mecillinam concentrations versus time for all 12 subjects.*

Table 2 shows the pharmacokinetic parameters calculated for mecillinam. The plasma half-life ranged from 39 to 66 min, with an average value of 51 min. This agrees well with the mean half-life of 55 min determined from urine excretion rate plots for each subject. The steady-state volume of distribution for mecillinam in the normal subjects reported here was calculated to be 0.23 liter/kg of body weight, or 16.1 liters for a 70-kg person.

Mecillinam was cleared from the plasma at an average rate of 3.5 ml/min per kg, or approximately 245 ml/min. The renal clearance of the drug accounted for more than 70% of the total plasma clearance. The average renal clearance of mecillinam was 175 ml/min, approximately twice the clearance of creatinine for these subjects, suggesting net tubular secretion.

High urinary concentrations of mecillinam were achieved since the majority of the drug was excreted in the urine, averaging 71% in 24 h. About 23% was excreted in 0.5 h. After 3 h, 64% of the drug was excreted. Only about 1.4% was excreted during the 6- to 24-h collection (Table 3). Thus, urine concentrations were as high as 360 to 2,444 μg/ml (mean, 1,139 μg/ml) in the first 0.5 h and remained in the range of 35 to 564 μg/ml at 4 h and 12 to 279 μg/ml for about 6 h (Table 3).

DISCUSSION

Mecillinam is active in vitro against a variety of gram-negative bacteria including *Escherichia coli, Klebsiella, Proteus, Salmonella, Shigella,* and *Enterobacter* species and some strains of *Serratia.* Serum concentrations achieved after

TABLE 2. *Pharmacokinetic parameters of mecillinam*

Subject	Plasma $t_{1/2}$ (min)	Urine $t_{1/2}$ (min)	Vd_{ss} (liter/kg)	CL_P (ml/min per kg)	fe (%)	CL_{R1} (ml/min per kg)	CL_{R2}[a] (ml/min per kg)
1	49.8	52.5	0.28	4.3	70.4	3.1	3.2 (43)
2	49.1	59.1	0.22	3.2	68.4	2.2	2.1 (21)
3	61.2	59.6	0.24	3.2	80.6	2.5	2.4 (8)
4	61.5	60.0	0.27	3.8	81.7	3.1	3.1 (18)
5	54.7	59.3	0.27	3.7	71.3	2.6	3.2 (45)
6	53.1	55.4	0.21	3.3	61.9	2.0	2.3 (16)
7	51.3	60.2	0.31	4.2	67.5	2.8	3.1 (25)
8	42.5	50.6	0.19	3.3	72.4	2.4	2.5 (16)
9	41.4	52.5	0.19	3.3	66.2	2.2	2.5 (37)
10	43.6	51.1	0.17	3.1	65.1	2.0	2.1 (21)
11	39.4	51.2	0.19	3.9	75.5	2.9	3.4 (26)
12	65.9	54.1	0.20	3.0	70.8	2.1	2.4 (23)
Mean	51.1	55.5	0.23	3.5	71.0	2.5	2.7
±SD[b]	8.6	3.9	0.04	0.4	5.9	0.4	0.5

[a] Average of eight or nine incremental renal clearance determinations, calculated by using equation 4, over the first 5- or 6-h period after drug administration. Numbers in parentheses represent the coefficient of variation, expressed as percent.

[b] SD, standard deviation.

TABLE 3. *Average urine concentration and excretion data for mecillinam*

Time (min)	Concn (μg/ml) ± SD[a]	Cumulative % dose ± SD[a]
30	1,139 ± 801	23.0 ± 5.2
60	830 ± 605	39.2 ± 5.5
90	357 ± 115	49.2 ± 5.3
120	397 ± 417	55.9 ± 4.3
150	325 ± 281	60.8 ± 4.1
180	339 ± 386	63.7 ± 4.3
240	135 ± 143	67.0 ± 4.6
300	113 ± 59	69.3 ± 4.3
360	97 ± 80	69.6 ± 4.8
1,440	8.6 ± 8.7	71.0 ± 6.0

[a] SD, Standard deviation.

a 10-mg/kg intravenous dose of mecillinam remain at or above the usual minimum inhibitory concentrations for many of these organisms for as long as 4 h after the dose. For example, most strains of *E. coli* are susceptible to 1 μg or less of mecillinam per ml (2). At 4 h after the dose in our study, the mean serum concentration was 1.4 μg/ml.

Urine concentrations may be as high as 1,000 μg/ml and remain far in excess of the usual minimum inhibitory concentration for these organisms for as long as 6 h. Concentrations of mecillinam in the pooled 6- to 24-h specimens of urine were usually also above the minimum inhibitory concentration.

The pharmacokinetic characteristics observed for mecillinam in this study are similar to those reported previously when microbiological assays were used. The average plasma half-life for mecillinam in our subjects was 51 min. Mitchard et al. (5) report a half-life of 49 min after intravenous dosing in their study of six healthy male volunteers. However, calculation of half-life from the terminal elimination rate constant (β phase) values gives an average half-life of 69 min. After intramuscular administration, the half-life of mecillinam has been found to range from 58 to 72 min in normal subjects (1, 8, 9).

The plasma clearance of mecillinam averaged 3.5 ml/min per kg, with the majority of the drug being excreted unchanged in the urine. Renal clearance obtained with equation 4 from 0 to 6 h was 2.7 ml/min per kg. This compares well with the 2.5-ml/min per kg value calculated by using the plasma clearance and fraction of dose excreted unchanged (equation 3). The high renal clearance of mecillinam relative to the creatinine clearance of these subjects indicates renal tubular secretion of the drug. In addition, others have reported that probenecid can increase the half-life and decrease the urinary excretion of mecillinam (1, 7, 8).

The percentage of the intravenous dose recovered in the urine (71%) in our study is higher than that reported by others. Studies by Roholt (7, 8) found 50 to 60% of the dose excreted unchanged in a 24-h urine collection after either intravenous or intramuscular administration to normal subjects. Virtually all of the drug excreted was found in the first 6-h period. Andrews et al. (1) recovered only 15% of an intramuscular dose in the urine over 6 h.

A partial explanation for the lower urinary recoveries found by others is most likely due to the instability of mecillinam in urine (1, 6, 9). Furthermore, our percentage of the dose recovered in the urine was calculated after correcting for the administered dose. Analysis of mecillinam in reconstituted vials revealed that the concentration averaged 114.8% of the expected concentrations. Thus, the actual dose administered to our subjects was 14.8% more than expected. If this correction was not made, our urinary recovery of mecillinam would have appeared even higher. It is not specified in previous studies whether this was taken into consideration.

In conclusion, the pharmacokinetics of mecillinam are similar to other β-lactam antibiotics, and little accumulation would be expected with multiple doses. High concentrations of mecillinam are achieved in the urine and, when administered every 6 h, should be useful in the treatment of urinary tract infections due to susceptible bacteria. Serum concentrations achieved after a 10-mg/kg dose also appear to be adequate for the treatment of systemic infection if the drug is administered every 4 h.

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