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Pharmacokinetics of Intravenous Piperacillin in Patients Undergoing Chronic Hemodialysis

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The pharmacokinetic properties of piperacillin, a piperazine derivative of ampicillin, were determined in seven patients with creatinine clearances less than 7 ml/min who were undergoing chronic, intermittent hemodialysis. A two-compartment linear model was used to analyze the data. Mean elimination half-life was 1.26 ± 0.1 h; the mean elimination constant was 0.95 ± 0.08 h^{-1}; the mean volume of distribution was 0.16 ± 0.02 liters/kg of body weight; the mean volume of the central compartment was 0.10 ± 0.01 liters/kg of body weight; and the mean clearance was 0.09 ± 0.01 liters/h per kg of body weight. Mean elimination half-life while off dialysis was 2.1 h.

Piperacillin, a new piperazine penicillin, has in vitro activity against many clinically relevant gram-positive and gram-negative bacteria (5, 15). Its gram-negative spectrum includes most of the clinically important *Enterobacteriaceae*, such as *Escherichia coli* and *Enterobacter cloacae*, *Proteus mirabilis* and approximately half of the *Klebsiella pneumoniae* and *Serratia marcescens*, and most indole-negative *Proteus*. It is four- to eightfold more active than carbenicillin in inhibiting *Pseudomonas aeruginosa* and fourfold more active against *Bacteroides fragilis* (5, 14). Clinical studies at our institution have shown piperacillin to be a useful agent in the treatment of serious infections due to *Enterobacteriaceae*, *Pseudomonas*, and *Bacteroides* (Pancoast, Prince, and Neu, manuscript in preparation). The pharmacokinetics of piperacillin have been studied in healthy individiauls (1, 4). For these reasons we studied the pharmacokinetics of piperacillin administered intravenously to seven volunteers undergoing chronic, intermittent dialysis.

MATERIALS AND METHODS

Subjects were seven adult volunteers undergoing chronic, intermittent hemodialysis at the Columbia-Presbyterian Medical Center. Demographic data are given in Table 1. Four patients were female, and three were male. Ages ranged from 32 to 75 years and weights ranged from 44.1 to 70.4 kg. All patients had an endogenous creatinine clearance less than 7 ml/min and were maintained on hemodialysis three times a week. No patient had a prior history of allergic reaction to any penicillin, and all patients had received penicillins on previous occasions. None of the patients had received an antimicrobial agent during the month before inclusion in the study.

After obtaining informed, written consent from each patient in accordance with guidelines of the Institutional Committee on Human Investigation, a single intravenous bolus injection of 1.0 g of piperacillin in a volume of 10 ml was given over 5 min at the beginning of the dialysis period. All patients were dialyzed for 5 h with a Travenol RSP apparatus with an IM^2 cuprophane membrane dialyzer. Blood flow was maintained at a constant rate of 250 to 300 ml/min. Dialysate flow rate was held constant at 600 ml/min. Specimens of arterial blood were obtained at 5, 15, 30, 60, 120, 180, and 240 min after dosing. At the end of a subsequent dialysis treatment, at least 2 weeks later, three of the patients were given 2 g of piperacillin as an intravenous bolus injection over 5 min. Venous samples were drawn at 15, 30, 60, 120, 180, 240, and 300 min.

Blood was collected in evacuated glass tubes and allowed to clot at room temperature, and the serum was separated by centrifugation. All samples were stored frozen at −20°C until assayed. The piperacillin content of the serum samples was determined by a modification of the agar well diffusion method of Bennett al. (2) with *P. aeruginosa* from our collection as the assay microorganism (12). Serum samples at 5, 15, 30, and 60 min were diluted 1:3 in normal pooled human serum lacking antibacterial activity at the time of preparation of assay plates. Standard curves were prepared for each assay with the same pooled human serum. Five standards and 11 samples were assayed per plate, each in quadruplicate. Samples of dialysate obtained at the outflow drain were assayed by the same technique, with *Sarcina lutea* as the assay organism. Standards for assay of dialysate were prepared in potassium phosphate buffer, 0.05 M, pH 7.0. All samples were assayed in quadruplicate.

Data were examined by using a two-compartment linear model. This model has been shown to describe adequately the course of most β-lactam antibiotics (4, 13). Solutions for the two-compartment model were performed as described by Bischoff and Dedrick (3). Elimination half-life for each of the three patients

given 2 g of piperacillin between dialyses was also determined by the same model.

RESULTS

The arterial serum levels are given in Table 2. The 5-min serum levels ranged from 98 to 229 μg/ml, with a mean of 153 ± 17 μg/ml. Mean serum level at 30 min was 60 ± 3.9 μg/ml, and that at 4 h was 8.4 ± 1.9 μg/ml. The mean elimination half-life of piperacillin during hemodialysis was 1.26 ± 0.14 h (Table 3). The mean clearance of piperacillin was 0.09 ± 0.01 liters per kg per h; mean total volume of distribution was 0.16 ± 0.02 liters per kg of body weight; and the mean volume of distribution for the central compartment was 0.10 ± 0.01 liters per kg of body weight. No significant intersubject variation could be demonstrated for any of these values. Approximately 48% of the administered dose was recovered in the dialysate during 4 h of dialysis. Elimination half-lives for a 2-g dose of piperacillin while off dialysis are listed in Table 4, and range from 1.19 to 3.11 h.

DISCUSSION

The pharmacokinetics of intravenously administered piperacillin with a two-compartment open model to analyze the data have been reported for normal individuals (1, 4). The half-life of piperacillin in individuals with creatinine clearances above 90 ml/min ranged from 1.3 to 1.5 h (1, 4). In this study of patients with creatinine clearances less than 7 ml/min, the piperacillin half-life ranged from 1.2 to 3.1 h, which is identical to that $T_{1/2}$ found by Kashiwabara et al. (8) for patients in renal failure. This range may be due to differences among the individuals in biliary excretion, residual renal clearances, and metabolism of piperacillin. It is known that there is significant biliary excretion of some of the penicillins (8), and some of the penicillins undergo metabolism to a degree that prevents their accumulation in the presence of decreased renal function.

Some piperacillin is removed by hemodialysis, since 48% of the 1-g dose is recovered in the dialysate during 4 h of hemodialysis. However, the elimination half-life of 1.26 ± 0.1 h after a 1-g intravenous bolus injection is similar to the elimination half-life while off dialysis. The half-lives in three patients with creatinine clearances less than 7 ml/min while off dialysis were 1.2, 2, and 3.1 h. Since 48% of the 1-g intravenous dose of piperacillin could be accounted for in the dialysate during 4 h of dialysis, about 40% of a dose is removed from the body by means other than dialysis during the same period. In undialyzed patients, however, about 70% of a 2-g dose is eliminated during 4 h. The difference in nondialysate removal may be due to differences in metabolism and nonrenal excretion via the biliary tract, particularly with a larger dose.

TABLE 1. *Demographic data of the subjects*

Patient	Age (yr)	Sex	Wt (kg)	Ht (cm)	BSA[a] (m^2)	Diagnosis
1	67	F	50.8	165	1.63	Hypertensive renal disease
2	55	F	44.1	152	1.42	End-stage renal disease, undetermined etiology
3	72	F	51.5	165	1.55	Systemic lupus erythematosus
4	75	M	99.6	193	2.30	Hypertensive renal disease
5	36	M	60.1	170	1.69	Hypertensive renal disease
6	54	F	70.4	157	1.71	Polycystic kidneys
7	61	M	68.8	180	1.86	Hypertensive renal disease

[a] BSA, Body surface area.

TABLE 2. *Arterial serum levels of piperacillin*

Patient	Piperacillin serum level (μg/ml) at:						
	5 min	15 min	30 min	60 min	120 min	180 min	240 min
1	177	95	53.0	56.2	36.9	28.3	19.3
2	156	96	53.7	48.1	24.2	14.0	7.5
3	147	84	55.1	33.7	23.2	6.6	2.8
4	98	79	58.0	39.2	24.0	14.7	9.0
5	108	67	52.5	37.5	17.2	10.6	6.3
6	157	129	77.5	47.5	25.5	14.1	6.6
7	230	102	73.2	46.9	23.4	14.1	7.3
Mean ± SE[a]	153 ± 17	94 ± 7.5	60.4 ± 3.9	44.1 ± 2.9	24.9 ± 2.2	14.6 ± 2.5	8.4 ± 1.9

[a] SE, Standard error.

TABLE 3. *Parameters derived by using two-compartment linear model for intravenous 1-g injection*

Parameter	Mean	Standard error
α (h^{-1})	1.99	0.239
β (h^{-1})	0.55	0.060
K_{12} (h^{-1})	0.50	0.134
K_{21} (h^{-1})	1.27	0.078
K_e (h^{-1})	0.954	0.080
Cl (liter/h/kg)	0.094	0.012
V_1 (liter/kg)	0.099	0.011
V_d (liter/kg)	0.164	0.016
$T_{1/2\alpha}$ (h)	0.349	0.042
$T_{1/2\beta}$ (h)	1.26	0.138

TABLE 4. *Elimination half-lives and clearances per kilogram for piperacillin after a 2-g bolus injection*

Patient	$T_{1/2\beta}$ (h)	Cl (liter/h per kg)
1	2.05	0.048
2	1.19	0.070
3	3.11	0.062
Mean	2.12	0.060

Overall, after the distribution phase is complete, there is about a 45% reduction in serum level per hour if hemodialysis is functioning under optimal conditions of pressure and flow rates. Thus, when a 1-g dose of piperacillin is given by intravenous bolus injection at the start of dialysis, a serum level of approximately 50 to 75 μg/ml would be achieved by 30 min, but by 4 h the level would be less than 10 μg/ml. The minimal inhibitory concentration for susceptible streptococci, including enterococci, non-β-lactamase-producing staphylococci, and *Haemophilus* and *Neisseria* species, is less than 3 μg/ml. The majority of susceptible strains of *E. coli*, *P. mirabilis*, *Enterobacter*, and *Bacteroides* are inhibited by 12 μg/ml. Many *Klebsiella* and indole-positive *Proteus* are inhibited by 25 μg/ml, as are the majority of *Pseudomonas* (5).

The precise serum and tissue concentrations needed to eradicate different types of infection are unknown. However, Klastersky et al. (8) showed that patients whose serum drawn at peak periods inhibited growth of infecting bacteria at 1:8 dilution had an 80% chance of cure of the infection. Use of an initial intravenous dose of 1 g of piperacillin in patients with creatinine clearances less than 10 ml/min would provide peak serum levels of approximately 150 μg/ml and serum levels of 25 μg/ml at 2 h. This would be well in excess of eight times the minimum inhibitory concentration for susceptible gram-positive organisms, *Neisseria* and *Haemophilus*, but not for many susceptible *Enterobacteriaceae*, *Pseudomonas*, and *B. fragilis*. Thus, in patients with creatinine clearances less than 10 ml/min, an initial dose of 1 g should be followed by a dose of 1 g every 6 h to treat streptococcal, *Haemophilus*, or *Neisseria* infections. A dose of 2 g given at the end of dialysis would produce a peak of about 200 μg/ml and levels in excess of 50 μg/ml at 120 min. Such a dose would be adequate to treat most susceptible *Enterobacteriaceae*, *Bacteroides*, and *P. aeruginosa*. In addition, sodium administration (1.7 mEq/g) with such a dose would be considerably less than the amount given with a dose of carbenicillin or ticarcillin (5 mEq/g) sufficient to treat these organisms.

The pharmacokinetic properties of piperacillin in renal failure and during dialysis are unlike those of carbenicillin and ticarcillin (6, 10, 12). These drugs accumulate, and marked reduction in dosage is necessary to avoid toxicity (9). Piperacillin is cleared from the body so rapidly by means other than renal excretion that dosage adjustments would yield levels too low to inhibit the additional organisms for which piperacillin would be useful. This fact may be of particular importance if this drug is used to treat infection in the immunocompromised patient with decreased renal function. Further studies are needed to determine whether the metabolism of piperacillin and the nonrenal excretion are similar or different in normals and patients with markedly reduced renal function.

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