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Pharmacokinetics of Piperacillin in Patients with Moderate Renal Failure and in Patients Undergoing Hemodialysis

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The pharmacokinetics of piperacillin administered intravenously were studied in five patients with stable mild to moderate renal impairment and in five patients undergoing hemodialysis. Patients with stable renal failure given 1 g of piperacillin intravenously had peak serum concentrations within 30 min ranging from 78 to 280 μg/ml. The mean serum half-life was 3.57 ± 1.36 h; the mean apparent volume of distribution was 28.6 ± 13.5 liters/100 kg; and the plasma clearance was 4.10 ± 1.46 liters/h per 1.73 m^2. Neither serum half-life nor clearance correlated with serum creatinine, implying significant nonrenal elimination. Patients undergoing hemodialysis had peak serum concentrations within 30 min of 66 to 138 μg/ml after 1 g of piperacillin infused intravenously. During hemodialysis, the serum half-life was 3.6 ± 2.5 h; the mean apparent volume of distribution was 26.7 ± 16.7 liters/100 kg; and the plasma clearance was 3.28 ± 0.76 liters/h per 1.73 m^2. Mean hemodialysis clearance was 0.484 ± 0.282 liters/h per 1.73 m^2, and only 10.0 ± 5.3% of the total dose could be recovered in the dialysate.

Piperacillin, sodium 6-[D(−)-α(4-ethyl-2,3-dioxo-1-piperazinylcarbonyl amino)-α-phenylacetamido] penicillinate, is a new semisynthetic penicillin with antimicrobial activity against both gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*, *Proteus* sp., and *Klebsiella* sp. (4, 8, 10, 11). The inhibitory activity of piperacillin against most *Enterobacteriaceae*, *Pseudomonas* species, and some streptococci is 4 to 16 times that of carbenicillin (4, 8). Piperacillin pharmacokinetics have been studied in normal subjects (1, 2, 9) and in patients undergoing hemodialysis (3). We report pharmacokinetic studies in patients with stable renal impairment and in patients with chronic renal failure undergoing hemodialysis.

MATERIALS AND METHODS

Five patients with mild to moderate renal impairment and five patients undergoing hemodialysis were studied at The Mount Sinai Medical Center. The 10 patients included 4 males and 6 females, ages 21 to 60 years, with serum creatinine concentrations ranging from 2.5 to 18.6 mg/100 ml. All patients gave informed consent according to institutional policy. Penicillin-allergic patients, patients taking other antibiotics, and pregnant patients were excluded.

In the group with moderate renal failure, a 1-g intravenous dose of piperacillin in 250 ml of dextrose and water was given over 30 min. Blood samples were obtained at the beginning of the infusion, at 10, 20, 30, and 45 min, and at 1, 2, 4, 8, 12, 24, 48, and 72 h. Patients performed their usual daily activities during the study.

Patients undergoing hemodialysis received an intravenous infusion of 1 g of piperacillin over 30 min and were immediately placed on a Cobe Centry II hemodialysis machine for 4 h. Blood samples were drawn when starting dialysis, at 10, 20, 30, and 45 min, and at 1, 2, 4, 8, 24, and 48 h. Both arterial and venous samples were drawn at 1 and 4 h.

Blood samples were centrifuged immediately at 15°C, and the serum was stored at −70°C. Serum concentrations of piperacillin were assayed by the paper disk assay method, using *Sarcina lutea* 9341 as the test organism (6).

Every patient had a complete blood count and a serum biochemical profile before and after the administration of the drug. No biochemical or hematological changes occurred during this study. All the patients had normal serum bilirubin and aspartate and alanine aminotransferase values. All patients were asymptomatic throughout the study.

A two-compartment pharmacokinetic model was used as described previously (5, 9). The pharmacokinetic parameters of piperacillin, including the half-life of the beta elimination phase ($t_{1/2\beta}$), elimination constant (K_e), transfer rate constants between central (V_1) and peripheral (V_2) compartments, K_{12} and K_{21}, area under the curve ($AUC_{0-\infty}$), apparent volume of distribution per 100 kg, and plasma clearance per 1.73 m^2 of body surface area, were calculated by using a program written for the Wang 700B series advanced programming calculator (9). Dialysis clearance (7) was calculated by the formula χ/AUC_{0-t}, where χ is the amount of drug in the total dialysate and AUC_{0-t} is the area under the curve from time zero to 4 h, when dialysis was stopped; dialysis clearance was expressed per 1.73 m^2 of body surface area.

RESULTS

Patients with mild to moderate renal dysfunction. The serum piperacillin concentrations

after a single intravenous dose of 1 g are shown in Table 1. The patient's serum creatinine levels ranged from 2.5 to 7.5 mg/100 ml. Peak serum piperacillin concentrations ranged from 78 to 280 μg/ml. Patient 2 had much higher serum concentrations of piperacillin than the other four patients. The reasons for this are not entirely clear. This patient was much thinner than the other patients and appeared to have less muscle mass. The total apparent volume of distribution (V_d) was lower in this patient. At 30 min the concentration of piperacillin exceeded 48 μg/ml in all patients, but by 1 h the concentration ranged from 14 to 164 μg/ml. Pharmacokinetic parameters are given in Table 2. The serum half-life ($t_{1/2\beta}$) varied from 2.44 to 5.88 h, with a mean of 3.57 h, and did not correlate with the creatinine level. The elimination constant (K_e) ranged from 0.649 to 1.49 h^{-1}. The apparent volume of distribution was smaller (mean, 28.6 liters/100 kg) than that found in normal volunteers (mean, 47.62 liters/100 kg) (9). However, the steady-state volume of distribution [$V_{d(ss)}$] (mean, 126 liters/100 kg, mostly the contribution of one patient's result) was higher than that found in normal subjects (30.72 liters/100 kg) (9). As expected, the AUC showed a higher value (mean, 290.38 μg/ml per h) compared with that of normal subjects (mean, 92.77 μg/ml per h) (9). Plasma clearance was markedly reduced (mean, 4.10 liters/h per 1.73 m^2) as compared with that in normal patients (mean, 20.48 liters/h per 1.73 m^2) (9) and did not correlate with serum creatinine.

Patients undergoing hemodialysis. The serum piperacillin concentrations and respective dialysate concentrations after a single intravenous dose of 1 g in patients undergoing hemodialysis are shown in Table 3. Dialysis was started at the end of the infusion (time zero).

TABLE 1. *Serum concentrations of piperacillin in patients with stable moderate renal failure*

Time	Serum concn (μg/ml) in given patient no.				
	1	2	3	4	5
0 (end of infusion)	42	280	78	54	164
10 min	100	210	70	120	104
20 min	58	144	64	78	56
30 min	50	100	54	48	48
45 min	38	108	26	38	18
1 h	36	164	30	34	14
2 h	32	80	17.6	30	12
4 h	7.25	30	5	5.25	19
8 h	3.4	5.5	3.3	3.0	4.3
12 h	1.7	4	1.72	2.2	2.4
24 h	0	1.5	0	0	0
48 h	0	0	0	0	0
72 h	0	0	0	0	0

TABLE 2. *Pharmacokinetic parameters of piperacillin in patients with stable moderate renal failure*

Patient no.	Wt (kg)	Body surface area (m^2)	Serum creatinine (mg/100 ml)	$t_{1/2\beta}$ (h)	AUC (μg/h per ml)	V_d (liters/100 kg)	$V_{d(ss)}$ (liters/100 kg)	K_r (h^{-1})	K_{21} (h^{-1})	K_{12} (h^{-1})	Plasma clearance (liter/h per 1.73 m^2)
1	66.8	1.81	7.5	2.44	227.04	23.2	48.2	0.704	0.624	2.56	4.21
2	51.8	1.55	5.6	3.76	576.19	18.2	69.3	0.792	0.480	7.41	1.93
3	77.3	1.82	2.5	2.77	188.28	27.4	58.4	0.649	0.531	2.40	5.05
4	78.6	1.90	7.3	3.03	253.56	22.0	61.7	0.775	0.476	4.07	3.59
5	54.5	1.46	4.5	5.88	206.83	52.1	391.0	1.49	0.332	21.63	5.72
Mean				3.57	290.38	28.6	126.0	0.787	0.487	7.61	4.10
Standard deviation				±1.38	±161.60	±13.5	±148.0	±0.331	±0.105	±8.08	±1.46

TABLE 3. *Serum concentrations of piperacillin in patients undergoing hemodialysis*

Patient no.	Time												Dialysate concn of piperacillin (μg/ml)				
	0 (end of infusion)	10 min	20 min	30 min	45 min	1 h		2 h	4 h		8 h	24 h	48 h	Vol (liters, at 4 h)	1 h		4 h	
						Arterial	Venous		Arterial	Venous					Pure sample	Cumulative	Pure sample	Cumulative
6		100	82		76	37	58	49	20	20	3.3	0	0	123.4	1.4	0.78	0	0.5
7		138	86	64	70	11.6	58	37.6	19.8	21.3	7.4	0	0	180.7	1.1	1.0	0	0.6
8		12.4	36	76	66	36	64	7.4	4.3	5.8	3.9	0	0	175.5	4.6	1.3	<0.5	1.1
9	102.0	124.0	82	66	76	70	70	53	23.4	28	9.6	0	0	169.6	2.9	1.0	0	1.7
10		62	66	62	28	19	24	21.3	14.8	14	9.9	0	0	130.4	2.3	0.5	0	0.5

TABLE 4. *Pharmacokinetic parameters of piperacillin in patients undergoiong hemodialysis*

Patient no.	Wt (kg)	Body surface area (m^2)	Serum creatinine (mg/100 ml)	$t_{1/2\beta}$ (h)	AUC (μg/h per ml)	V_d (liters/100 kg)	$V_{d(ss)}$ (liters/100 kg)	K_e (hr^{-1})	K_{21} (h^{-1})	K_{12} (h^{-1})	Plasma clearance (liters/h per 1.73 m^2)
6	47.7	1.47	12.5	1.64	282.34	17.5	18.4	0.431	0.549	0.034	4.16
7	75.4	1.86	16.9	2.41	367.4	12.6	18.5	0.502	0.589	0.937	2.53
8	78.6	1.93	18.6	6.53	231.96	51.7	447.0	1.04	0.164	13.79	3.86
9	46.8	1.46	11.6	2.43	479.64	15.6	118.0	0.697	0.374	6.79	2.46
10	70.9	1.68	8.3	5.41	303.84	36.2	1084.0	0.608	0.134	18.91	3.39
Mean				3.68	333.0	26.7	337.0	0.655	0.362	8.09	3.28
Standard deviation				±2.15	±95.2	±16.7	±453.0	±0.237	±0.21	±8.17	±0.76

Peak concentrations ranged from 66 to 138 μg/ml and were reached in the first 30 min after infusion. At 1 h, serum concentrations varied from 24 to 70 μg/ml. Pharmacokinetic parameters are listed in Table 4. The half-life ($t_{1/2\beta}$) value ranged between 1.64 and 6.53 h, with a mean of 3.68 h. No correlation between serum creatinine level and half-life was found. The calculated elimination constants (K_e) ranged from 0.431 to 1.01 h^{-1}. During a 4-h hemodialysis, approximately 10% of the piperacillin infused was recovered in the dialysate and approximately 80% was removed from the central compartment (Table 5).

DISCUSSION

The pharmacokinetics of intravenously administered piperacillin, using a two-compartment model, have been described in normal patients (1, 2, 9) and in patients undergoing hemodialysis (3), but not in patients with mild to moderate renal failure not requiring dialysis. The half-life of intravenous piperacillin in patients with normal renal function varies from 0.86 to 1.5 h (1, 2, 9). In patients with mild to moderate renal failure (serum creatinine, 2.5 to 7.5 mg/100 ml), we calculated half-lives varying from 2.44 to 5.88 h. These values are higher than those reported for individuals with normal renal function, and thus the dosage of piperacillin should be reduced in patients with mild to moderate renal failure. We did not find a correlation between half-life and serum creatinine, implying that nonrenal mechanisms of metabolism or excretion play a significant role in the pharmacokinetics of this antibiotic. Apparent volumes of distribution appeared smaller than those found in normals, although at the steady state the volume of distribution was increased. Similar findings had been noted in a prior study of tobramycin in patients with renal failure (7).

In view of the increased half-life of piperacillin in patients with mild to moderate renal failure and the serum levels of piperacillin found in this study, we suggest using a dose of 1 g every 4 to 6 h in this group of patients. With this regimen one can achieve, at 1 h, serum levels of piperacillin sufficient to inhibit 78% of *Bacteroides fragilis*, 95% of *Pseudomonas aeruginosa*, 60% of *Enterobacteriaceae*, 87% of *Staphylococcus aureus* strains, and most strains of *Haemophilus influenzae* and *H. parainfluenzae*, *Streptococcus pneumoniae*, *Neisseria gonorrheae*, and β-hemolytic streptococci (4). By 4 h the levels achieved would still inhibit 35% of *Enterobacteriaceae*. Notably, only about 35% of *Serratia* sp. and 36% of *Acinetobacter* sp. would be inhibited by piperacillin at 1 h (4). For patients with stable moderate renal failure and infections with highly resistant bacteria such as *Serratia* sp., higher dosages may be needed but should be used with careful monitoring of serum levels of piperacillin. The combination of piperacillin and an aminoglycoside, which has demonstrated synergy against *P. aeruginosa* and *Enterobacteriaceae* (4), may be necessary in such patients.

In patients undergoing hemodialysis one must adjust dosages appropriately to account both for a reduced renal clearance between hemodialysis treatments as well as for removal of antibiotic during the hemodialysis procedure. With the 1-g dose used, the serum levels achieved in this group were virtually the same as described above for patients with stable moderate renal failure. In our patients, 4 h of hemodialysis removed approximately 10% of the piperacillin dose. Approximately 80% of the dose administered was removed from the central compartment by a nonrenal mechanism. We found a mean half-life during hemodialysis of 3.68 h. Our findings do not agree with those of Francke et al. (3), who reported a mean hemodialysis half-life of 1.26 h, approximately 40% nonrenal elimination, and 48% removal by dialysis, but the methods used differed. Their recommendation was to use a dose of 1 or 2 g every 6 h in hemodialysis patients (3). We suggest that even higher doses may be tolerated. Finally, the nonrenal mechanism of piperacillin removal deserves further study. From results in a recent study (J. A. Giron, B.

TABLE 5. *Hemodialysis clearance of piperacillin*

Patient no.	Amt of drug in dialysate (mg)	% of dose dialyzed	AUC 0–4 h (μg/h per ml)	Dialysis clearance (liters/h per 1.73 m^2)	Total plasma clearance (liters/h per 1.73 m^2)
6	61.7	6.17	234.1	0.309	4.16
7	108.4	10.8	282.8	0.362	2.53
8	193.0	19.3	174.6	0.986	3.86
9	118.7	11.8	368.8	0.380	2.46
10	65.2	6.5	176.6	0.381	3.39
Mean		10.91		0.484	3.28
Standard deviation		±5.3		±0.282	±0.76

R. Meyers, and S. Z. Hirschman, submitted for publication), it appears that biliary excretion may play a major role in piperacillin pharmacokinetics.

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