Piperacillin: Human Pharmacokinetics After Intravenous and Intramuscular Administration

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The pharmacokinetics of piperacillin were studied in a total of 26 Caucasian normal male volunteers. Single intramuscular doses of 0.5, 1.0, and 2.0 g were given to three groups, each containing eight volunteers. Mean peak serum concentrations of 4.9, 13.3, and 30.2 $\mu\text{g/ml}$ were assayed at 30 to 50 min, and measurable levels were present up to 4, 6, and 8 h, respectively, after dosing. Single intravenous bolus doses of 1.0, 2.0, 4.0, and 6.0 g were given to four groups of five subjects, and mean serum concentrations of 70.7, 199.5, 330.7, and 451.8 $\mu\text{g/ml}$ were measured at the end of the injections. The antibiotic had a mean terminal serum half-life of 60 to 80 min after the intramuscular doses and 36 to 63 min after intravenous administrations, depending on the dose. The apparent distribution volume was 20 to 24 liters/1.73 m^2 , and distribution volume at steady state was 16 to 19 liters/1.73 m^2 . Mean urinary recovery in 24 h was 74 to 89% for the intravenous doses and 57 to 59% for the intramuscular doses. The piperacillin-creatinine clearance ratios indicated that the proportion of renal excretion of piperacillin through tubular secretion was 56 to 73%, and this was confirmed by the renal clearance data from eight volunteers receiving probenecid treatment before the piperacillin dose. Probenecid (1 g given orally before administration of piperacillin) increased peak serum concentration by 30%, terminal serum half-life by 30%, and the area under the plasma concentration curve by 60%, and it decreased the apparent distribution volume by 20% and the renal clearance of the intramuscularly administered (1 g) antibiotic by 40%. Injections of piperacillin by both parenteral routes were well tolerated.

Piperacillin (T-1220) is the generic name for sodium 6-[D(-)- α (4-ethyl-2,3-dioxo-1-piperazinylcarbonyl-amino)- α -phenylacetamido] penicillinate, a new semisynthetic aminobenzyl penicillin derivative with an unusually wide spectrum of activity (2, 7, 9). In vitro testing showed piperacillin to be active against all members of the *Enterobacteriaceae*, including *Klebsiella* (of which 58% were inhibited by 8 $\mu\text{g/ml}$), and also against *Pseudomonas aeruginosa*. The activity of piperacillin was at least equivalent, but generally superior to, that of ampicillin and carbenicillin, especially against *Enterobacter* species, *Klebsiella* species, *Serratia marcescens*, all *Proteus* species, including the indole-positive species, and *Providencia* species. Most striking was its activity on *P. aeruginosa*, of which 50% were inhibited by 2 $\mu\text{g/ml}$ and 83% were inhibited by 4 $\mu\text{g/ml}$ (9).

Klebsiella pneumoniae, *Escherichia coli*, *P. aeruginosa*, *Enterobacter* species, and, increasingly, *S. marcescens* are the major organisms causing life-threatening infections in debilitated patients. The activity of ampicillin is virtually

limited to *E. coli*; that of carbenicillin is extended to *Enterobacter* species, *S. marcescens*, and *P. aeruginosa*, but the majority of the latter species are only inhibited by carbenicillin at concentrations of 32 $\mu\text{g/ml}$ or above. The substantially higher activity and wider spectrum of piperacillin made it important to conduct human pharmacokinetic studies, which are presented in this paper.

Preliminary pharmacokinetic studies in laboratory animals (mice, rats, rabbits, dogs) and in humans, employing both labeled and unlabeled piperacillin, have indicated that the drug is poorly absorbed orally but is well absorbed after parenteral administration. It is bound to serum proteins by approximately 22%, and only minimal amounts of the drug appear to be metabolized in the body because most of the administered dose is excreted unchanged, primarily (66%) through the kidneys. The animal studies also disclose the presence of a wide range of variation among species but a significant biliary excretion of the drug (1). Previous pharmacokinetic and clinical evaluations of this antibiotic

were performed in Japan with both normal volunteers and patients receiving this drug.

The present study was designed to evaluate both tolerance to piperacillin and the pharmacokinetics of the antibiotic after single intravenous (i.v.) and intramuscular (i.m.) doses of this drug given to a group of Caucasian healthy volunteers. Data on the effect of probenecid on the pharmacokinetics of piperacillin after i.m. injection are also included in this report.

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MATERIALS AND METHODS

Subjects. The pharmacokinetic studies were carried out in 26 Caucasian subjects after informed consent. All were healthy male volunteers, ranging in age from 18 to 29 years (mean $\pm$ standard error of the mean, 22 ± 0.42 years) and in weight from 60 to 85 kg (mean $\pm$ standard error of the mean, 70.4 ± 1.41 kg). Physical examinations, hematological and biochemical indexes (peripheral blood count, renal and liver function tests, complete urinary examination), chest X rays, and electrocardiograms were normal. None was altered after administration of the antibiotic. None of the subjects was taking any drug therapy for at least 2 weeks before the start of the study and during the whole course of piperacillin studies. Subjects with a history of drug allergy were excluded.

Drugs and routes of administration. Piperacillin as the sodium salt was made available in vials of 1,000 mg by American Cyanamid Co., Lederle Laboratories Div., Pearl River, N. Y. Solutions were prepared immediately before injection by dissolving the antibiotic in pyrogen-free sterile water for injections. Final volumes for the various dose of i.m. (0.5 and 1 g) and i.v. (1 to 4 g) injections were 4 ml and up to 20 ml (diluted with 5% dextrose) for the 6-g i.v. dose. Groups of eight volunteers received piperacillin as single i.m. administrations deep into the buttock in doses of 0.5, 1, and 2 g. The i.v. administrations were given as slow bolus injections over 3 min, with single doses of 1, 2, 4, and 6 g in groups of five subjects each. Subjects participating in more than one trial had an interval of at least 1 week between two subsequent studies.

The influence of probenecid was studied in a cross-over design involving eight subjects. Probenecid was given orally in a single dose of 1 g (two 0.5-g Benemid tablets; Merck Sharp & Dohme) at approximately 1 h before the i.m. administration of 1 g of piperacillin. Before each study, all subjects were fasted overnight and hydrated (water intake, 750 ml) 30 min before piperacillin administration.

Blood and urine collections for antibiotic assay. Venous blood samples (10 ml) were withdrawn from an arm vein through an indwelling butterfly needle into collection tubes for clotted blood before, just at the end of, and at specified intervals after piperacillin injection; these samples were taken at 5, 10, 20, 30, 60, and 90 min and 2, 3, 4, and 6 h after the

i.v. dose and 15, 30, and 60 min and 2, 3, 4, 6, and 8 h after the i.m. dose.

In subjects receiving probenecid treatment, an additional blood sample was obtained at 24 h for probenecid assay. Blood specimens were allowed to stand in cold environment (crushed ice) for about 1 h. After centrifugation serum was removed and frozen (-20°C) before assay (within 1 to 2 weeks).

Urine was collected before the start of the experiment and during the periods 0 to 2 h, 2 to 4 h, 4 to 6 h, 6 to 12 h, and 12 to 24 h after the piperacillin dose. All urine volumes were measured, and samples were stored at -20°C before analysis. The excretion of creatinine in the urine collected over 24 h was measured, and its clearance was calculated. Creatinine was measured by using the autoanalyzer modification of the method of Jaffe.

Antibiotic assay. Concentrations of piperacillin in serum and urine were determined by an agar well method with the test organism *Bacillus subtilis* ATCC 6633 in spore suspension (Difco Laboratories, Detroit, Mich.) incorporated in seed agar medium (Baltimore Biological Laboratory, Cockeysville, Md.) adjusted to pH 6.0. Further details of this method have been described in a previous paper (8). For standards, piperacillin of certified potency from Lederle Research Laboratories was used. All samples were assayed in duplicate and calculated according to the regression lines of the standards in serum or in phosphate buffer (pH 6.0) in final concentrations of 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78, and $0.39 \mu\text{g/ml}$. Samples were diluted when necessary with pooled human serum (for serum samples) or with phosphate buffer at pH 6.0 (for urine samples) until concentrations were in the range of the standard curves.

The correlation coefficients of the regression lines varied from $r = 0.9967$ to $r = 0.9999$ in serum and from $r = 0.9978$ or $r = 0.9999$ in buffer. The sensitivity of the assay was limited to $0.4 \mu\text{g/ml}$. All serum and urine blanks were negative.

Pharmacokinetic analysis. Piperacillin serum level data after i.v. administrations were analyzed by the two-compartment open pharmacokinetic model designed for rapid injection of a drug into the vascular compartment (11).

The decline in piperacillin serum concentration after i.v. administration was fitted by a computer program for each subject by using the least-squares regression analysis and the method of residuals to the sum of the two exponentials: $C_p' = Ae^{-\alpha t} + Be^{-\beta t}$, where C_p' represents the serum concentration at time t after the dose, α and β are the first-order rate constants of the fast and slow disposition processes, respectively, and A and B are the zero-time intercepts of the two components of the biexponential curves. These constants were estimated from the postinjection plasma concentration data in the usual fashion (as for rapid i.v. administration) because drug administration of over 3 min in the present study was not sufficiently long to attain steady state. Specific first-order rate constants for distribution into (k_{12}) and out of (k_{21}) the peripheral compartment and for elimination from the body (k_{el}), as well as volume parameters describing the disposition of i.v.-administered piperacillin according to the two-compartment open model, were calcu-

lated from the usual equations (3, 6, 10). The area under the serum concentration-time curve (AUC) was derived from the expression $AUC_{i.v.} = (A/\alpha) + (B/\beta)$ or determined by the trapezoidal rule (after either i.v. or i.m. dosing) and extrapolated to infinity. After i.m. administrations, the terminal serum half-life ($t_{1/2\beta}$) of the antibiotic was estimated by using the equation $t_{1/2\beta} = \ln 2/\beta$. Each regression line was based on at least four points of serum concentrations from the 1- to 8-h data. The apparent volume of distribution (Vd area) was calculated from the equation $Vd \text{ area} = (F \cdot D_0)/(AUC_{0-\infty} \cdot \beta)$, where F is the fraction of the dose entering the systemic circulation as unchanged drug ($F = 1$ after i.v. dose). Because the fractional absorption F derived from $AUC_{i.m.}/AUC_{i.v.}$ calculation was 0.767, our calculations were based on the assumption that the i.m.-administered doses of piperacillin were 77% available. Total clearance (Cl_{Tot}) values were estimated from $Cl_{Tot} = (F \cdot D_0)/AUC_{0-\infty}$.

Renal clearance (Cl_R) was calculated from: $Cl_R = X_{u0-t}/AUC_{0-t}$. The binding of piperacillin to human plasma proteins was reported to be 22% (1). Assuming that the bound portion is not filtered during its passage through the glomerulus, the following equations can be used to apportion the renal excretion of the antibiotics in both: (i) percentage filtered by glomerulus (PFG) = (endogenous creatinine clearance/renal clearance of drug) $\times$ (percentage of drug not bound to plasma proteins); and (ii) percentage secreted by tubules = $100 - PFG$. Nonrenal clearance (Cl_{NR}) can be derived from the equation $Cl_{NR} = Cl_{Tot} - Cl_R$. Where appropriate, results have been standardized to 1.73 m² body surface area. The results are presented as mean $\pm$ standard error of the mean in the text and the tables. Statistical analyses were performed by using Student's t test, and a P value of 0.05 or less was considered to be statistically significant.

RESULTS

Tolerance to piperacillin and safety in volunteers. The three parts of the present study in which parenteral piperacillin doses (i.v. and i.m.) as well as i.m. doses of the antibiotic with and without probenecid were used were satisfactorily completed with all the 26 healthy volunteers. Both the i.v. and i.m. injections of piperacillin were well tolerated without any adverse local or systemic effects, and no abnormalities in any of the hematological or biochemical indexes or in urinalysis were observed.

Administration by i.v. injection. The average serum levels of piperacillin obtained from the normal subjects receiving single i.v. injections of the antibiotic (1, 2, 4, and 6 g) are shown in Fig. 1. As can be seen, the serum levels decline in a biexponential manner. An initial rapid fall over the first 1 h was followed by a monoexponential decline over the remaining period of observation. The mean pharmacokinetic parameters estimated from serum and urine data after the i.v. doses are shown in Table 1. The average concentrations immediately at the end of the 3-min slow bolus injection for the four doses were 71, 199, 331, and 452 $\mu\text{g/ml}$. Mean concentrations at 3 h were 0.9, 4.7, 17.7, and 32.8 $\mu\text{g/ml}$, respectively, after the four increasing doses and 1.4 $\mu\text{g/ml}$ at 8 h after the 6.0-g dose.

The mean $t_{1/2\beta}$ for these doses were 36, 54, 61, and 63 min, respectively, showing clearly prolonged $t_{1/2\beta}$ values with increasing doses from 1 to 4 g, whereas the additional increase of the

FIG. 1. Mean serum concentrations of piperacillin after single i.v. injections of increasing doses of from 1 to 6 g in four groups of five normal volunteers. S.E.M., Standard error of the mean.

TABLE 1. *Pharmacokinetic data of piperacillin in healthy volunteers after i.v. administration*

Dose (g)	Serum concn at end of injection ($\mu\text{g/ml}$)	A ($\mu\text{g/ml}$)	α (h^{-1})	$t_{1/2\alpha}$		B ($\mu\text{g/ml}$)	β (h^{-1})
				h	min		
1.0 (n = 5)	70.7 $\pm$ 12.7 ^a	32.7 $\pm$ 3.5	-5.51 $\pm$ 1.74	0.17 $\pm$ 0.03	10.0 $\pm$ 1.9	34.5 $\pm$ 4.6	-1.19 $\pm$ 0.10
2.0 (n = 5)	199.5 $\pm$ 37.4	131.6 $\pm$ 19.4	-3.93 $\pm$ 0.37	0.18 $\pm$ 0.02	10.9 $\pm$ 1.1	52.6 $\pm$ 4.4	-0.79 $\pm$ 0.07
4.0 (n = 5)	330.7 $\pm$ 67.8	252.7 $\pm$ 76.4	-4.40 $\pm$ 0.81	0.18 $\pm$ 0.03	10.7 $\pm$ 1.7	134.7 $\pm$ 5.9	-0.69 $\pm$ 0.04
6.0 (n = 5)	451.8 $\pm$ 21.8	314.1 $\pm$ 100.9	-2.75 $\pm$ 0.80	0.32 $\pm$ 0.06	19.0 $\pm$ 3.4	218.1 $\pm$ 18.5	-0.67 $\pm$ 0.04

Dose (g)	$t_{1/2\beta}$		AUC _{0-∞} ($\mu\text{g/ml} \cdot \text{h}$)	Distribution volumes (liters/1.73 m ²)		
	h	min		V ₁ (central compartment)	V ₂ (peripheral compartment)	Vd _∞ (steady state)
1.0 (n = 5)	0.60 $\pm$ 0.05	35.8 $\pm$ 3.1	36.0 $\pm$ 1.0	14.5 $\pm$ 1.3	4.6 $\pm$ 0.5	19.0 $\pm$ 1.4
2.0 (n = 5)	0.90 $\pm$ 0.08	54.0 $\pm$ 4.7	102.0 $\pm$ 11.5	10.9 $\pm$ 1.3	7.4 $\pm$ 0.6	18.3 $\pm$ 1.9
4.0 (n = 5)	1.02 $\pm$ 0.05	61.2 $\pm$ 3.1	250.3 $\pm$ 12.5	11.2 $\pm$ 1.9	7.4 $\pm$ 1.1	18.6 $\pm$ 1.1
6.0 (n = 5)	1.05 $\pm$ 0.07	63.0 $\pm$ 4.4	437.9 $\pm$ 21.6	11.9 $\pm$ 1.6	4.2 $\pm$ 1.0	16.1 $\pm$ 1.3

Dose (g)	Vd _β (liters/1.73m ²)	Intercompartmental rate constants (h ⁻¹)			Cl _{Tot} (ml/min per 1.73 m ²)	Cl _R (ml/min per 1.73 m ²)
		k ₁₂	k ₂₁	k _{el}		
1.0 (n = 5)	21.6 $\pm$ 1.7	1.30 $\pm$ 0.58	3.55 $\pm$ 1.12	1.86 $\pm$ 0.16	408.6 $\pm$ 16.8	303.6 $\pm$ 29.5
2.0 (n = 5)	24.3 $\pm$ 3.1	1.18 $\pm$ 0.12	1.71 $\pm$ 0.16	1.84 $\pm$ 0.18	301.8 $\pm$ 32.3	245.7 $\pm$ 30.3
4.0 (n = 5)	24.3 $\pm$ 1.3	1.61 $\pm$ 0.54	1.96 $\pm$ 0.10	1.51 $\pm$ 0.24	254.2 $\pm$ 19.3	203.7 $\pm$ 19.5
6.0 (n = 5)	20.2 $\pm$ 1.5	0.76 $\pm$ 0.43	1.44 $\pm$ 0.16	1.22 $\pm$ 0.23	209.6 $\pm$ 8.3	186.9 $\pm$ 17.5

Dose (g)	Cl _{NR} (ml/min per 1.73 m ²)	Endogenous creatinine clearance (ml/min per 1.73 m ²)	Ratio of piperacillin to creatinine clearance	Proportion of renal excretion via tubules (%)	% of dose recovered in urine (unchanged form) at:	
					0-2 h	0-24 h
1.0 (n = 5)	105.1 $\pm$ 26.3	101.8 $\pm$ 4.6	3.0 $\pm$ 0.3	72.9 $\pm$ 2.9	49.0 $\pm$ 12.1	74.1 $\pm$ 6.3
2.0 (n = 5)	54.7 $\pm$ 13.7	86.5 $\pm$ 10.2	3.1 $\pm$ 0.7	69.7 $\pm$ 6.5	65.3 $\pm$ 4.3	81.4 $\pm$ 4.5
4.0 (n = 5)	53.8 $\pm$ 2.6	86.5 $\pm$ 5.0	2.4 $\pm$ 0.4	65.4 $\pm$ 4.1	61.6 $\pm$ 3.6	79.8 $\pm$ 2.3
6.0 (n = 5)	24.3 $\pm$ 15.2	103.1 $\pm$ 10.0	1.8 $\pm$ 0.2	56.4 $\pm$ 3.7	64.2 $\pm$ 3.2	89.1 $\pm$ 7.5

^a Values given are mean $\pm$ standard error of the mean.

dose to 6.0 g did not result in further prolongation of the half-life.

The mean areas under the concentration-time curves (AUC_{0-∞}) were 38.3, 110.4, 254.8, and 452.2 $\mu\text{g/ml} \cdot \text{h}$, respectively, showing that the area is reasonably proportional to the adminis-

tered dose, in particular with the higher doses of 2, 4, and 6 g. This relationship, however, did not hold for the 1-g dose, which resulted in a disproportionately smaller AUC value of less than one-third of that achieved after a 2-g dose (Fig. 1).

The Vd area of piperacillin was not signifi-

cantly altered with increasing dose; the mean volumes were 21.6, 24.3, 24.3, and 20.2 liters/1.73 m². The corresponding AUCs at steady state were 19.0, 18.3, 18.6, and 16.1 liters/1.73 m², respectively.

Piperacillin was rapidly excreted in high concentrations through the kidney. Approximately 50 to 65% of the dose was recovered in the urine within 2 h after the i.v. injection, and the cumulative urinary excretion in 24 h amounted to from 75 to 90% of the dose. The Cl_R of piperacillin was more rapid with the lower dose and decreased with increasing dosage; the mean clearance rates adjusted to a body surface area of 1.73 m² were 303.6, 245.7, 203.7, and 186.9 ml/min after doses of 1, 2, 4, and 6 g, respectively. In all subjects, the Cl_R rate of piperacillin was found to be more rapid than the simultaneously measured endogenous creatinine clearance, thus indicating the presence of an active tubular secretion of the drug in addition to glomerular filtration. Mean ratios of piperacillin to creatinine clearance were 3.0 and 3.1 for the 1- and 2-g doses, respectively, but they were lowered to 2.4 and 1.8 with the increased doses of 4 and 6 g, respectively. Taking into account a 22% protein binding of piperacillin, these data indicate that between 73 and 56% of the drug excreted by the kidneys is cleared by tubular secretion (Table 1).

Administration by i.m. injection. For the three i.m. doses the mean serum concentration curves are shown in Fig. 2, and the mean phar-

macokinetic data of piperacillin are given in Table 2. Average peak serum concentrations after 0.5-, 1.0-, and 2.0-g injections were 4.9, 13.3, and 30.2 µg/ml, respectively. The mean times to peak concentrations occurred at approximately 30 to 50 min after the i.m. doses. The mean $t_{1/2\beta}$ for the three increasing doses were 60.2, 68.7, and 80.6 min (differences not statistically significant).

Disproportionately lower values of the AUC with decreasing doses were also observed after i.m. doses, the mean areas being 85.2 µg/ml·h after the 2-g dose, 29.2 µg/ml·h after the 1-g dose, and only 10.3 µg/ml·h after the lowest dose tested, 0.5 g (Fig. 2). Comparison of the AUC values of piperacillin achieved through the i.v. and i.m. routes disclosed an available fraction of approximately 70 to 80% for the i.m. administered dose. The Vd area of piperacillin appears to be decreased with increasing i.m. dose, the mean Vd areas being 51.5, 41.1, and 33.1 liters/1.73 m². Approximately 60% of the i.m. doses were recovered in urine after 24 h.

Effects of probenecid. Probenecid (1.0 g), given orally approximately 1 h before i.m. piperacillin administration (1.0 g), had a clear effect on several pharmacokinetic parameters (Table 3). Concomitant probenecid administration resulted in a significantly increased mean peak serum concentration (30%), an increased total AUC (65%), as well as a prolonged terminal serum half-life (30%). It decreased the Vd area of the drug by 20% and its Cl_R by 40%. Lowering

FIG. 2. Mean serum concentrations of piperacillin after i.m. injection of 0.5, 1.0, and 2.0 g in three groups of eight normal volunteers. S.E.M., Standard error of the mean.

FIG. 3. Piperacillin serum concentrations after i.m. injection of 1 g of piperacillin from a cross-over study with and without probenecid pretreatment (1 g orally at 1 h before piperacillin dose) in eight normal volunteers. S.E.M., Standard error of the mean.

of the urinary excretion by probenecid was especially noticeable during the first 4 to 5 h after probenecid administration. However, there was only a delay, not a significant decrease in the total 24-h urinary excretion of the antibiotic (62.7% of the dose without probenecid and 60.5% with concomitant probenecid). The ratio of piperacillin to creatinine clearance was significantly lowered (from 2.4 to 1.3) by oral probenecid treatment.

DISCUSSION

The pharmacokinetics of parenterally administered piperacillin were analyzed in the present study by using a two-compartment kinetic model (i.v. doses) and a one-compartment model (i.m. doses).

The 2-g i.v. dose in our study functioned as a reference when considering our pharmacokinetic data after bolus i.v. doses of 1, 2, 4, and 6 g of piperacillin given to Caucasian healthy volunteers. After a slow (3-min) i.v. bolus injection of 2 g, piperacillin appears to be rapidly distributed (average half-life for distribution [$t_{1/2\alpha}$] = 10.8 min) within the extracellular fluids (V_1 = 10.9 liters/1.73 m²) and to some extent within the peripheral tissue compartment (V_2 = 7.4 liters/1.73 m²). The V_d area of the drug was 24.3 liters, and its distribution volume at steady state (V_{dss}) was 18.3 liter/1.73 m². The mean serum half-life during the β -elimination phase was 54 min, and the $AUC_{0-\infty}$ was 102.0 $\mu\text{g/ml} \cdot \text{h}$. Cl_{Tot} of the antibiotic averaged 301.8 ml/min per 1.73

m², whereas the Cl_R rate was approximately 20% lower (245.7 ml/min per 1.73 m²), indicating that piperacillin undergoes biotransformation or extrarenal elimination to some extent in addition to renal excretion. Approximately 80% of the administered dose was recovered in urine after 24 h.

The Cl_R rate values consistently exceed their corresponding glomerular filtration rate, as estimated by the endogenous creatinine clearance; average ratios of piperacillin to creatinine clearance were 3.1 after the 2-g i.v. dose, thus suggesting that active renal tubular secretion of the antibiotic does take place.

The binding of piperacillin to human plasma proteins is reported to be 22% (1). Assuming that the bound fraction is not filtered during its passage through the glomerulus, about 70% of the renal excretion of piperacillin after the 2-g i.v. dose would seem to be by tubular secretion (Table 1), the remainder being by glomerular filtration. This finding is supported by our studies with probenecid in which peak serum concentrations and $t_{1/2\beta}$ (after i.m. injections of 1 g of piperacillin) increased by 30%, $AUC_{0-\infty}$ increased by 65%, and Cl_R decreased by 40% (Table 3).

The kinetic data obtained after the lower i.v. dose of 1 g suggest that piperacillin is cleared from plasma by both the kidneys and nonrenal mechanisms in a greater proportion than it is in the case of the higher doses; Cl_R was 304 ml/min per 1.73 m² after the 1-g dose and 246, 204, and

TABLE 2. *Derived pharmacokinetic indexes of piperacillin after i.m. administration*

Dose (g)	Peak serum concn ($\mu\text{g/ml}$)	Peak time (min)	$t_{1/2\beta}$ (min)	$\text{AUC}_{0-\infty}$ ($\mu\text{g/ml}\cdot\text{h}$)	Urinary recovery (%) at:			Cl_{TD} (ml/min per 1.73 m^2)	Cl_R (ml/min per 1.73 m^2)	Cl_{NR} (ml/min per 1.73 m^2)	Endogenous creatinine clearance (ml/min per 1.73 m^2)	Ratio of piperacillin to creatinine clearance
					0-2 h	0-24 h						
0.5, $n = 8$	4.9 ± 0.4^a	33.8 ± 3.7	60.2 ± 2.9	10.3 ± 0.5	51.5 ± 4.2	37.0 ± 1.8	57.0 ± 2.9	584.0 ± 22.6	431.6 ± 22.0	152.4 ± 23.2	104.1 ± 8.5	4.3 ± 0.3
1.0, $n = 8$	13.3 ± 0.8	37.5 ± 4.9	68.7 ± 4.3	29.2 ± 1.4	41.1 ± 2.6	34.0 ± 2.7	57.1 ± 4.7	422.3 ± 18.3	314.3 ± 27.4	108.0 ± 25.2	121.6 ± 2.7	2.6 ± 0.2
2.0, $n = 8$	30.2 ± 1.9	48.8 ± 5.5	80.6 ± 4.0	85.2 ± 4.5	33.1 ± 2.4	29.5 ± 2.2	58.7 ± 3.9	290.8 ± 14.6	219.8 ± 20.8	71.0 ± 16.7	106.0 ± 3.4	2.2 ± 0.2

^a Values given are mean $\pm$ standard error of the mean.TABLE 3. *Effect of oral probenecid pretreatment on pharmacokinetic parameters after a 1.0-g i.m. dose of piperacillin^a*

Treatment	Peak serum concn ($\mu\text{g/ml}$)	$t_{1/2\beta}$ (min)	$\text{AUC}_{0-\infty}$ ($\mu\text{g/ml}\cdot\text{h}$)	Vd area (liters/ 1.73 m^2)	Urinary recovery (%) at:			Cl_{TD} (ml/min per 1.73 m^2)	Cl_R (ml/min per 1.73 m^2)	Endogenous creatinine clearance (ml/min per 1.73 m^2)	Ratio of piperacillin to creatinine clearance
					0-2 h	0-24 h					
Without probenecid	15.3 ± 5.7^b	65.3 ± 6.3	37.8 ± 1.3	38.6 ± 3.8	40.4 ± 1.4	62.7 ± 2.0		412.8 ± 16.5	264.2 ± 14.8	112.0 ± 7.0	2.0 ± 0.2
With probenecid	20.0 ± 2.1	84.6 ± 4.6	62.3 ± 3.6	30.9 ± 2.3	35.3 ± 1.4	60.5 ± 2.2		252.6 ± 14.2	157.2 ± 12.0	122.0 ± 8.0	1.3 ± 0.1
% change	$+30.6$	$+29.6$	$+65.05$	-20.0	-12.5	-3.4		-38.8	-40.5	$+9.0$	-45.9
P	NS ^c	<0.01	<0.01	<0.05	<0.01	NS		<0.001	<0.001	NS	<0.01

^a Data were obtained from a cross-over study in eight volunteers, with and without oral probenecid pretreatment (1 g) at 1 h before piperacillin administration.^b Values given are mean $\pm$ standard error of the mean.^c NS, Not significant.

187 ml/min after the three subsequent higher doses of 2, 4, and 6 g, respectively, whereas the corresponding Cl_{NR} values were 105 ml/min (after 1 g), 55 ml/min (after 2 g), 54 ml/min (after 4 g), and 24 ml/min (after 6 g). The presence of disproportionately higher clearance values for the lower doses of piperacillin is reflected in the disproportionately lower $AUC_{0-\infty}$ which were 36, 102, 250, and 438 $\mu\text{g/ml}\cdot\text{h}$ after doses of 1, 2, 4, and 6 g, respectively. The mean $t_{1/2\beta}$ of piperacillin after the four increasing i.v. doses were 36, 54, 61, and 63 min, respectively, showing that the half-life is clearly shortened in the case of the lowest dose tested (1 g), whereas the values obtained after 4- and 6-g doses were similar (half-life of approximately 1 h), suggesting some saturation process in the clearance mechanisms. Obviously higher clearance rates (Cl_R and Cl_{NR}) of piperacillin with the lower doses were also observed after the three increasing i.m. doses tested (0.5, 1, and 2 g). Cl_R was 432 ml/min per 1.73 m^2 after the 0.5-g i.m. dose, compared with 314 and 220 ml/min after the 1- and 2-g doses, respectively, and the corresponding Cl_{NR} values were 153, 108, and 71 ml/min (Table 2). The peak serum concentrations were achieved within 30 to 50 min after i.m. injection. The 0.5-g dose resulted in disproportionately lower peak serum levels and AUCs compared with the higher doses (Table 2). Bioavailabilities of piperacillin after i.m. administration, as judged from the area under the curve ratios (i.m./i.v.) after the 1- and 2-g doses, were approximately 70 to 80%. Thus, piperacillin does indeed appear to be rapidly and reliably absorbed after i.m. administration.

The 24-h urinary recovery of the antibiotic averaged 57 to 58% after i.m. administration (Table 2) and 74 to 89% after the i.v. route (Table 1). This lower urinary recovery implies a larger proportion of nonrenal mechanism of elimination when piperacillin is administered through the i.m. route.

The fact that the ratio of the Cl_R of piperacillin to the Cl_R of creatinine was significantly higher than 1 indicates that piperacillin, in addition to being excreted by glomerular filtration, is also secreted by renal tubules. This is strongly supported by the inhibiting effect of oral probenecid administration (Table 3). The Cl_R of piperacillin was significantly (40%) lowered, and the ratio of piperacillin clearance to creatinine clearance decreased from 2.4 to 1.3 after probenecid treatment. The 24-h urinary recovery of piperacillin after a 1-g i.m. dose was not significantly altered by probenecid; recovery was 62.7% in the absence and 60.5% in the presence of probenecid,

indicating that probenecid delayed but did not decrease the urinary excretion.

The pharmacokinetic data with and without probenecid treatment (Table 3) show that probenecid diminishes the Cl_R of piperacillin by 40.5%, which is consistent with its usual effects on organic acid transport in the kidney. Most unusual, however, was the fact that a concomitant decrease of 35.9% in the Cl_{NR} of piperacillin during probenecid treatment was observed in the present study. These two alterations should thus be responsible for the observed increases in plasma piperacillin concentrations, i.e. a 30% increase in the peak serum concentrations, a 30% prolongation of serum half-life, and a 65% increase in $AUC_{0-\infty}$. As has been reported earlier for several other penicillin derivatives, e.g., ampicillin, ancillin, nafcillin, and cephaloridine (4), a similar apparent decrease in the distribution parameters was observed for piperacillin (20% decrease in V_d area) in the presence of probenecid. Such a decrease in the V_d area parameter has been shown to be an artifactual finding resulting from the reduced elimination rate of penicillin during probenecid treatment, which allows more drug to reach the tissue compartment (5). Such an apparent decrease in V_d area appears to be a reflection that the system was closer to reaching steady-state equilibrium with probenecid.

The good human tolerance to parenteral piperacillin and the favorable pharmacokinetic properties comparable to those known for other penicillin compounds, together with its good antibacterial activity, suggest that extensive clinical trials with this antibiotic are highly desirable for the evaluation of its usefulness in treating bacterial infections in humans.

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