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Pharmacokinetics of Piperacillin in Subjects with Various Degrees of Renal Function

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The pharmacokinetics of piperacillin were examined after single intravenous doses to three groups of male patients with creatinine clearances of ≥60 (group I), ≥20 but <60 (group II), and <20 (group III) ml/min per 1.73 m^2. Each of 32 patients received either 1 or 4 g of piperacillin as a bolus injection. Three patients received both doses. After a rapid 0.5- to 1-h distribution phase, antibiotic levels in serum declined monoexponentially. After the 1-g dose, mean peak piperacillin levels in serum were 60, 103, and 67 μg/ml and the β phase elimination half-lives were 1.0, 1.6, and 3.9 h in groups I, II, and III, respectively. After the 4-g dose, the respective mean peak piperacillin levels in serum were 329, 232, and 262 μg/ml and β phase half-lives were 1.4, 2.3, and 2.6 h in the three groups. There was no clear evidence of significant dose-dependent effects on any pharmacokinetic parameters in any of the groups. Piperacillin levels in urine were far higher than those in serum, generally exceeding the minimal inhibitory concentrations for susceptible organisms during the 24 h after both the 1- and the 4-g dose. Piperacillin dosage modification is required only in patients with severe renal impairment.

Piperacillin is a new semisynthetic parenteral penicillin with a broad spectrum of activity against gram-positive and gram-negative organisms (4, 8). Previous studies on the pharmacokinetics of piperacillin in healthy individuals have shown that it behaves similarly to other penicillins (1, 14), distributing into an apparent body volume representing 20 to 25% of body weight and having a serum half-life of approximately 1 h. One study has suggested that piperacillin clearance is dose dependent, its half-life in serum increasing as the dose is increased from 1 to 4 g (14). Similar serum half-lives were obtained after 4- and 6-g doses (12).

Recent studies have shown that, although 70 to 80% of dosed piperacillin is cleared unchanged via the kidneys, the half-life of the drug in serum increases only moderately to 2 to 3.5 h in patients with severe renal impairment (2, 6, 13), perhaps owing partly to a compensating increase in biliary excretion (5). As piperacillin may be useful in the treatment of some urinary tract infections (11, 12), it is important to determine the antibiotic levels obtained in patients with various degrees of renal function and urine output. This information does not appear to be presently available.

The study described in this report was designed (i) to provide a more general description of piperacillin pharmacokinetics in patients with a wider cross-section of renal function than has hitherto been available, (ii) to examine the possible dose dependency of piperacillin pharmacokinetics, and (iii) to determine piperacillin concentrations in urine during the 24 h after the administration of 1- and 4-g doses to patients with normal, moderately impaired, and severely impaired renal functions.

For logistical reasons, it was not possible in most cases to administer the two different piperacillin doses to the same patients; however, three patients with severe renal impairment received both the 1- and the 4-g dose.

MATERIALS AND METHODS

Subjects. Thirty-two hospitalized male patients suffering from a variety of diseases participated in the study. Subjects were restricted to their wards but were not necessarily at bed rest.

Before participating, all subjects underwent a physical examination including urinalysis, hematology, blood chemistry, and drug history. All laboratory values were within the normal range for this patient population. Patients with a history of penicillin allergy or major disorders of the hepatobiliary, cardiovascular, central nervous, or respiratory systems were excluded. Some patients were receiving other medication but no antibiotics.

Procedures. Subjects were divided into three groups on the basis of initial 24-h creatinine clearances. Patients with creatinine clearances of ≥60, 20 to 59, and <20 ml/min per 1.73 m^2 were assigned to groups I, II, and III, respectively. Final group assignment was based on averaged creatinine clearance values obtained from four urine collections at 0 to 2, 2 to 4, and 4 to 6 h after piperacillin dosage. No group reassignments were indicated by the final creatinine clearance values. Subjects within each group were randomly assigned to receive a piperacillin dose of either 1 or 4 g. Three patients in group III received both doses on different occasions at least 1 month apart.

Characteristics of the patients in this study, including final creatinine clearance and serum creatinine values, are summarized in Table 1.

At 8 a.m., subjects received a single intravenous dose of 1 or 4 g of sodium piperacillin (Lederle Laboratories, Pearl River, N.Y.) dissolved in 20 ml of sterile physiological saline during a 2-min period. Subjects drank 500 to 600 ml of water just before dosing. Those with creatinine clearances below 40 ml/min per 1.73 m^2 drank smaller quantities of water, depending on their fluid restrictions.

Blood samples (5 ml) were taken for serum from a forearm vein in the arm opposite to that used for drug administration immediately before and then serially from 5 min to 24 h after dosing. The bladders of all subjects who could produce urine were emptied before dosing, and urine was then collected quantitatively up to 24 h postdose. Serum and urine samples were stored at −20°C until assay, which was done uniformly within 1 week.

Assay. Serum and urine were assayed in triplicate for piperacillin activity with a microbial cup-plate diffusion method, using Antibiotic Medium No. 1 (BBL Microbiology Systems, Cockeysville, Md.) as the growth medium and *Sarcina lutea* ATCC 9341 as the indicator organism. When necessary, serum was diluted with human serum and urine was diluted with 0.1 M phosphate buffer (pH 7) before assay. Serum and urine standards were prepared in human serum and in 0.1 M phosphate buffer (pH 7), respectively. The relationship between inhibition zones of bacterial growth and the logarithm of piperacillin concentration were linear over an antibiotic range of 1 to 100 μg/ml. Assay reproducibility was within 10% at the higher concentration range and within 12% at the lower.

Data analysis. The decline in individual serum piperacillin profiles was biexponential, and the data were analyzed by the following equation:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where C is the concentration of piperacillin at t hours after injection, A and B are the intercepts, and α and β are first-order rate constants. As the injection time of 2 min was short compared with the duration of the α phase (30 min to 1 h) of the serum profiles, it was considered negligible. Equation 1 is consistent with the pharmacokinetic two-compartment open model, so that analysis was extended to include estimation of the microscopic rate constants, by the following equation: following equation:

$$\frac{\alpha}{\beta} = 0.5\,[(K_{12} + K_{21} + K_{el}) \pm [(K_{12} + K_{21} + K_{el})^{1/2} - 4K_{21}\,K_{el})] \quad (2)$$

and also distribution parameters associated with this model (15). Estimates of pharmacokinetic parameters were obtained by nonlinear regression analysis on a Univac digital computer (7). Piperacillin concentrations were weighted by their reciprocals during computer-fitting procedures.

Areas under piperacillin serum profiles from zero to infinite time were calculated by trapezoidal rule with end correction. Renal clearances were calculated as mean values from 2 to 4, 4 to 6, 6 to 12, and 12 to 24 h postdose urine collections. Serum and urine values and some pharmacokinetic constants were compared by analysis of variance, and significant group or dose effects were further examined by t test, as described previously (3).

RESULTS

Mean piperacillin serum profiles during the 12-h period after the 1- and 4-g doses are shown in Fig. 1 and 2. After the 1-g dose, mean peak piperacillin levels in serum were 60, 103, and 67 μg/ml in groups I, II, and III, respectively. Drug levels declined rapidly until 0.5 to 1 h postdose and subsequently at a slower, monoexponential rate. In group I and II subjects, drug was essentially cleared from serum at 12 h. In group III subjects, the mean serum level was 2.5 μg/ml at 12 h and <1 μg/ml (data not shown) at 24 h.

TABLE 1. Subject characteristics

Group	n	Dose (g)	Mean (range)[a]				
			Age (yr)	Ht (m)	Wt (kg)	Cl_{cr} (ml/min per 1.73 m^2)	S_{cr} (mg/100 ml)
I	6	1	67 (60–93)	1.8 (1.6–1.9)	76 (64–99)	83 (61–102)	1.1 (0.7– 1.5)
	5	4	63 (55–82)	1.8 (1.7–1.9)	83 (61–96)	84 (71–111)	1.3 (0.8– 1.7)
II	6	1	69 (49–81)	1.7 (1.6–1.9)	64 (50–80)	44 (26–56)	1.7 (0.9– 2.5)
	6	4	67 (51–93)	1.8 (1.7–1.9)	88 (66–116)	34 (22–53)	1.8 (0.9– 2.7)
III	6	1	73 (57–84)	1.8 (1.7–1.9)	77 (66–91)	6.7 (0–15)	7.6 (3.4–17.8)
	6	4	70 (53–84)	1.7 (1.2–1.9)	77 (56–87)	8 (0–19)	7.0 (2.2–17.8)

[a] Cl_{cr}, Creatinine clearance; S_{cr}, serum creatinine.

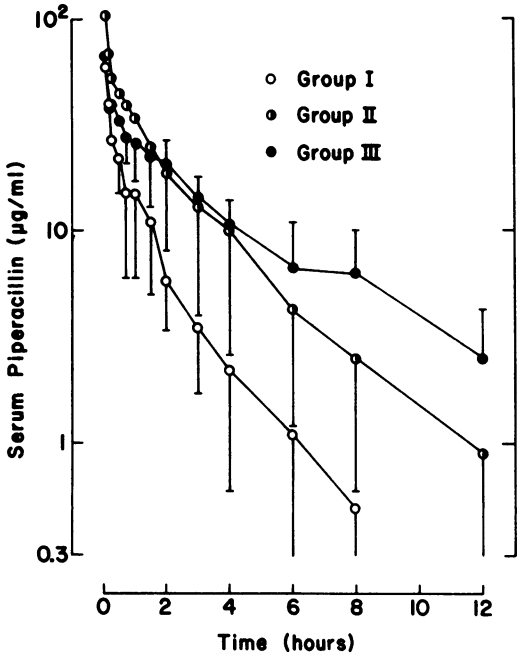

FIG. 1. Mean antibiotic levels in serum after single 1-g intravenous doses of piperacillin. Vertical bars indicate 1 standard deviation.

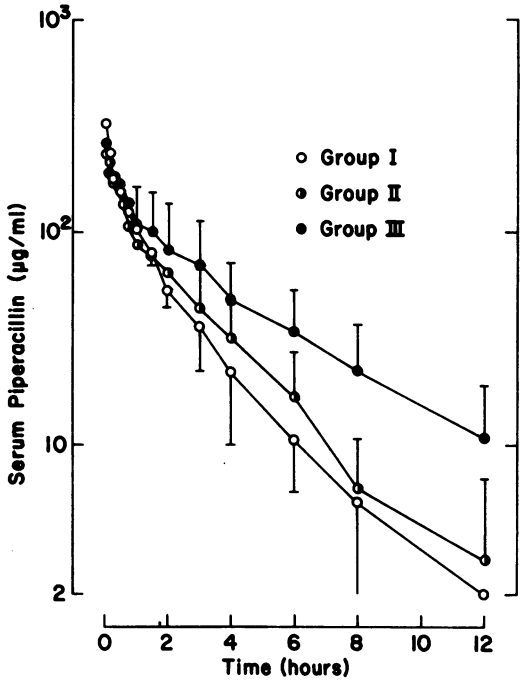

FIG. 2. Mean antibiotic levels in serum after single 4-g intravenous doses of piperacillin. Vertical bars indicate 1 standard deviation.

After the 4-g dose, mean peak piperacillin levels in serum were 329, 232, and 262 μg/ml in groups I, II, and III, respectively. Drug levels then declined rapidly to approximately 100 μg/ml at 0.5 to 1 h in all three groups and then at a slower, monoexponential rate, to reach mean levels of 2, 3, and 11 μg/ml at 12 h. The piperacillin level in serum at 24 h was 4.5 μg/ml in group III but was reduced to negligible levels in the other two groups.

Mean piperacillin concentrations in urine during each collection interval are given in Table 2. Although they were variable, levels of antibiotic activity in urine were generally many times higher than those in serum in all three subject groups and, in most cases, exceeded the minimal inhibitory concentrations for susceptible organisms up to 12 to 24 h postdosing (4, 8). Piperacillin levels in urine were similar in group I and II subjects, although they tended to be higher in group II than in group I during the 6- to 12-h and 12- to 24-h collections after the 1-g dose. In group III, mean antibiotic levels in urine were approximately 40% of those in group I until 6 h postdose but increased to 44 to 57% during the 6- to 12-h interval and to 91 to 94% during the 12- to 24-h interval. The mean cumulative recovery of piperacillin activity in urine accounted for 64 to 69, 58 to 61, and 13 to 20% of the doses in groups I, II, and III, respectively. There were no dose-dependent trends in these values.

Some pertinent pharmacokinetic parameters are given in Table 3. The mean coefficients of

TABLE 2. Mean piperacillin concentrations in urine after doses of 1 and 4 g

Dose (g) and time (h)	Mean ± SD piperacillin concn (μg/ml) in group:[a]		
	I	II	III
1			
0–2	1,837 ± 575	1,549 ± 1,253	712 ± 1,090
2–4	839 ± 410	1,049 ± 634	364 ± 297
4–6	394 ± 312	724 ± 486	110 ± 125
6–12	185 ± 191	333 ± 337	82 ± 115
12–24	18 ± 26	49 ± 61	17 ± 15
4			
0–2	5,768 ± 1,561	5,990 ± 4,056	2,083 ± 2,087
2–4	2,940 ± 1,370	4,291 ± 3,010	1,158 ± 1,421
4–6	1,808 ± 1,064	2,148 ± 1,463	836 ± 1,192
6–12	840 ± 792	668 ± 411	480 ± 593
12–24	202 ± 301	157 ± 75	183 ± 324

[a] The cumulative percentages of piperacillin excreted in urine from 0 to 24 h were (mean ± standard deviation) 69 ± 14, 61 ± 21, and 13 ± 23% in groups I, II, and III, respectively, for the 1-g dose and 64 ± 12, 58 ± 17, and 20 ± 31% in groups I, II, and III, respectively, for the 4-g dose.

TABLE 3. Pharmacokinetic parameters for piperacillin

Group and dose (g)	Mean ± SD[a]				
	α (h^{-1})	β (h^{-1})	$t_{1/2\beta}$ (h)	K_{12} (h^{-1})	K_{21} (h^{-1})
I					
1 (n = 6)	8.2 ± 1.0	0.72 ± 0.19	1.0 ± 0.3	4.0 ± 0.3	3.0 ± 0.5
4 (n = 5)	9.1 ± 2.9	0.53 ± 0.15	1.4 ± 0.4	4.9 ± 1.9	4.3 ± 2.8
II					
1 (n = 6)	9.3 ± 4.9	0.46 ± 0.10	1.6 ± 0.4	5.2 ± 3.6	2.6 ± 1.0
4 (n = 6)	4.8 ± 4.4	0.35 ± 0.13	2.3 ± 1.2	2.6 ± 2.9	1.7 ± 1.3
III					
1 (n = 6)	12.7 ± 11.0	0.28 ± 0.19	3.9 ± 3.2	8.9 ± 9.8	2.6 ± 0.9
4 (n = 6)	5.1 ± 3.6	0.23 ± 0.12	3.6 ± 1.6	3.3 ± 2.3	2.5 ± 1.3

[a] α and β, larger and smaller of the two rate constants from equation 1, respectively; $t_{1/2\beta}$, serum half-life of piperacillin, calculated from $t_{1/2\beta} = 0.693/\beta$; K_{12} and K_{21}, first-order rate constants for transfer of piperacillin from the central to the peripheral compartments and from the peripheral to the central compartments of the two-compartment open model, respectively; K_{el}, first-order rate constant for elimination of piperacillin from the central compartment by all routes; V_1, apparent volume of the central compartment of the two-compartment open model; V_{dss}, steady-state distribution volume of piperacillin, calculated from $V_{dss} = V_1 [1 + (K_{12}/K_{21})]$; $AUC^{0-\infty}$, area under the piperacillin concentration in serum versus time curve from zero to infinite time; Cl_r, renal clearance of piperacillin, calculated from Cl_r = total urinary recovery/$AUC^{0-\infty}$; Cl_s, serum clearance of piperacillin, calculated from $Cl_s = V_1 K_{el}$.

[b] The value for the 1-g dose was significantly greater than that for the 4-g dose ($P < 0.05$).

determination from nonlinear regression analysis of serum piperacillin profiles from the two doses and three patient groups, using equation 1, were uniformly >0.99, indicating that the serum profiles were adequately described by a two-compartment kinetic model.

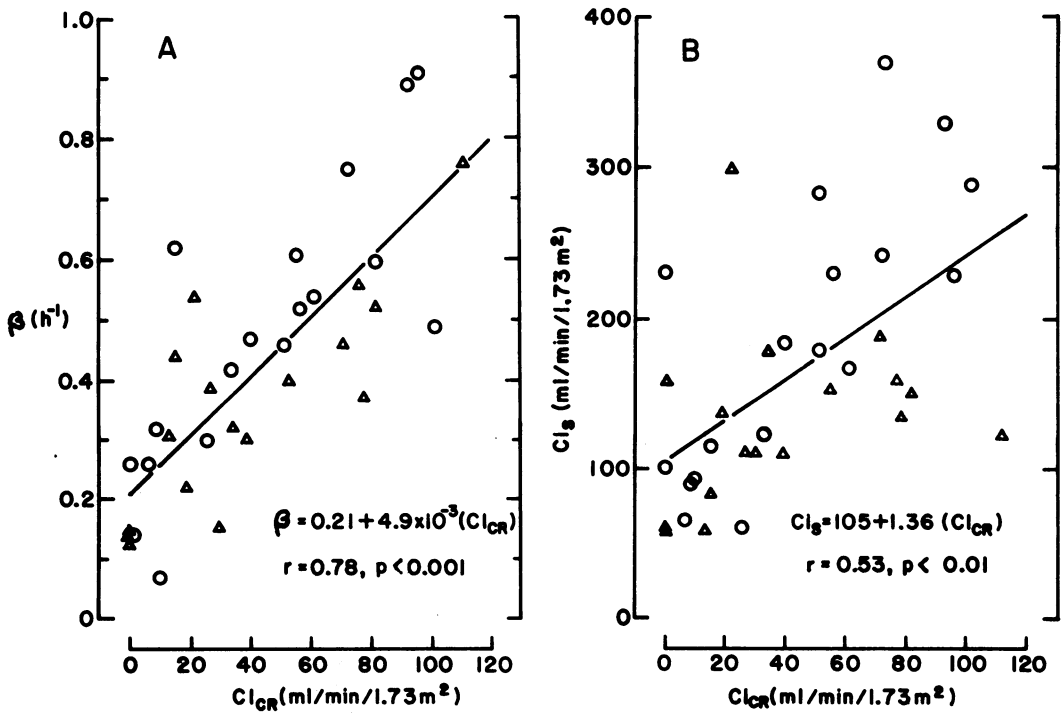

FIG. 3. Regressions of the piperacillin terminal elimination rate constant (β) (A), serum clearance (Cl_s) (B), renal clearance (Cl_R) against creatinine clearance (Cl_{CR}) (C), and the elimination half-life ($t_{1/2\beta}$) against serum creatinine (S_{CR}) (D) after 1 g (○) and 4 g (△) of piperacillin; n = 35 in each case.

TABLE 3—*Continued*

K_{el} (h^{-1})	V_1 (liters/kg)	V_{dss} (liters/kg)	AUC $^{0-\infty}$ (μg · h/ml)	Cl_r (ml/min per 1.73 m^2)	Cl_s (ml/min per 1.73 m^2)
2.1 ± 0.3	0.11 ± 0.03	0.30 ± 0.06	49 ± 23	215 ± 61[b]	297 ± 73[b]
1.5 ± 0.1	0.09 ± 0.03	0.21 ± 0.09	384 ± 72	95 ± 8	153 ± 25
1.9 ± 1.7	0.11 ± 0.04	0.30 ± 0.07	130 ± 76	113 ± 87	175 ± 101
1.0 ± 0.5	0.16 ± 0.07	0.29 ± 0.03	406 ± 156	98 ± 59	163 ± 83
1.6 ± 1.6	0.11 ± 0.08	0.35 ± 0.20	145 ± 49	16 ± 25	116 ± 59
0.7 ± 0.3	0.14 ± 0.05	0.32 ± 0.20	719 ± 419	21 ± 27	101 ± 46

The parameters primarily associated with drug distribution, α rate constant, first-order rate constants for drug transfer from the central to the peripheral and from the peripheral to the central compartments, and apparent volumes of distribution of the central compartment and at steady state, were not significantly different between doses or among groups ($P \geq 0.05$). The rate constant for drug loss from the central compartment after the 4-g dose tended to be smaller than that after the 1-g dose within each group, but the differences were not significant. A similar nonsignificant trend was observed in the elimination half-life in groups I and II, but there was no dose effect for this parameter in group III. On the other hand, the elimination half-life significantly increased in the group order I < II < III ($P < 0.05$) after both the 4- and the 2-g dose.

Both serum and renal clearances after the 1-g dose were significantly larger ($P < 0.05$) than those after the 4-g dose in group I, but there

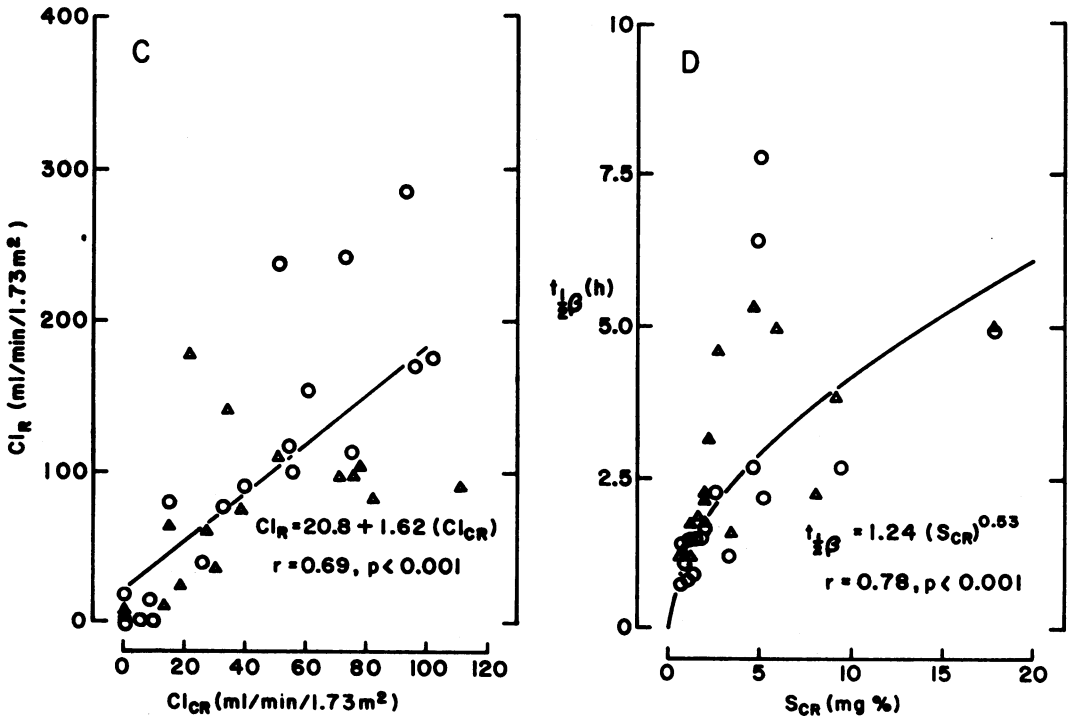

FIG. 3—*Continued*

were no dose effects within the other groups. Renal clearance of piperacillin was significantly reduced in group III subjects as compared with other groups at both dose levels. Serum clearance was significantly larger in group I than in the other groups after the 1-g dose, but there were no significant group effects in this parameter after the 4-g dose.

The relationships between piperacillin elimination and renal function for all subjects and both drug doses are shown in Fig. 3. Despite only moderate influence of renal function on piperacillin kinetics, significant correlations were obtained between creatinine clearance and the piperacillin elimination rate constant β, renal clearance, and serum clearance. The correlation coefficient for β, 0.78, was higher than those for renal and serum clearances, and there was considerable intersubject variation for the latter two parameters. A high correlation was also obtained between the piperacillin elimination half-life and serum creatinine when this relationship was expressed as a power function of the form $y = ax^b$. This type of nonlinear relationship has been described previously (9) and is expected for a drug which is eliminated partly by extrarenal routes.

DISCUSSION

The overall relationship between piperacillin pharmacokinetics obtained in this study are in close agreement with that found in previous reports (2, 6, 13) and confirms that, unlike the closely related compounds carbenicillin and ticarcillin, piperacillin elimination is not markedly affected by renal function. The reason that declining renal function has such a small effect on piperacillin kinetics has not been explained by previous studies or by the present results; however, piperacillin is known to concentrate in bile (5, 10), and this may provide an alternate route of elimination in uremia.

Although the mean recovery of piperacillin in urine was markedly reduced from ca. 70% in patients with normal renal function to ca. 13 to 20% in patients with severe renal impairment, the antibiotic concentration in urine was high in all individuals capable of producing urine. After the 1-g dose, piperacillin levels in urine exceeded 100 μg/ml in most patients in group I and II and in some patients in group III up to 12 h postdose. After the 4-g dose, average piperacillin levels remained in excess of 100 μg/ml even during the 12- to 24-h sampling period in all three groups. In vitro studies have shown piperacillin to be effective against most urinary tract pathogens at drug concentrations ranging from 0.1 to 25 μg/ml (4, 11), so that adequate treatment of urinary tract infections requiring this type of medication may be obtained even in cases of impaired renal function.

The lack of effect of different renal statuses on piperacillin distribution characteristics indicates that penetration of this antibiotic into tissue and the relationship between circulating drug levels and those in extravascular tissues and fluids are similar in individuals with normal and impaired renal function.

The elimination half-life of piperacillin was somewhat prolonged after the 4-g dose as compared with the 1-g dose in groups I and II, but the differences did not reach the 95% significance level. The piperacillin half-life was independent of dose in group III subjects. Of the three individuals in group III who received both doses, two yielded longer piperacillin half-lives after the 4-g dose, whereas the other showed the reverse effect. Our data therefore do not entirely support the previous suggestion that piperacillin elimination is dose dependent (14). Any differences observed in this study are unlikely to be clinically important.

The results of this study confirm that the elimination of piperacillin, unlike those of carbenicillin and ticarcillin, is affected only to a small extent by different renal functions. In addition, they have shown that, even in patients with marked renal impairment, antibiotic levels in urine are adequate to inhibit most urinary tract pathogens, and this effect may extend through 24 h after a 4-g dose. Any dose-dependent effects on piperacillin elimination are unlikely to be clinically important.

Piperacillin dosage modification is necessary only in patients with severe renal impairment. A single doubling of the usual dosage interval, i.e., from 4 to 6 h to 8 to 12 h, in such patients would provide trough antibiotic levels similar to those observed in patients with normal renal function.

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