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Mezlocillin Pharmacokinetics After Single Intravenous Doses to Patients with Varying Degrees of Renal Function

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The pharmacokinetics of mezlocillin were examined after single 2- and 4-g intravenous injections to three groups of male patients with creatinine clearances of I $\geq$ 60, II = 21 to 59, and III $\leq$ 20 ml min^{-1} 1.73 m^{-2}. The decline in serum antibiotic levels was biphasic in all groups, and serum data were interpreted in terms of the pharmacokinetic two-compartment model. The mean elimination half-life of mezlocillin after the 2-g dose was 1.3, 1.5, and 2.3 h in groups I, II, and III, respectively. Equivalent values after the 4-g dose were 1.2, 1.6, and 4.4 h. In three functionally anephric patients the mean serum half-life of mezlocillin was 1.5 h during hemodialysis. Mean antibiotic levels in serum were greater than 10 μg ml^{-1} for 4 h after the 2- and 4-g doses in group I and 8 h in group II. In group III, levels greater than 10 μg ml^{-1} were maintained for 6 h after the 2-g dose and over 12 h after the 4-g dose. Mezlocillin distribution characteristics were largely independent of renal function and dose size. The only observable change occurred in the value of V_{dss}, which was significantly increased to 0.32 with 0.38 liter kg^{-1} in severe renal impairment, compared to ca. 0.2 liter kg^{-1} in subjects with normal or slightly impaired renal function. Cumulative 24-h urinary excretion accounted for 50, 40, and 3.2% of the dose in groups I, II, and III, respectively. Urine levels of mezlocillin were uniformly greater than the minimum inhibitory concentration for susceptible organisms for 12 h after dosing in all patients who produced urine. Because of the relatively small increase in the mezlocillin elimination half-life with declining renal function, dose reduction is necessary only in cases of severe renal impairment.

Mezlocillin is a recently developed acylureidopenicillin for intravenous administration. In vitro studies have shown this antibiotic to have a spectrum of activity encompassing that of the cephalosporins and penicillins, including activity against *Escherichia coli*, species of the *Klebsiella-Enterobacter-Serratia* group, *Proteus*, *Pseudomonas*, *Haemophilus influenzae*, and *Neisseria gonorrhoea* (3, 16). It is more active than ampicillin, carbenicillin, and cephalothin against some gram-negative bacilli (17). It is also active against *Streptococcus faecalis* and other gram-positive bacteria which do not produce β-lactamase.

In view of the potential use of mezlocillin against susceptible organisms in both systemic and urinary tract infections, it is necessary to examine the circulating and urinary levels, and also the general pharmacokinetic behavior, of this compound in patients. The pharmacokinetics of mezlocillin have been described after different dose levels in individuals with normal renal function (1, 9), and also in uremic patients after single 1-g doses (2). In this study the pharmacokinetics of mezlocillin have been studied after single 2- and 4-g intravenous doses to 31 male patients with varying degrees of renal impairment.

MATERIALS AND METHODS

Subjects. The subjects were 31 hospitalized male patients suffering from a variety of diseases, including renal insufficiency, and with no known history of allergy to pencillins. All subjects were restricted to their wards during the study, but were not necessarily at bed rest.

Before participating in the study, all subjects underwent complete physical examinations including urinalysis, hematology, blood chemistry, and drug history. Liver function was assessed by serum glutamic oxalacetic transaminase (SGOT) and alkaline phosphatase values. The SGOT or alkaline phosphatase values or both obtained before the study indicated that all but five of the subjects had normal hepatic enzyme function. Of these five subjects, one had elevated SGOT and three had elevated alkaline phosphatase, while one showed elevated values for both tests. Two of the subjects with elevated alkaline phosphatase had prostatic malignancies. Because these values cannot be considered absolute predictors of hepatic

drug biotransformation capacity, the subjects with the elevated SGOT and alkaline phosphatase values were allowed to participate in the study.

Some subjects received other medications during the study. One subject received Septra (Burroughs-Wellcome). However, neither trimethoprim nor sulfamethoxazole show activity against the test organisms used in the mezlocillin assay. One subject received phenytoin. This subject was included in the study because his SGOT and alkaline phosphatase values determined twice before and twice after the study day were all normal. None of the other drugs given to the subjects during the study was a known hepatic enzyme inducer. No other patients received concurrent antibiotic therapy.

Patients with major disorders of the hepatabiliary, cardiovascular, central nervous, or respiratory systems were excluded from the study.

Procedures. Subjects were divided into three groups on the basis of initial 24-h creatinine clearance values. Groups I, II, and III had creatinine clearances of ≥60, 21 to 59, and ≤20 ml min^{-1} 1.73 m^{-2}, respectively. Subjects within each group were randomly assigned to receive either a 2- or a 4-g dose of mezlocillin. Final assignment to subject groups was based on averaged creatinine clearance values obtained during 0 to 2, 2 to 4, and 4 to 6 h after mezlocillin injection. No group reassignments were indicated by the final creatinine clearance values. Subject details, including final creatinine clearance and serum creatinine values as well as the doses administered, are described in Table 1.

Subjects received a single intravenous dose of sodium mezlocillin (Delbay Pharmaceuticals Inc., Florham Park, N.J.) dissolved in 20 ml of sterile physiological saline into a forearm vein during a 5-min period. The dose was administered at approximately 8 a.m. Each subject drank 500 to 600 ml of water just before dosing. Subjects with creatinine clearances below 40 ml min^{-1} 1.73 m^{-2} drank smaller quantities of water, depending on their particular fluid requirements.

Three severely uremic patients also received a dose of mezlocillin while on hemodialysis. These patients were given either the 2- or 4-g dose just after dialysis was begun. A Travenol coil dialyser was used for the dialysis, which was carried out for 6 h, with the last serum sample taken before discontinuation of dialysis.

Blood samples (5 ml) were taken from a forearm vein, in the opposite arm than that used for drug administration, serially from 5 min through 12 h after the start of the infusion. The bladders of subjects who could produce urine were emptied before dosing, and urine was then collected quantitatively during 0 to 2-, 2- to 4-, 4- to 6-, 6- to 12-, and 12- to 24-h postdosing. Serum and urine samples were stored at −20°C until assay, which was done uniformly within 1 week.

Serum and urine samples were assayed in triplicate for antibiotic activity by a microbiological cup-plate diffusion method using Antibiotic Medium No. 1 (BBL Microbiology Systems, Cockeysville, Md.) as the growth medium. *Bacillus subtilis* ATCC 6633 was used as the indicator organism for mezlocillin concentrations > 10 μg/ml. *Sarcina lutea* ATCC 9341 served as the indicator organism for concentrations ≤10 μg/ml. Incubation was for 18 h at 32°C for both organisms. The use of two organisms decreased the number of serum and urine samples requiring dilution before assay. When necessary, serum samples were diluted with human serum, and urines were diluted with 0.1 M phosphate buffer, pH 7. Serum standards were prepared in human serum, and urine standards in 0.1 M phosphate buffer, pH 7. The relationships between the inhibition zones of bacterial growth and the logarithm of mezlocillin concentration were linear over the drug concentration ranges 1 to 10 and 10 to 500 μg/ml. Assay reproducibility was 2 to 5% at the lower concentration range and 5 to 8% at the higher.

Data analysis. The decline in individual serum levels of mezlocillin activity was clearly biexponential, and the data were therefore analyzed in terms of equation 1:

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

where C is the concentration in serum at time t. A and

TABLE 1. *Subject details*

Group	n^a	Dose (g)	Age (yr)	Ht (cm)	Wt (kg)	$Cl_{CR}{}^b$ (ml min^{-1} 1.73 m^{-2})	$S_{CR}{}^c$ (mg%)
I	7	2	65	169	75	104	1.1
			(11)[d]	(12)	(15)	(27)	(0.2)
	8	4	67	177	81	93	1.2
			(16)	(8)	(17)	(23)	(0.3)
II	4	2	76	170	83	51	1.5
		4	(10)	(4)	(23)	(9)	(0.3)
	5		85	165	62	38	2.0
			(4)	(19)	(11)	(11)	(0.4)
III	4	2	59	170	70	5.6	11.8
			(8)	(5)	(8)	(9.7)	(6.9)
	3	4	61	169	66	3.0	9.5
			(13)	(6)	(5)	(2.9)	(3.2)

[a] Number of subjects in each group receiving 2- and 4-g doses.
[b] Creatinine clearance normalized to a body surface area of 1.73 m^2.
[c] Concentration of creatinine in serum.
[d] Figures in parentheses are standard deviations.

B are the intercepts, and α and β are rate constants obtained from the first and second phases of the plot of log serum mezlocillin concentration versus time, respectively.

Initial estimates of the functions in equation 1 were obtained by standard curve-stripping procedures. Improved estimates were obtained by nonlinear regression analysis using the program NREG on a Univac digital computer (MACC Nonlinear Regression Routines, Academic Computer Center, University of Wisconsin, Madison). All mezlocillin concentrations were weighted according to their reciprocals during the computer fitting procedure.

As the mezlocillin doses were injected over a period of 5 min, the results of the computer analysis were analyzed by using the appropriate equations for the biphasic decay of log concentration versus time after the termination of an intravenous infusion (12).

Areas under the log serum concentration versus time curves to infinite time, $AUC^{0\rightarrow\infty}$, were calculated for each subject by the trapezoidal rule. Renal clearances were calculated as mean values of the clearances from 2 to 4 h, 4 to 6 h, and 6 to 12 h postdosing. These clearances were calculated as:

$$C_u V/C_s t \quad (2)$$

where C_u is the urine concentration for that time interval, C_s is the serum concentration at the mid-time point, and V/t the urine volume collected during the time interval.

The pharmacokinetic constants obtained were compared by using a 2 × 3 analysis of variance for the two dosage levels and the three renal function groups. Due to unequal cell sizes, ANOVA was performed by the regression method (9). Significant group or dose effects were further examined by unpaired t test.

RESULTS

The mean mezlocillin profiles in serum resulting from the 2- and 4-g doses to the three groups are shown in Fig. 1 to 3. The mean data for all three groups, with doses normalized to 40 mg kg^{-1}, are summarized in Fig. 4. The biexponential decay of serum mezlocillin levels is evident in each case. The phase of rapid drug loss from serum lasted approximately 1 h, after which time drug loss from serum was monoexponential. Mezlocillin levels in serum were dose related, particularly during the first 2 to 3 h postdosing. This relationship was maintained during the entire 12-h sampling period in group II, whereas the serum profiles resulting from the 2- and 4-g doses tended to converge in group I and to diverge in group III at later sampling times.

Despite the considerable differences in renal function between the three groups, the rates at which mezlocillin was lost from serum did not differ markedly. Mean antibiotic levels in serum were greater than 10 $\mu g\ ml^{-1}$ for 4 h after the 2- and 4-g doses in group I, and 8 h in group II. In group III, mezlocillin levels > 10 $\mu g\ ml^{-1}$ were

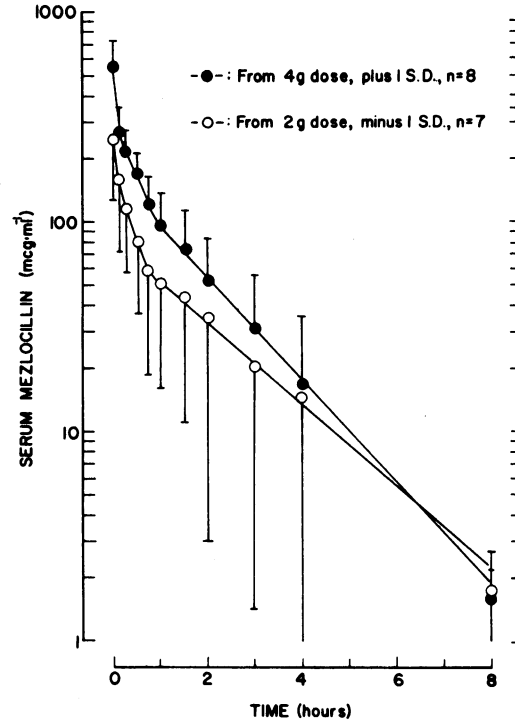

FIG. 1. *Mean serum levels of mezlocillin in group I subjects receiving single intravenous doses of mezlocillin. Error bars indicate plus or minus one standard deviation. The solid lines are hand drawn.*

maintained for 6 h after the 2-g dose and for 12 h after the 4-g dose.

The urinary concentrations of mezlocillin are shown in Table 2. In all three groups, all subjects who produced urine maintained urinary concentrations of mezlocillin which were above the minimum inhibitory concentrations of most susceptible organisms for at least 12 h postdosing.

The cumulative urinary excretion plot in Fig. 5 illustrates that, even in cases of relatively good kidney function, only about one-half of the dose of mezlocillin is cleared unchanged by this route. This proportion was maintained in group II, but dropped to less than 5% of the dose in the subjects with severe renal impairment.

The pharmacokinetic parameters obtained for the groups at both dosage levels are presented in Table 3. Statistical analysis of the values appears in Table 4. The minor effect of renal function on the rate of mezlocillin clearance from the body is indicated by the small changes in the values of β, $t_{1/2(\beta)}$, k_{el}, and Cl_p. The mean β-phase serum half-life of mezlocillin increased from 1.2 to 1.3 h in group I to 2.3 to 4.4 h in group III, while the plasma clearance decreased from 194 to 202 ml min^{-1} to 68 to 118 ml min^{-1}. The rate constants associated with mezlocillin distribu-

tion, k_{12} and k_{21}, were essentially independent of renal function. However, as is often the case, there was considerable variation in these values. The relatively large values for V_1 and V_{dss} in group III compared with the other groups suggest that tissue up-take of mezlocillin is increased in renal insufficiency. While the overall elimination of mezlocillin is changed only moderately in decreasing renal function, the renal

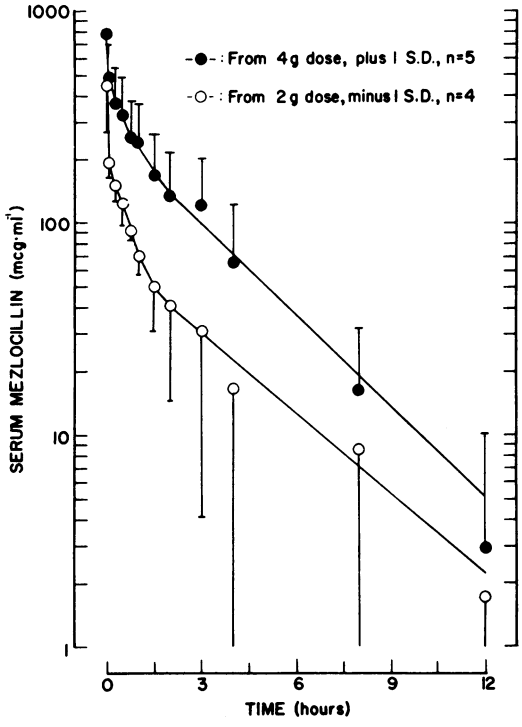

FIG. 2. *Mean serum levels of mezlocillin in group II subjects receiving single intravenous doses of mezlocillin. Error bars indicate plus or minus one standard deviation. The solid lines are hand drawn.*

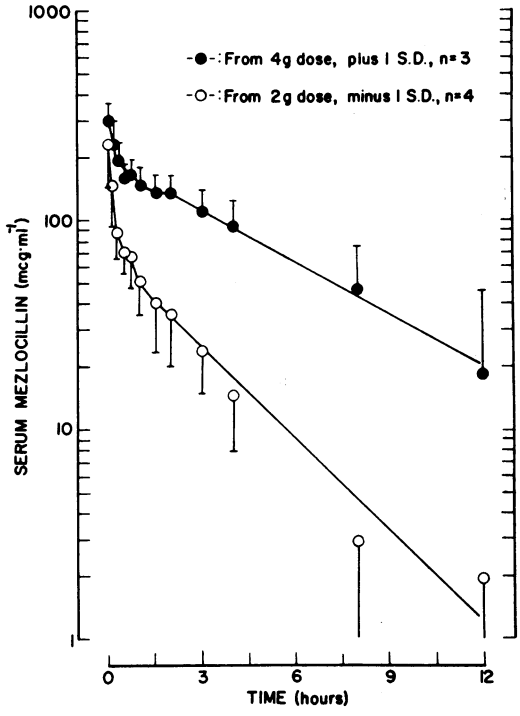

FIG. 3. *Mean serum levels of mezlocillin in group III subjects receiving single intravenous doses of mezlocillin. Error bars indicate plus or minus one standard deviation. The solid lines are hand drawn.*

TABLE 2. *Mean concentrations of mezlocillin in urine*

Group	Dose (g)	Mezlocillin concn ($\mu g\ ml^{-1}$)				
		0-2 h	2-4 h	4-6 h	6-12 h	12-24 h
I	2	2,914	514	505	314	20
		(2,326)[a]	(241)	(556)	(713)	(33)
	4	8,317	2,586	1,097	241	20
		(6,826)	(1,090)	(771)	(256)	(22)
II	2	1,274	943	677	243	247
		(867)	(848)	(488)	(275)	(405)
	4	6,527[b]	4,915	3,667	682	106
		(8,680)	(5,609)	(3,879)	(757)	(124)
III	2	283[c]	272	179	194	11
	4	533[c]	608	375	81	63

[a] Figures in parentheses are standard deviations.

[b] The large standard deviations obtained in this group are due to one subject yielding very high concentrations of mezlocillin in urine and another subject yielding negligible values.

[c] Average of two values. All other subjects in the group were essentially anephric and produced no urine during the collection period.

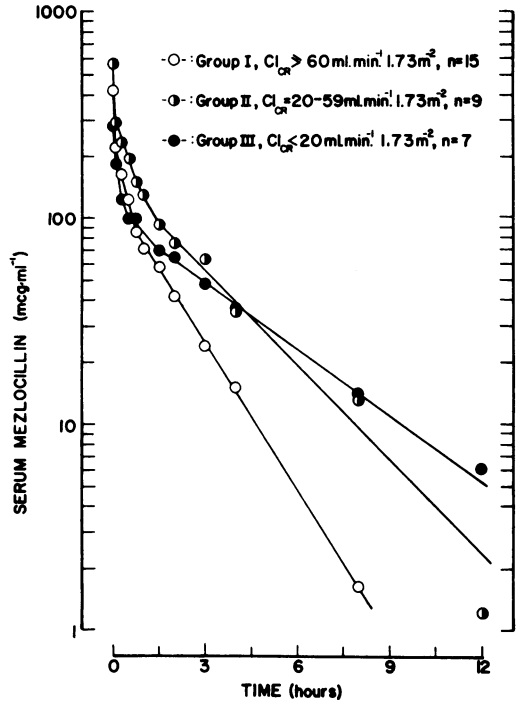

FIG. 4. *Mean serum levels of mezlocillin in groups I, II, and III, with all doses normalized to a value of 40 mg kg^{-1}.*

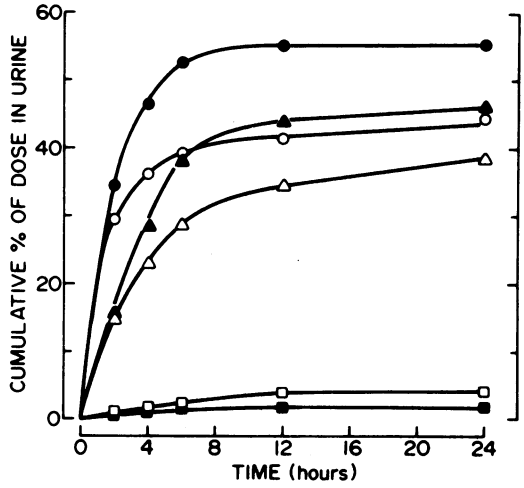

FIG. 5. *Mean cumulative percentage of the mezlocillin dose excreted in urine for group I [2-g (○) and 4-g (●) dose], group II [2-g (△) and 4-g (▲) dose], and group III [2 g (□) and 4 g (■) dose].*

clearance of mezlocillin is more sensitive to kidney function. Although the renal clearance of mezlocillin in group II, with mild renal impairment, was statistically indistinguishable from group I, it was markedly reduced in group III.

Examination of Table 4 for dose effects shows an apparent absence of dose dependency in mezlocillin pharmacokinetics. The only statistically significant dose effect was in the normalized AUCs from group III.

Based on observed correlations between some pharmacokinetic parameters and the renal function indicators creatinine clearance and serum creatinine, regression analysis was used to obtain equations to estimate the expected values of these pharmacokinetic parameters given values for the renal function indicator. Parameters associated with overall mezlocillin elimination, such as β in Fig. 6a and Cl_s in Fig. 6b, generally correlated well with creatinine clearance, whereas the best linear correlation ($r = +0.733$, $P < 0.01$) was obtained between renal clearance and creatinine clearance as shown in Fig. 6c. Volume terms, associated with mezlocillin distribution efficiency, correlated poorly with renal function. Serum creatinine provided somewhat poorer correlations due to an uneven distribution of this value among the subjects. Examples of the correlations obtained with serum creatinine values are shown in Table 5.

The serum mezlocillin profiles in three severely uremic patients, who received mezlocillin while undergoing dialysis, are shown in Fig. 7. The decline in antibiotic levels was again biphasic, and the mean β-phase half-life was reduced from an off dialysis value of 4.2 to 1.5 h, i.e., similar to the half-lives obtained from subjects in groups I and II. Other pharmacokinetic parameters from the dialysis patients were also similar to the values obtained in subjects with normal or only slightly impaired renal function.

DISCUSSION

Results obtained for the patients showing abnormal SGOT or alkaline phosphatase values, and for the patients who received phenytoin and Septra, were in agreement with other subjects of the same groups. Thus, inclusion of these subjects does not appear to have introduced bias into the results. A lack of effect of concomitant sulfamethoxazole-trimethoprim therapy on the mezlocillin assay is supported by the absence of detectable antimicrobial activity after 8 h postdosing in the patient receiving Septra.

This study shows that the pharmacokinetic behavior of mezlocillin is, for the most part, similar to that of other penicillins (4, 5, 7, 8, 11). After intravenous dosage, the antibiotic distributes initially into an apparent fluid volume representing approximately 10% of body weight and subsequently into a volume representing approximately 20% of body weight. Distribution equilibrium is achieved within 1 h, and serum levels

TABLE 3. *Mezlocillin mean pharmacokinetic parameters*

Group and dose	A ($\mu g\ ml^{-1}$)	α (h^{-1})	B ($\mu g\ ml^{-1}$)	β (h^{-1})	$t_{1/2(\alpha)}$ (h)	$t_{1/2(\beta)}$ (h)	k_{12}[a] (h^{-1})	k_{21}[b] (h^{-1})	k_{el}[c] (h^{-1})	(V_1[d]) (liters kg^{-1})	V_{dss}[e] (liters kg^{-1})	$AUC^{0\rightarrow\infty}$[f] ($\mu g\ h\ ml^{-1}$)	Cl_R[g] (ml min^{-1})	Cl_{CR}[h] (ml min^{-1})	Cl_S[i] (ml min^{-1})	r^2[j]
I																
2 g	163	6.8	83	0.56	0.14	1.3	3.4	2.4	1.6	0.12	0.24	235	148	104	202	0.997
(n = 7)	(86)[k]	(4.0)	(54)	(0.17)	(0.09)	(0.4)	(3.0)	(1.1)	(0.7)	(0.07)	(0.12)	(169)	(89)	(27)	(152)	(0.002)
4 g	324	47	205	0.68	0.26	1.2	39	5.4	3.9	0.07	0.18	402	176	93	194	0.999
(n = 8)	(155)	(91)	(82)	(0.28)	(0.54)	(0.4)	(84)	(3.8)	(4.1)	(0.05)	(0.05)	(149)	(144)	(23)	(82)	(0.001)
II																
2 g	296	21.8	155	0.70	0.04	1.5	13.6	6.2	2.7	0.05	0.13	396	53	51	123	0.998
(n = 4)	(144)	(9.6)	(43)	(0.33)	(0.01)	(1.3)	(8.6)	(1.7)	(2.3)	(0.03)	(0.05)	(233)	(56)	(9)	(52)	(0.002)
4 g	459	11.2	369	0.47	0.13	1.6	7.1	3.2	1.4	0.07	0.18	1013	39	38	102	0.997
(n = 5)	(446)	(8.4)	(187)	(0.11)	(0.12)	(0.5)	(6.7)	(1.4)	(0.7)	(0.03)	(0.09)	(583)	(23)	(11)	(72)	(0.002)
III																
2 g	148	13.0	69	0.36	0.18	2.3	9.0	2.8	1.5	0.12	0.38	257	4.1	5.6	118	0.996
(n = 4)	(53)	(12.0)	(37)	(0.15)	(0.22)	(1.3)	(8.8)	(2.5)	(1.1)	(0.09)	(0.16)	(84)	(3.3)	(9.7)	(45)	(0.003)
4 g	110	13.5	182	0.19	0.10	4.4	7.1	6.2	0.38	0.17	0.32	1196	3.5	3.0	68	0.997
(n = 3)	(27)	(13.7)	(27)	(0.07)	(0.07)	(2.3)	(8.3)	(5.2)	(0.21)	(0.03)	(0.05)	(605)	(1.4)	(2.9)	(28)	(0.002)

[a] First-order rate constant for transfer of mezlocillin from the central compartment to the peripheral compartment of the two-compartment open model.
[b] First-order rate constant for transfer of mezlocillin from the peripheral compartment to the central compartment of the two-compartment open model.
[c] First-order rate constant for elimination of mezlocillin from the central compartment by all routes.
[d] Apparent volume of the central compartment of the two-compartment open model.
[e] Steady-state distribution volume of mezlocillin, calculated from $V_{dss} = V_1 (1 + k_{12}/k_{21})$.
[f] Area under the mezlocillin concentration in serum versus time curve from zero to infinite time, calculated by the trapezoidal method.
[g] Renal clearance of mezlocillin, normalized to a body surface area of 1.73 m^2.
[h] Creatinine clearance, normalized to a body surface area of 1.73 m^2.
[i] Serum clearance of mezlocillin, calculated from $Cl_S = V_1 k_{el}$.
[j] Coefficient of determination indicating the accuracy with which equation 1 describes individual serum data, calculated from $r^2 = (\sum obs^2 - \sum dev^2)/\sum obs^2$.
[k] Figures in parentheses are standard deviations.

TABLE 4. *Significance levels (P values) of differences in pharmacokinetic parameters within and between subject groups and dosages*

Method	$t_{1/2(\alpha)}$	$t_{1/2(\beta)}$	k_{12}	k_{21}	k_{el}	V_1	V_{dss}	AUC[a]	Cl_R	Cl_{CR}	Cl_S
ANOVA											
Group	NS[b]	$P < 0.001$	NS	NS	NS	$P < 0.05$	$P < 0.005$	$P < 0.01$	$P < 0.005$	$P < 0.05$	$P < 0.05$
Dose	NS	NS	NS	NS	NS	NS	NS	$P < 0.001$	NS	NS	NS
Interaction	NS	NS	NS	$P < 0.05$	NS	NS	NS	$P < 0.05$	NS	NS	NS
t Test											
Group at 2 g		I < III					II < III		I, II > III	I > II > III	
		$P < 0.05$					$P < 0.05$		$P < 0.05$	$P < 0.05$	
Group at 4 g		I, II < III				I, II < III	I, II < III	I < II, III	II > III	I > II > III	I > III
		$P < 0.05$				$P < 0.05$	$P < 0.05$	$P < 0.02$	$P < 0.05$	$P < 0.005$	$P < 0.05$
Dose in group III								2 < 4			
								$P < 0.05$			

[a] AUC normalized to 2-g dose.
[b] NS, $P > 0.05$.

of antibiotic then decline monoexponentially with a half-life of ca. 1.2 to 1.3 h. The pharmacokinetic behavior of mezlocillin within the subject groups was similar after 2- and 4-g intravenous doses.

Unlike many other penicillins, mezlocillin is either extensively metabolized or is subject to biliary excretion, as only about 50% of the dose was accounted for in normal urine. The considerable extrarenal elimination of mezlocillin accounts for the only moderate impairment in the clearance of this antibiotic from the serum with declining renal function (15).

Although mezlocillin has previously been shown to exhibit dose-dependent pharmacokinetics in subjects with normal renal function (1), no such dependency was obtained in this study. This may be the result of the somewhat narrower dosage range (2 g, 4 g) used here compared with the 2- to 5-g range used previously, but may also have been due to the more heterogeneous nature of the subject population in the present study.

In this regard, it is interesting to compare the results obtained here with those reported after a 1-g dose of mezlocillin in a smaller number of subjects (2). After the 1-g dose, the biological half-life of mezlocillin was essentially unaffected by impaired renal function, despite the reduction in urinary recovery of active antibiotic from 50% in normal individuals to 10% in patients with severe uremia. Whereas the mezlocillin half-life was also unaffected in moderate renal impairment in the present study, it was significantly increased to 2.3 and 4.4 h, respectively, after the 2- and 4-g doses in patients with severe renal impairment. Thus, although we could not confirm the dose dependency of mezlocillin pharmacokinetics in patients with normal renal function, it is clear that the effect of renal impairment on the rate of mezlocillin elimination is dose dependent, the effect being greater at high dose levels.

Although the relative Cl_s and Cl_R values for mezlocillin in Table 3 agree quite well with the percentage of drug cleared unchanged via the urine in groups II and III, agreement is less close in group I. In this group, the mean renal clearance of mezlocillin after the 2- and 4-g doses is 73 and 91%, respectively, of the serum clearance, although only 45 and 55% of the doses, respectively, were cleared unchanged in the urine.

The possible overestimation of renal clearance in group I may be due to bladder holdup, which may be observed whenever circulating drug levels are rapidly fluctuating. This situation results in the quantity of drug voided during a time interval being influenced by some drug

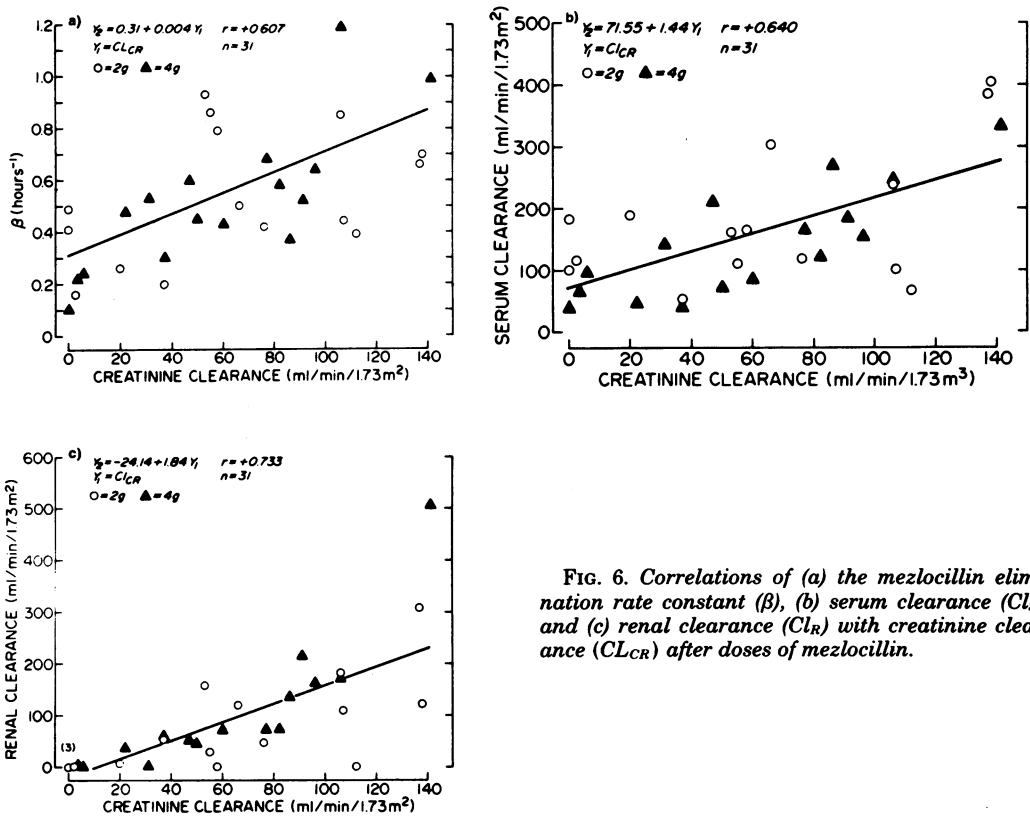

FIG. 6. *Correlations of (a) the mezlocillin elimination rate constant (β), (b) serum clearance (Cl_S), and (c) renal clearance (Cl_R) with creatinine clearance (CL_{CR}) after doses of mezlocillin.*

TABLE 5. *Results of linear regressions of some pharmacokinetic parameters against serum creatinine values*

Regression	Equation	*n*	*r*[a]	*P*
$t_{1/2}(\beta)$ vs S_{CR}	$Y_2 = 1.3 + 0.14\ Y_1$	31	+0.493	<0.01
V_1 vs S_{CR}	$Y_2 = 5.94 + 0.269\ Y_1$	31	+0.284	NS[b]
V_{dss} vs S_{CR}	$Y_2 = 14.05 + 0.710\ Y_1$	31	+0.424	<0.02

[a] Coefficient of correlation.
[b] $P > 0.05$.

which has entered the urine previously. The problem is aggravated when urine collection intervals are long relative to the drug elimination rate, an unavoidable situation in the present study, but appears to be less serious when the drug elimination rate is reduced, or less drug is voided in urine, as in groups II and III. It is noteworthy that Bergan et al. (2) obtained renal clearances of mezlocillin in two patients with normal renal function that were double the equivalent total body or serum clearances, despite the recovery of only 50% of the dose unchanged in urine.

The apparent increase in the mezlocillin distribution volume after the 2- and 4-g doses in severe renal impairment (Table 3) is difficult to explain. Apparent increases in drug distribution volumes have previously been reported for compounds which are highly bound to serum proteins, due to displacement of the drugs from the proteins by other substances, and consequent redistribution of the increased proportion of free drug into extravascular sites (13, 14). However, mezlocillin is only moderately bound to serum proteins, with reported values ranging from 16% (Investigators' Brochure: Mezlocillin [Bay f 135], Delbay Research, Bloomfield, N.J.) to 59% (17). Even at the higher of these values, it is unlikely that displacement of mezlocillin from proteins in uremic patients would lead to an observable increase in the apparent distribution volume (6).

Due to the relatively small effect that renal impairment has on the pharmacokinetics of mezlocillin, and also the adequate urinary levels of antibiotic in patients with variable renal func-

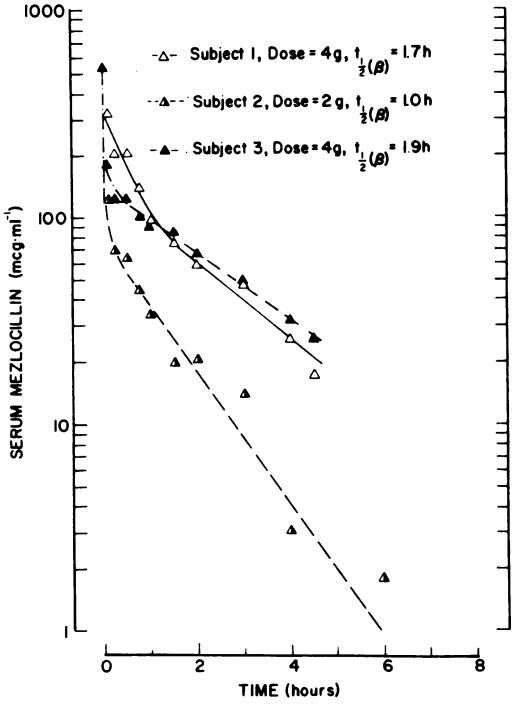

FIG. 7. *Serum levels of mezlocillin in three functionally anephric subjects during hemodialysis after single intravenous doses of 2 or 4 g of mezlocillin. The solid lines were generated from nonlinear regression analysis of the individual data sets.*

tion, it is inappropriate to suggest dose adjustment in patients other than those with severe renal impairment. In these patients some accumulation of antibiotic might be expected, particularly at higher dose levels, and dose adjustment may be necessary (15). Mezlocillin is readily and efficiently cleared from the circulation during hemodialysis.

LITERATURE CITED

1. **Bergan T.** 1978. Pharmacokinetics of mezlocillin in healthy volunteers. Antimicrob. Agents Chemother. **14**: 801-806.
2. **Bergan, T., E. K. Brodall, and E. Wilk-Larsen.** 1979. Mezlocillin pharmacokinetics in patients with normal and impaired renal functions. Antimicrob. Agents Chemother. **16**:651-654.
3. **Bodey, G. P., and T. Pan.** 1977. Mezlocillin: in vitro studies of a new broad-spectrum penicillin. Antimicrob. Agents Chemother. **11**:74-79.
4. **Bodey, G. P., C. Vallejos, and D. Stewart.** 1972. Flucloxacillin: A new semisynthetic isoxazolyl penicillin. Clin. Pharmacol. Ther. **13**:512-515.
5. **Cole, M., M. D. Kenig, and V. A. Hewitt.** 1973. Metabolism of penicillins to penicilloic acids and 6-aminopenicillanic acid in man and its significance in assessing penicillin absorption. Antimicrob. Agents Chemother. **3**:463-468.
6. **Craig, W. A., and P. G. Welling.** 1977. Protein binding of antimicrobials: Clinical pharmacokinetic and therapeutic implications. Clin. Pharmacokin. **2**:252-268.
7. **Jusko, W. J., and G. P. Lewis.** 1973. Comparison of ampicillin and hetacillin pharmacokinetics in man. J. Pharm. Sci. **62**:69-76.
8. **Kampmann, J., J. Mølholm Hansen, K. Siersboek-Nielsen, and H. Laursen.** 1972. Effect of some drugs on penicillin half-life in blood. Clin. Pharmacol. Ther. **13**:516-519.
9. **Neter, J., and W. Wasserman.** 1974. Applied Linear Statistics Models, p. 627-633. Richard D. Irwin, Inc., Homewood, Illinois.
10. **Pancoast, S. J., and H. C. Neu.** 1978. Kinetics of Mezlocillin and Carbenicillin. Clin. Pharmacol. Ther. **24**: 108-116.
11. **Rolinson, G. N.** 1973. Laboratory evaluation of amoxycillin. Chemotherapy **18**(Suppl.):1-10.
12. **Wagner, J. G.** 1975. Fundamentals of clinical pharmacokinetics, p. 82-101. Drug Intelligence Publications, Inc., Hamilton, Ill.
13. **Welling, P. G., W. A. Craig, G. L. Amidon, and C. M. Kunin.** 1973. The pharmacokinetics of trimethoprim and sulfamethoxazole in normal subjects and in patients with renal failure. J. Infect. Dis. **128**(Suppl.):S556-S566.
14. **Welling, P. G., W. A. Craig, G. L. Amidon, and C. M. Kunin.** 1974. Pharmacokinetics of cefazolin in normal and uremic subjects. Clin. Pharmacol. Ther. **15**:344-352.
15. **Welling, P. G., W. A. Craig, and C. M. Kunin.** 1975. Prediction of drug dosage in patients with renal failure using data derived from normal subjects. Clin. Pharmacol. Ther. **18**:45-52.
16. **White, G. W., J. B. Malow, V. M. Zimelis, H. Pahlavanzadeh, A. P. Panwalker, and G. G. Jackson.** 1979. Comparative in vitro activity of azlocillin, ampicillin, mezlocillin, piperacillin, and ticarcillin, alone and in combination with an aminoglycoside. Antimicrob. Agents Chemother. **15**:540-543.
17. **Wise, R., A. P. Gillet, J. M. Andrews, and K. A. Bedford.** 1978. Activity of azlocillin and mezlocillin against gram-negative organisms: Comparison with other penicillins. Antimicrob. Agents Chemother. **13**: 559-565.