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Mezlocillin Pharmacokinetics in Patients with Normal and Impaired Renal Functions

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The pharmacokinetics of intravenous bolus doses of 1.0 g of mezlocillin were studied in 13 persons with normal and reduced renal functions. In renal failure a moderate increase was observed for the terminal serum half-life ($t½\beta$). This changed from a mean of 1.1 h at a glomerular filtration rate of 100 ml/min to 1.6 h at 10 ml/min. The difference was not statistically significant. The excretion of unchanged drug in urine during 24 h was reduced from a mean of 59.4% (range, 52 to 77) in subjects with glomerular filtration rate above 50 ml/min to 10% (range, 7.9 to 12.1) in two patients with glomerular filtration rate of 10 to 20 ml/min. The volume of distribution during the β-phase, $V_{d,\beta}$, was 14% of the body weight. Much of the antibiotic was metabolized, and this proportion increased upon reduction in renal function.

Mezlocillin is one of the newer penicillins with broad-spectrum activity comprising multiresistant enterobacteria, anaerobes, and *Pseudomonas aeruginosa* (6). The pharmacokinetics have been studied in subjects with normal renal function (1, 5, 7, 8).

The present communication reports on pharmacokinetic changes with reduction in renal function.

MATERIALS AND METHODS

Antibiotic. Mezlocillin was received from Bayer Chemie AG, Leverkusen, West Germany. One dose of 1.0 g was given as a 10% aqueous solution by intravenous bolus (2-min) injection.

Patients. Studied were 13 informed volunteer patients referred to the Medical Department B for assessment of renal function (Table 1). Other antibacterial drugs were not given concomitantly. The patients were supine during the study.

Samples. Blood samples were withdrawn from a cubital vein (not same arm as used for injection) at 0, 0.5, 1, 2, 3.5, 6, 8, 12, and 24 h after medication. The zero-time sample was taken immediately after the injection was completed. Urine was collected for the periods 0 to 3, 3 to 4, 4 to 8, 8 to 12, and 12 to 24 h postprandially. A permanent urethral catheter and bladder lavage ensured complete recovery of urine for each time interval. Urine volumes were measured, and 10-ml samples were taken from each portion. Serum was separated within 1.5 h. All samples were stored at −20°C to avoid inactivation before assay.

Assay. The concentrations were determined by an agar diffusion technique, with well reservoirs filled with 0.5-ml samples and *Escherichia coli* as the test strain (3). Square plates (16 by 16 cm) with 16 holes and random distribution (Latin square) of standards and samples in triplicate were used. Incubation temperature was 37°C. The assay could measure down to 0.4 μg/ml. The experimental error was 3 to 7% of the observed levels.

Calculations. For pharmacokinetic evaluations, curve fitting was done with the AUTOAN 2/NONLIN program of Wagner, Sedman, and Metzler (9). For patients 5, 7, and 12, the best-curve fit was achieved by the first-order, one-compartment open model, whereas the majority of the curve fitting was best with the first-order, two-compartment open model. The values obtained from the two-compartment program were the rate constants for transfer from the central to the peripheral compartment (k_{12}), for transfer in the opposite direction (k_{21}), elimination from the central compartment (k_E), and sum of intercepts for each model compartment (c_o). The intercepts (A, B), hybrid rate constants (α, β), serum half-life during β-phase ($t½\beta$), total area under the serum curve till infinity (F), and total body clearance (Cl_B) were calculated by the method of Wagner (9) from the values derived from AUTOAN 2/NONLIN. For this purpose, an additional program developed by the Norwegian Computer Center, Oslo, was used. The renal clearance of mezlocillin was estimated as described previously (2).

Variance is indicated by standard deviation.

RESULTS

Serum concentrations. Initial concentrations ranged from 62.5 to 170 μg/ml, dropping to subdetectable levels after 8 to 24 h.

Urine concentrations. Urinary recovery of unchanged drug was lower with reduced than with normal renal function. Reduced urinary recovery of unchanged mezlocillin was only noted in patients with glomerular filtration rates

TABLE 1. *Characteristics of patients studied*

Patient no.	Sex	Wt (kg)	Age (yr)	Diagnosis	Renal clearance (ml/min)		
					Inulin	*para*-Aminohippuric acid	Creatinine[a]
1	M	76	20	Goodpastures syndrome	118	759	63
2	M	70	36	Glomerulonephritis chronica	116	538	110
3	M	81	51	Hypertensio arteriae gravis	56	180	28
4	F	53	16	Glomerulonephritis chronica	55	268	54
5	M	85	56	Hypertensio arteriae gravis	48	179	33
6	M	58	32	Enteritis regionalis, amyloidosis	41	239	32
7	F	68	33	Nephropathia diabetica	34	102	43
8	M	90	53	Hypertensio arteria gravis	33	146	52
9	M	66	15	Glomerulonephritis chronica	32	140	27
10	F	47	53	Granulomatosis Wegneri	27	146	45
11	F	45	51	Pyelonephritis chronica, lymphoma malignum (reticulosarcoma)	25	130	29
12	M	65	59	Myelomatosis	14	43	2
13	F	60	52	Periarteritis nodosa	11	30	ND[b]

[a] Twenty-four-hour values.
[b] ND, Not determined.

(GFR) below 50 ml/min. In the subjects with a better renal function, 59.4 ± 10.2% (range [*R*], 52.1 to 77.1) of the dose was recovered during 24 h. In the patients with GFR in the range 30 to 40 ml/min, the recovery was 40.3 ± 18.9% (*R*, 19.3 to 55.8%). The two patients within the GFR range of 20 to 30 ml/min excreted 19.1 and 39.0%, and the two with 10 to 20 ml/min excreted 7.9 and 12.1% of the dose.

Pharmacokinetic characteristics. Since the patients were heterogeneous regarding renal function, means for the whole group have not been computed. Hence, individual values are shown.

Table 2 shows the hybrid intercepts and rate constants of curves fitted to the two-compartment model. The rates of transport between compartments and distribution volumes were all within the same range regardless of renal function. The rate constant for passage from the central to the peripheral compartment, k_{12}, was 0.996 ± 0.501 (*R*, 0.303 to 2.000) h^{-1}, and the constant for passage in the opposite direction, k_{21}, was 0.322 ± 0.504 (*R*, 0.050 − 0.678) h^{-1}.

The constant of the overall elimination from the body (k_E), terminal serum half-life ($t_{1/2}\beta$), total area under the serum curves (F), overall body clearance (Cl_B), and renal clearance (Cl_{mez}) are shown in Table 3. It is apparent that the elimination rate is diminished only slightly in reduced renal function. The $t_{1/2}\beta$ values for the patients with the most reduced GFR were statistically not significantly different from those with normal renal functions. The relationship between the $t_{1/2}\beta$ and the glomerular filtration rate measured by inulin clearance is illustrated in Fig. 1.

TABLE 2. *Characteristics of mezlocillin plasma curves of individual patients given 1.0-g bolus intravenously*[a]

Patient no.[b]	*A*	*B*	α	β
1	277.55	20.42	2.666	0.424
2	118.70	131.14	2.358	0.929
3	71.93	15.40	1.196	0.584
4	114.27	17.35	0.944	0.392
6	97.51	5.79	1.733	0.480
8	99.33	62.36	1.271	0.630
9	220.26	49.70	1.799	0.659
10	220.36	10.52	2.069	0.552
11	92.83	116.62	1.516	0.408
13	61.70	59.52	0.957	0.498

[a] *A* and *B* are constants, and α and β are exponents of the polynomial describing the serum curves.
[b] In patients 5, 7, and 12 the serum curves followed a one-compartment course.

The central distribution volume was $V_c = 6.21$ ± 2.83 liters, the distribution volume at steady state was $V_{d,\ ss} = 7.52 \pm 2.58$ liters, the distribution during the β-phase was $V_{d,\ \beta} = 10.0 \pm$ 3.48 liters, or 14% of the body weight.

The k_E intercept with the ordinate in a Cl_l versus k_E diagram is at 0.337 h^{-1}. Since this equals the rate of elimination during anuria, this represents the rate of metabolization. It corresponds to a $t_{1/2}\beta$ of 2.1 h.

The total body clearance values were higher than the renal clearance values calculated from

TABLE 3. *Rate of elimination from the central compartment (k_E), terminal serum half-life ($t_{\frac{1}{2}\beta}$), area under the serum curve (F), total body clearance (Cl_B), and renal clearance (Cl_{mez})*

Patient no.	k_E (h^{-1})	$t_{\frac{1}{2}\beta}$ (h)	F ($\mu g \cdot h \cdot ml^{-1}$)	Cl_B		Cl_{mez} (ml/min)
				liter/h	ml/min	
1	1.958	1.6	152.2	6.57	109.5	220.8
2	1.304	0.7	191.6	5.22	87.0	182.8
3	0.642	1.2	136.0	7.35	122.5	32.3
4	0.110	1.6	165.2	6.05	100.8	44.4
5	0.586	1.2	231.2	4.32	72.0	19.4
6	0.500	1.4	206.6	4.84	80.7	79.9
7	0.504	1.4	213.7	4.68	78.0	53.3
8	0.913	1.1	177.1	5.00	83.0	69.0
9	1.365	1.1	197.8	5.06	84.3	ND[a]
10	0.571	1.3	404.1	2.47	41.2	6.5
11	0.603	1.7	347.4	2.88	48.0	36.0
12	0.446	1.6	180.0	5.56	92.7	2.1
13	0.659	1.4	184.0	5.44	90.7	5.4

[a] ND, Not determined.

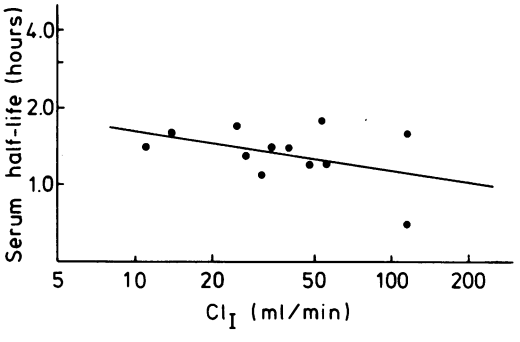

FIG. 1. *Relationship between serum half-life during β phase ($t_{½\beta}$) and inulin clearance (Cl_I).*

the urinary recovery in all but two subjects. These discrepancies are related to overestimates of amounts excreted. Proportionately, the Cl_B values are higher in relation to the plain renal clearances, Cl_{mez}, in patients with low GFR than in those with normal renal functions.

DISCUSSION

The serum levels reached in the present study correspond to concentrations noted in previous studies (1, 5, 7, 8). The relative volume of distribution, 14% of the body weight, was comparable to 15.2 and 14.4% reported previously.

In normal renal function, the terminal serum half-life after intravenous mezlocillin has been reported to be 1.0 h after 1.0 g (1), 0.8 h after 2.0 and 4.0 g (1, 8), 1.1 h after 3.0 g (5), and 1 and 1.2 h after 5.0 g (1, 7).

The serum half-life of mezlocillin is only moderately increased upon reduction in renal function. We found an increase in $t_{½\beta}$ from a regression mean of 1.1 h at GFR = 100 ml/min to 1.6 h with a GFR of 10 ml/min. Few data are available for comparison. Kosmidis et al., after administering 5.0 g intravenously, found a $t_{½}$ of 1.0 h for patients with a creatinine clearance (Cl_{cr}) above 80 ml/min and 3.0 h for the interval 10 to 30 ml/min (6). The pharmacokinetic estimations in our study of 1.0 g and that of Kosmidis et al. of 5.0 g were not carried out by identical approaches since a computer-assisted curve fitting was not reported for the 5.0-g study. The fact that lower serum half-life values were found with renal impairment in our patients than in those studied by Kosmidis et al. may, however, also be related to the fact that we gave a 4.0-g-lower dose. This is because the rate of elimination has exhibited a slight dose dependence in subjects with normal renal function, although this problem has not been studied directly in renal function impairment (1).

Since mezlocillin and azlocillin have a similar chemical structure and comparable pharmacokinetics in normals, it is interesting to see that the two compounds also appear similar in renal impairment. Thus, after administering 2.0 g of azlocillin, Fielder and Becker (4) observed a mean $t_{½}$ of 0.9 h for C_{cr} = 100 ml/min and 2.3 h for 10 ml/min.

The reason for the modest impact of renal function on elimination is probably that a major portion of the drug is eliminated or inactivated by extrarenal mechanisms. In normal volunteers, only 45 to 70% of the mezlocillin dose is excreted unchanged in the urine (1).

On the basis of our results with intravenous boluses of 1.0 g of mezlocillin intravenously, modification of the dosage would appear to be necessary only with a renal insufficiency below GFR = 10 ml/min. Then serum concentrations should be determined until further experience has been accumulated. This conclusion presupposes both that the toxicity of mezlocillin parallels that of other penicillins and that mezlocillin metabolites (not determined here) do not accumulate more than the parent compound.

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LITERATURE CITED

1. **Bergan, T.** 1978. Pharmacokinetics of mezlocillin in healthy volunteers. Antimicrob. Agents Chemother. **14**: 801-806.
2. **Bergan, T., E. K. Brodwall, and A. Øyri.** 1971. Renal excretion of gentamycin in chronic pyelonephritis. Acta Med. Scand. **189**:1-5.
3. **Bergan, T., and B. Øydvin.** 1972. Microbiological assay of josamycin. Acta Pathol. Microbiol. Scand. Sect. B **80**:101-106.

4. **Fiegel, P., and K. Becker.** 1978. Pharmacokinetics of azlocillin in persons with normal and impaired renal functions. Antimicrob. Agents Chemother. **14**:288–291.
5. **Issell, B. F., G. P. Bodey, and S. Weaver.** 1978. Clinical pharmacology of mezlocillin. Antimicrob. Agents Chemother. **13**:180–183.
6. **J. Kosmidis, V. P. Doundoulaki, Ch. Stathakis, N. Zerefos, A. Bounia, and G. K. Daikos.** 1979. Elimination kinetics of mezlocillin in normal and impaired renal function including the effect of dialysis, p. 174–181. lst Int. Symp. Acylureidopenicillins, Stuttgart 1978. Verlag für angewordte Wissenschaften, München 1978.
7. **Lode, H., U. Niestrath, P. Koeppe, and H. Langmaack.** 1977. Azlocillin und Mezlocillin: Zwei neue semisynthetische Acylureido-Penicilline. Infection **5**: 163–169.
8. **Pancoast, S. J., and H. C. Neu.** 1978. Kinetics of mezlocillin and carbenicillin. Clin. Pharmacol. Ther. **24**: 108–116.
9. **Wagner, J. G.** 1978. Fundamentals of clinical pharmacokinetics. Drug Intelligence Publications, Hamilton, Ill.