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Effect of Saturable Clearance During High-Dose Mezlocillin Therapy

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As mezlocillin has been shown to display nonlinear pharmacokinetics in single-dose evaluations, we evaluated a crossover trial in patients with renal dysfunction the impact on serum clearance of fixed-dose versus fixed-interval administration of identical daily doses of the drug. In four patients with creatinine clearances of 0.00 to 1.78 liters/h per 1.73 m^2, equal serum clearances were observed when the calculated daily total dose of mezlocillin was given either as a fixed dose of 5,000 mg at various intervals or every 4 h at various doses. We found that repetitive large daily doses that are equivalent to 30 g/day in patients with normal renal function can be administered to patients with impaired renal function as a reduced dose every 4 h instead of prolonging the dosing interval, as suggested by Mangione et al. (Antimicrob. Agents Chemother. 21:428–435, 1982). The observed serum clearances were equal for the two schedules, probably owing to the degree of continuing saturation of the nonlinear clearance mechanisms of mezlocillin.

The single-dose pharmacokinetics of mezlocillin has been well described (1, 5, 11) and shown to be nonlinear by Bergan (1). Because of this nonlinearity, Mangione et al. conducted a trial of single doses of 1 and 5 g administered to volunteers with renal dysfunction (10). They found, as did Bergan, that mezlocillin displayed nonlinearity with characteristics of saturation that showed significant differences in clearance (and, therefore, dose-normalized area under the curve) between the 1- and 5-g doses. The coefficients of distribution (V_c and V_{ss}) also differed significantly by dose size. Based on these findings, they recommended that dosage be adjusted for renal dysfunction by fixing the dose at 5,000 mg and altering the dosing interval. These adjustments in patients with renal dysfunction were deemed necessary to provide maximum (peak) and average (area under the curve divided by τ) concentrations over the course of a dose interval (τ) equivalent to those obtained with 5-g doses in patients with normal renal function.

Prediction of steady-state clearances and maintenance regimens from single-dose data requires the assumption that accumulation associated with repeated dosing will not significantly increase the degree of saturation of nonlinear mechanisms of elimination. In a randomized crossover trial of mezlocillin therapy in acutely infected, traumatized patients with renal dysfunction, we wished to characterize the effect on clearance of using a 5,000-mg dose with adjusted dosing intervals as compared with the same daily dose with a fixed dosing interval of 4 h.

MATERIALS AND METHODS

Patients. All patients were being treated at the Maryland Institute for Emergency Medical Services Systems for infections related to multiple trauma; at least three systems were compromised by their injuries. The study was approved by the Human Volunteers Research Committee of the University of Maryland School of Medicine, and informed consent was obtained.

Study design. As standard therapy in our unit, patients with normal renal function, here defined as a creatinine clearance greater than 4.2 liters/h per 1.73 m^2, receive 5 g of mezlocillin administered as a 30-min intravenous infusion every 4 h. Patients with renal impairment had a 12-h creatinine clearance determined (normalized to 1.73 m^2), and this value was inserted into the regression equation of Mangione et al. to produce a predicted normalized mezlocillin serum clearance (10). This was used to calculate a daily dose predicted to provide average steady-state levels equivalent to those achieved by 30 g per day in a patient with a creatinine clearance of 6 liters/h and body surface area (BSA) of 1.73 m^2. Equation 1 displays this calculation: grams per 24 h = (30 g/24 h) × [(serum clearance (pt)/9.59 liters per h per 1.73 m^2) × (BSA (pt)/1.73 m^2)].

The daily dose was rounded to the nearest multiple of 5 g, i.e., 5, 10, 15, or 20 g, and the patient was assigned by a table of random numbers of initially receive this total daily dose either as a fixed-dose (5,000 mg) or fixed-interval (4 h) regimen, both given as a 30-min intravenous infusion. The patient's serum concentration-time profile was allowed to approach the steady state; the patient received the regimen for at least 5 days before blood samples were taken. The therapy was crossed over to the other regimen. The patient was brought back to the steady state; a minimum of 4 days was allowed to elapse before samples were again taken. A 12-h creatinine clearance was determined within 24 h of each sampled interval. In no instance was a change in creatinine clearance greater than 10% of initial value noted.

Sample acquisition. After the steady state had been achieved on each regimen, samples of blood were obtained before the initiation of an infusion, immediately after the 30-min infusion, and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, and 3.5 h after the termination of the infusion. For patients with dosing intervals longer than 4 h, further samples were obtained every 2 h until the end of the interval. Specimens from the patient with a dosing interval of 24 h were obtained every 4 h after h 12. Samples were promptly centrifuged; the serum was separated and stored at −80°C until assayed.

Mezlocillin assay. Serum concentrations of mezlocillin were determined by high-pressure liquid chromatography by a refinement of a previously published method (8). This method was tested with standards and exhibited linearity between 6 and 600 μg/ml. The lower limit of detection was at

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TABLE 1. Patient characteristics

Paitent no.	Age (yr)	Sex	Height (in.)[a]	Weight (kg)	BSA[b] (m^2)	Creatinine clearance (liter/h per 1.73 m^2)	Infection
1	27	Female	63.0	54.6	1.57	1.78	*Pseudomonas pneumonia*
2	71	Male	66.0	55.7	1.66	1.31	*Pseudomonas* sp. urinary tract infection
3	27	Male	73.0	86.2	2.12	0.80	*Pseudomonas sepsis*
4	46	Male	69.0	72.9	1.91	0.00	Peritonitis

[a] One inch is ca. 2.5 cm.
[b] BSA, Body surface area.

least 1.6 μg/ml. Within-assay coefficients of variation were 1.6% at 600 μg/ml, 3.2% at 404 μg/ml, 3.0% at 235 μg/ml, 7.6% at 91.2 μg/ml, and 5.6% at 44.6 μg/ml. Between-assay variation was 3.5% at 416 μg/ml and 4.0% at 93.2 μg/ml. The method is described in detail elsewhere (4). All patients were also receiving an aminoglycoside, which did not interfere with the assay.

Pharmacokinetic analysis. Serum concentrations were fit to a one-compartment or two-compartment open model with elimination from the central compartment. Model parameters (K_{12}, K_{21}, K_{10}, V_c) were identified by an iterative, nonlinear least-squares weighted regression technique, a variant of the ADAPT package of D'Argenio and Schumitzky (3). Hybrid parameters (alpha, beta, V_{ss}, V_{area}) were calculated in a standard fashion (7). Because patients with renal dysfunction were to be sampled during short dose intervals (4 h) relative to their expected rate of elimination, microscopic rate constants defining the model are not always reliably identifiable. Consequently, for each patient, the area under the curve for the steady-state dosing interval was determined by the trapezoidal rule, and this value was divided into the administered dose to calculate the serum clearance. This will be referred to as the model independent determination (6).

RESULTS

Patient description. Four patients were studied with creatinine clearances between 0 and 1.78 liters/h per 1.73 m^2. No patients were receiving peritoneal dialysis or hemodialysis at the time of study. Patient characteristics are summarized in Table 1.

Pharmacokinetic parameters. Table 2 displays the serum concentrations determined for all patients on each regimen. Table 3 displays clearance values and areas under the curve as determined by the model independent method and as fitted by the weighted nonlinear least-squares regression technique on both fixed dose and fixed schedule with identical daily doses. The agreement between model dependent and independent methods was good. Of particular note is the extremely close agreement of the clearance values determined on fixed-dose and fixed-schedule regimens.

All data sets were well described by a two-compartment model. The microscopic and hybrid (derived) parameters estimated by a least squares regression are also shown in Table 3. Of particular interest is the wide range of values obtained for V_{area} and V_{ss}. These patients were critically ill, at least one having a leaky capillary syndrome; consequently, extremely variable volumes of distribution are not surprising. There is considerable intrapatient variation for both the volume terms and the terminal excretion half-life between the fixed-dose and fixed-interval regimens. Clearly, in three of the four patients, the terminal excretion half-life was long enough to preclude reliable determination of the parameter values in the fixed-interval arm. Therefore, the model independent estimation, which does not depend upon determination of the terminal excretion half-life, was of critical importance in validating the model dependent clearances.

TABLE 2. Serum concentrations of mezlocillin in traumatized patients receiving high-dose mezlocillin

Patient no.	Dose (mg)	Interval (h)	Serum concn of mazlocillin (μg/ml) at h posttreatment:										
			Pre-treatment	0	0.25	0.5	1.0	2.0	3.5	5.5	7.5	11.5	15.5	23.5
1	5,000	12	65.7	319	295	221	178	160	141	98.8	62.0	50.1		
	1,667	4	87.9	174	145	137	115	106	76.5					
2	5,000	8	269	860	437[a]	436	418	411	368	256	234			
	2,500	4	251	411	344	333	316	293	242					
3	5,000	12	29.9	257	190	188	175	142	106	72.8[b]	57.0	23.5		
	1,667	4	52.8	141	113	107	92.4	ND[c]	60.1					
4	5,000	24	115	296	272	264	240	214	202	192	185[d]	162[e]	155	124
	833	4	169	200	195	191	164	154	143					

[a] Actually drawn at 0.33 h.
[b] Actually drawn at 6.0 h.
[c] ND, Not drawn.
[d] Actually drawn at 6.5 h.
[e] Actually drawn at 9.75 h.

TABLE 3. Pharmacokinetic parameters for traumatized patients receiving high-dose mezlocillin

Patient no.	Dose (mg)	Interval (h)	Serum clearance (liters/h per 1.73 m^2)		V_c (liters/kg)	V_{area} (liters/kg)	V_{ss} (liters/kg)	α (h^{-1})	β (h^{-1})	$t_{1/2}\beta$ (h)	K12 (h^{-1})	K21 (h^{-1})	K10 (h^{-1})
			Model independent	Model dependent									
1	5,000	12	4.16	4.03	0.23	0.58	0.54	2.39	0.115	6.02	1.26	0.949	0.290
	1,667	4	4.02	4.04	0.20	0.48	0.46	3.96	0.139	4.98	2.15	1.60	0.344
2	5,000	8	1.82	1.90	0.05	0.39	0.38	23.45	0.085	8.13	19.82	3.06	0.654
	2,500	4	2.12	2.10	0.07	0.38	0.37	23.54	0.096	7.23	19.03	4.05	0.557
3	5,000	12	3.84	3.87	0.14	0.31	0.30	10.43	0.181	3.84	5.37	4.85	0.388
	1,667	4	3.72	3.83	0.09	0.25	0.24	9.55	0.221	3.14	5.65	3.52	0.599
4	5,000	24	1.16	1.14	0.35	0.70	0.68	0.823	0.025	27.99	0.388	0.411	0.050
	833	4	1.11	1.07	0.17	0.94	0.88	1.37	0.017	39.91	1.04	0.241	0.098

DISCUSSION

Mezlocillin is an acylureidopenicillin whose broad spectrum of activity makes it a useful compound for patients with mixed aerobic and anaerobic infections (9). Because many of the patients admitted to our unit are critically ill, doses and schedules of antibiotics are more aggressive than in other settings. We have routinely given 5 g of mezlocillin intravenously every 4 h to our patients who have required this drug. A number of our patients have experienced renal dysfunction related to their trauma, requiring an alteration of the dose. Beta-lactam antibiotics lack a post-antibiotic effect for aerobic or facultative gram-negative bacilli (2). Because of this, we attempt to maintain drug levels above the MIC of the offending pathogen throughout the dosing interval. Consequently, the recommendations of Mangione et al. to fix the dose and extend the dosing interval altering mezlocillin regimens for patients with renal dysfunction seemed a suboptimal solution. Rather, a shorter interval with a smaller dose seemed preferable.

To determine the impact of schedule on serum clearance, we compared the AUC at the steady state of fixed-dose versus fixed-interval dosage regimens. Utilizing a very large standard daily dose of mezlocillin (30 g), adjusting this dose for renal dysfunction and body size and having the patient serve as his own control, we found that serum clearances were equal.

We conclude that, although the pharmacokinetic behavior of mezlocillin is clearly nonlinear, when repetitively administering large doses of the drug the degree of continuing saturation of the nonlinear clearance mechanisms is such that a fixed-dose, variable-interval regimen is unnecessary. We would caution that these findings, until demonstrated at lower doses, can only be applied to regimens that are equivalent to the dose of 30 g per day per 1.73 m^2 used in our unit for patients with normal renal function. The regimen for patients with renal dysfunction may be calculated by equation 1 (see above). The estimation of the serum clearance for this calculation may be obtained from the regression equation of Mangione et al: drug clearance (liters/hour per 1.73 square meters) = 1.44 × normalized creatinine clearance + 0.95. The daily dose resulting from equation 1 may then be divided into any convenient schedule.

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