Clinical Pharmacology of Mezlocillin

BRIAN F. ISSELL,* GERALD P. BODEY, AND SUSANNE WEAVER

Department of Developmental Therapeutics, The University of Texas System Cancer Center M.D. Anderson
Hospital and Tumor Institute, Houston, Texas 77030

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Mezlocillin is a new broad-spectrum semisynthetic penicillin that has shown encouraging in vitro activity against the infecting organisms most likely to cause mortality and morbidity in cancer patients receiving chemotherapy. The serum clearances and urine recoveries of mezlocillin, ampicillin, and carbenicillin were compared after the intravenous administration of single 3-g doses. The peak mean serum concentrations of mezlocillin and carbenicillin were 269 and 278 $\mu\text{g/ml}$, respectively, whereas the peak ampicillin level was lower at 167 $\mu\text{g/ml}$. The terminal half-life of mezlocillin, 66 min, was not significantly different from those of ampicillin and carbenicillin (63 and 77 min, respectively). Recoveries of mezlocillin, ampicillin, and carbenicillin from urine over 6-h periods after drug dosage were 45, 61, and 80%, respectively. A further study in 11 cancer patients examined serum maintenance levels of mezlocillin when 3-g doses were given intravenously every 4 h for at least 7 consecutive days. After 3 days of therapy, the mean serum concentrations were maintained above 50 $\mu\text{g/ml}$. Although therapeutic efficacy was not an objective of this study, all of three documented bacterial infections were cured, and no serious toxicity was encountered.

Mezlocillin, {2S-[2 α , 5 α , 6 β (S)]}-3,3-dimethyl-6-[[[3-(methylsulfonyl)-2-oxo-1-imidazolidinyl]carbonyl]-amino]phenylacetyl]amino]-7-oxo-4-thia-1-azabicyclo(3,2,0)heptane-2-carboxylic acid, is a new semi-synthetic penicillin with a broad spectrum of antibacterial activity. In vitro testing showed mezlocillin to be more active than ampicillin, carbenicillin, and cephalothin against *Escherichia coli*, *Enterobacter* sp., *Serratia* sp., *Pseudomonas aeruginosa*, and indole-positive *Proteus* sp. It was as active as cephalothin and more active than ampicillin and carbenicillin against *Klebsiella* sp. and was active against *Proteus mirabilis* and gram-positive cocci, except penicillin G-resistant *Staphylococcus aureus* (5).

Klebsiella pneumoniae, *P. aeruginosa*, and *E. coli* are the major infecting organisms causing mortality and morbidity in cancer patients (4). Carbenicillin, which is active against *Pseudomonas* sp., is less active against *E. coli* and has no activity against *Klebsiella* sp. The most effective therapy for these infections has been with penicillin derivatives or cephalosporins combined with an aminoglycoside, which has the potential for serious nephrotoxicity (3, 15). Because of the need to develop more effective and less toxic antibiotics, serum clearance and urine recovery studies of mezlocillin were conducted.

MATERIALS AND METHODS

Pharmacology studies were conducted in 20 cancer patients with a median age of 45 years (range 18 to 73 years). There were 14 males and 9 females. In all patients, urinalysis, concentrations of urea nitrogen in whole blood, and concentrations of bilirubin and glutamic-oxaloacetic transaminase in serum were within normal limits when measured within 7 days of starting the studies.

Nine patients received single doses of mezlocillin, carbenicillin, or ampicillin via random assignment with an interval of at least 2 days between serial drug studies. Three grams of the respective agents, dissolved in 50 ml of 5% dextrose solution, was administered intravenously in a 15-min period. Blood samples were collected before drug administration and 0.25, 0.5, 1, 1.5, 2, 3, 4, and 6 h thereafter. Urine samples were collected immediately before drug dosage and used for base line control assays. Thereafter, all voided urine was collected for 6 h, and during this time it was stored at the bedside on ice. At the end of 6 h, the total volume was recorded, and a 10-ml sample was taken for assay.

A serum maintenance study was conducted in 11 patients who had developed fever of 101°F (ca. 38°C) or greater and were suspected of having infection. Patients received 3 g of mezlocillin administered intravenously in 100 ml of 5% dextrose solution over a 2-h period every 4 h for at least 7 days. Blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, and 4 h on days 1, 3, and 7.

Concentrations of antibiotics were determined by an agar well method (10). For mezlocillin and ampicil-

lin, a spore suspension of *Bacillus subtilis* (Difco Laboratories) was used. For carbenicillin, the test organism was *P. aeruginosa* (Ellsworth 1973 MCTC 10490). The standard curve was prepared by mixing the corresponding penicillin in pooled human serum or phosphate buffer (for urine samples). For mezlocillin, final concentrations of 25, 20, 15, 10, and 5 $\mu\text{g/ml}$ were used; for ampicillin, final concentrations of 2.5, 2.0, 1.5, 1.0, and 0.5 $\mu\text{g/ml}$ were used; and, for carbenicillin, final concentrations of 100, 40, 20, 10, and 5 $\mu\text{g/ml}$ were used. Samples to be analyzed were diluted with either serum (for serum samples) or phosphate buffer (for urine samples) until concentrations were in the standard curve range. A standard curve was prepared every time samples were assayed, and all assays were determined in triplicate.

The terminal serum half-life of each penicillin after intravenous administration was determined according to the best curve fitting by linear regression analysis (courtesy of Ti Li Loo). For mezlocillin, the formula was $C_2 = 113.07 \exp. (-0.6150t)$; for carbenicillin, the formula was $C_2 = 221.13 \exp. (-0.009t)$; and for ampicillin, it was $C_2 = 80.763 \exp. (-0.011t)$; where C_2 is drug concentration in $\mu\text{g/ml}$ and t is time in minutes. The differences between the serum concentrations of mezlocillin and the other penicillins at each sampled time were subjected to statistical analysis by Student's t test for each of the nine patients.

RESULTS

The serum concentrations at 0.25 h after rapid intravenous injection of 3-g doses of mezlocillin, carbenicillin, and ampicillin were 269, 278, and 147 $\mu\text{g/ml}$, respectively (Fig. 1). Mean serum concentrations of these drugs were 10, 25, and 6 $\mu\text{g/ml}$ at 4 h and 3, 7, and 2 $\mu\text{g/ml}$ at 6 h. The terminal half-life of mezlocillin was 66 min and was not significantly different from that of ampicillin or carbenicillin (63 and 77 min, respectively) when statistically analyzed as previously described. For mezlocillin compared with ampicillin, the P values ranged from 0.1 to 0.06, and, for mezlocillin compared with carbenicillin, the P values ranged from 0.3 to 0.2.

There were differences in the urinary excretion of the three penicillins during the 6-h observation, with recoveries ranging from 45% of the administered dose for mezlocillin to 61 and 80% for ampicillin and carbenicillin, respectively (Table 1). These differences in recovery were not due to differences of antibiotic stability. Each drug was added to fresh pooled human

urine and allowed to stand under the same conditions as for the study; 88% of mezlocillin, 83% of ampicillin, and 83% of carbenicillin were recoverable after 6 h.

Figure 2 shows the results of the serum maintenance study. The mean peak serum concentrations were achieved at 2 h and were over 100 $\mu\text{g/ml}$. Day 3 and day 7 studies showed mean serum levels maintained above 50 $\mu\text{g/ml}$ at all sampled times. Also, the levels on these days were almost identical, revealing no evidence of drug accumulation.

Although the objective of this study was not to determine therapeutic efficacy, 3 of the 11 patients on the serum maintenance study had documented bacterial infections and were cured.

FIG. 1. Serum clearance study of mezlocillin compared with carbenicillin and ampicillin in nine patients after single 3-g intravenous doses.

TABLE 1. 6-h urinary excretion of mezlocillin, ampicillin, and carbenicillin (3-g intravenous dosage)

Drug	Excretion (g) ^a	% Dose ^a	Mean urinary concn ($\mu\text{g/ml}$) ^a
Mezlocillin	1.34 (1.06–1.80)	45 (35–60)	3,442 (1,215–7,100)
Ampicillin	1.82 (1.02–2.18)	61 (34–73)	3,967 (1,400–9,000)
Carbenicillin	2.39 (1.60–2.88)	80 (53–96)	4,165 (1,400–5,900)

^a Numbers in parentheses indicate range.

FIG. 2. Serum maintenance study of mezlocillin in 11 patients given 3-g intravenous doses over 2 h every 4 h for 7 days.

These included one *P. aeruginosa* septicemia, one *K. pneumoniae* urinary tract infection, and one *S. aureus* pneumonia and empyema. The remaining eight patients had fever of unknown origin, which resolved during the study. No evidence of acute toxicity associated with mezlocillin dosage was observed. During the serum maintenance study, one patient had a 4+ sulfosalicylic acid test for proteinuria documented on day 4 and day 6 of antibiotic administration. Unfortunately, other tests for proteinuria were not completed. However, this was not associated with change in voided volume, abnormal urine microscopy, or deterioration of blood urea nitrogen and serum creatinine. Also no abnormality was found on retesting 72 h after mezlocillin was discontinued.

DISCUSSION

In the comparative single-dose serum clearance study, the mean peak serum level of mezlocillin was higher than that of ampicillin and similar to that of carbenicillin. The terminal half-life of mezlocillin, however, was not significantly different from that of ampicillin or carbenicillin. The half-lives of ampicillin and carbenicillin in this study are of the same order as

those previously reported for these penicillins (2, 9, 12).

The 6-h urine recovery of mezlocillin was the lowest and was closer to that of ampicillin than to that of carbenicillin. Mezlocillin, like ampicillin but unlike carbenicillin, has been shown to have significant biliary excretion. Gundert and co-workers found that between 20 and 25% of intravenous doses of mezlocillin was excreted in the bile of patients with T tube drainage over 8-h observation periods (U. Gundert, D. Forster, and P. Schacht, Abstract, 10th Int. Cong. Chemother., September, 1977, Zurich, Switzerland). Pinget and associates report ampicillin to be moderately excreted (4.1% of the administered dose over 12 h of observation) and carbenicillin to be poorly excreted in the bile (14). These differences in nonrenal excretion may in part account for the differences we found in urine recovery.

The serum concentrations achieved with the multiple-dose schedule in 14 patients exceeded the minimum inhibitory concentrations for all isolates of gram-positive cocci, excluding penicillin G-resistant *S. aureus*, 85% of isolates of *P. aeruginosa*, 75% of *Klebsiella* sp., and 65% of *E. coli*, *Enterobacter* sp. and *Serratia marcescens* (5). Also, this level should be effective against 70% of isolates of *Bacteroides fragilis* and most other anaerobic bacteria (17).

The only mezlocillin-associated abnormality observed was positive sulfosalicylic acid testing for proteinuria in one patient. This was fully reversible and was not associated with any other recognized renal abnormality. The renal toxicity of penicillins resulting in interstitial nephritis and occasionally in renal failure is well described (1, 6-8, 11, 16). However, proteinuria without any other associated abnormalities of renal function is unusual. Observations of further patients receiving mezlocillin at our institution suggest that this may represent a pseudoproteinuria, which has been reported with another penicillin, nafcillin (13). Further careful and more extensive observations of renal function are currently being undertaken in patients receiving this drug.

Mezlocillin appears to be a penicillin with a wide range of activity against the bacteria that are most likely to result in morbidity and mortality in the cancer patient population. Therapeutic blood levels are readily achieved, and no serious toxicity has been encountered. The three infections treated in this study responded. A further study critically evaluating the therapeutic efficacy of this antibiotic is active at our institution.

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