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Antimicrob. Agents Chemother. **1997, 41(11):2511.**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1997, p. 2511–2517 Vol. 41, No. 11
0066-4804/97/$04.00+0

Pharmacokinetics and Pharmacodynamics of Two Multiple-Dose Piperacillin-Tazobactam Regimens

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Received 28 August 1996/Returned for modification 27 February 1997/Accepted 31 August 1997

The pharmacokinetics and pharmacodynamics of two multiple-dose regimens of piperacillin-tazobactam (3.375 g every 6 h and 4.5 g every 8 h) were evaluated at steady state for 12 healthy adult volunteers. Inhibitory and bactericidal activities for the two regimens were determined with five American Type Culture Collection (ATCC) organisms (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*). The percentage of time that plasma concentrations remained above the MIC ($T > MIC$) for each organism and dosage regimen was calculated. Areas under the inhibitory ($AUIC_{0–24}$) and bactericidal activity ($AUBC_{0–24}$) curves were calculated with the trapezoidal rule by using the reciprocal of the inhibitory and bactericidal titers determined for each dosage regimen. In order to assess the validity of predicted measures of bactericidal ($AUC_{0–24}$/MBC) and inhibitory ($AUC_{0–24}$/MIC) activity to determine bacteriological response to β-lactam antimicrobial agents, $AUC_{0–24}$/MBC and $AUC_{0–24}$/MIC values were compared with measured $AUBC_{0–24}$ and $AUIC_{0–24}$ values. Total body clearance values were equivalent for piperacillin (183.96 ± 22.66 versus 181.72 ± 19.54 ml/min/1.73 m^2, $P > 0.05$) and tazobactam (184.71 ± 19.89 versus 184.87 ± 18.35 ml/min/1.73 m^2, $P > 0.05$) following the administration of the 3.375-g-every-6-h and 4.5-g-every-8-h dosages, respectively. Comparison of area under the plasma concentration-time curve ($AUC_{0–24}$) for piperacillin (967.74 ± 135.56 μg · h/ml versus 978.88 ± 140.96 μg · h/ml) and tazobactam (120.14 ± 15.78 μg · h/ml versus 120.01 ± 16.22 μg · h/ml) revealed no significant differences ($P > 0.05$) between the 3.375-g-every-6-h and 4.5-g-every-8-h regimens, respectively. Both regimens provided $T > MIC$ values of > 60% for all organisms tested. Measured values of bactericidal (AUBC) and inhibitory (AUIC) activity were significantly different ($P < 0.05$) from predicted values ($AUC_{0–24}$/MBC and $AUC_{0–24}$/MIC) for all organisms studied with the exception of the bactericidal activity for *P. aeruginosa* and *S. aureus*. Additionally, ATCC organisms possessing the same MICs and MBCs exhibited great differences in measured $AUBC_{0–24}$ and $AUIC_{0–24}$ values. Reasons for this difference may be inherent differences in organism specific susceptibility.

Antimicrobial resistance due to gram-negative β-lactamase enzymes continues to contribute to the morbidity of hospitalized patients (8, 25). Piperacillin-tazobactam is a β-lactam–β-lactamase inhibitor combination that has demonstrated antimicrobial activity against β-lactamase-producing strains of *Haemophilus influenzae*, *Staphylococcus aureus*, *Bacteroides* species, and members of the family *Enterobacteriaceae* (11, 12, 18, 27). Tazobactam appears to cause less induction of Richmond-Sykes type I β-lactamase enzymes than clavulanic acid and has a broader spectrum of activity against plasmid-mediated enzymes than sulbactam (15, 28). Piperacillin-tazobactam has demonstrated clinical efficacy in the treatment of intra-abdominal, skin and soft tissue, lower respiratory tract, and gynecological infections (6, 20, 27, 29, 30).

Similar to other ureidopenicillins, piperacillin exhibits disproportionate increases in area under the serum concentration-time curves (AUC) and decreases in total body clearance (CL) with incremental dosage increases (2, 4, 30). Decreases in CL have been attributed to saturation of tubular secretion mechanisms and alterations in metabolic transformation. Consequently, increases in elimination half-life ($t_{1/2\beta}$) may allow the administration of larger doses at longer dosing intervals to achieve equivalent AUC. A regimen that provides sustained concentrations of piperacillin over the dosing interval is desired, as maximization of the time above the MIC for a pathogen has been shown to correlate with β-lactam antimicrobial efficacy (9).

Area under the bactericidal curve (AUBC) and area under the inhibitory curve (AUIC) are terms that have been used to integrate pharmacokinetic and pharmacodynamic properties of antimicrobial agents (1, 26). AUBC and AUIC values are calculated by the trapezoidal rule by using the inverse of the bactericidal and inhibitory titers at different time points following antibiotic administration. $AUBC_{0–24}$ and $AUIC_{0–24}$ values have been suggested to be predictive of microbiologic response to β-lactam antibiotics because they consider not only the magnitude but also the duration of antimicrobial activity (14). Predicted measures of $AUBC_{0–24}$ and $AUIC_{0–24}$, calculated by dividing the AUC by the MIC and MBC ($AUC_{0–24}$/MBC and $AUC_{0–24}$/MIC), have been shown to correlate with measured $AUBC_{0–24}$ and $AUIC_{0–24}$ values for ciprofloxacin (14).

The purpose of this investigation was to evaluate the steady-state pharmacokinetics of piperacillin-tazobactam administered as dosage regimens of 4.5 g every 8 h (q8h) and 3.375 g every 6 h (q6h) and to determine the bactericidal and inhibitory activity of these two regimens against American Type

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Culture Collection (ATCC) strains of *Escherichia coli*, *S. aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*. In order to assess the validity of AUC_{0-24}/MBC and AUC_{0-24}/MIC values in determining the bacteriological response to β-lactam antimicrobial agents, predicted measures of bactericidal (AUC_{0-24}/MBC) and inhibitory (AUC_{0-24}/MIC) activity were determined and compared with measured $AUBC_{0-24}$ and $AUIC_{0-24}$ values for each organism.

MATERIALS AND METHODS

Study subjects. Twelve healthy male volunteers participated in the two-way randomized crossover study following written informed consent. The protocol was approved by the Institutional Review Board at The University of Illinois at Chicago. All subjects underwent general examination within 4 weeks of initiation of the study, which included a complete medical history, physical examination, and clinical laboratory testing (complete blood count with differential, serum chemistries, and urinalysis). All subjects were within ±15% of their ideal body weight for their ages and heights according to the Metropolitan Life Insurance Company (19). Renal function was evaluated during both phases of the study by 24-h urine collections for measurement of creatinine clearance.

Exclusion criteria included history or clinical evidence of hepatic or renal disease, abnormalities in baseline chemistries, and history of allergic responses to β-lactam antibiotics or β-lactamase inhibitors. Subjects were required to take no other medications for 1 week prior to and during the study period. Alcohol-, xanthine-, and caffeine-containing food and beverages were prohibited for 48 h before and during the study period. Standardized meals were provided during each study period.

Methodology. Subjects were admitted and housed overnight in the University of Illinois Clinical Pharmacy Research Unit for two 72-h periods. Each subject received 3.375 g of piperacillin-tazobactam (Zosyn; Lederle Laboratories, Division of American Cyanamid Company, Wayne, N.J.) administered q6h for 72 h and 4.5 g of piperacillin-tazobactam administered q8h for 72 h in random order separated by a minimum 4-day washout period. Piperacillin-tazobactam (lot no. F91-111-006AA) multiple-dose vials were reconstituted according to the manufacturer's recommendations and further diluted to a total volume of 50 ml with 0.9% normal saline. Piperacillin-tazobactam was administered through a peripheral venous catheter over 30 min via a constant-rate infusion pump.

Blood samples for pharmacokinetic and pharmacodynamic analysis were obtained through an indwelling peripheral venous catheter placed in the arm contralateral to that used for the infusion of piperacillin-tazobactam. Indwelling catheters were kept patent via intermittent injections of heparin. Blood samples were collected over 24 h, during the dosing periods between 48.0 and 72.0 h. Blood samples for pharmacokinetic analysis were obtained at the following times during the administration of piperacillin-tazobactam at 3.375 g q6h: 0 (prior to administration), 48.0, 48.5, 48.67, 49.25, 51.0, 52.5, 54.0, 54.5, 54.67, 56.0, 58.0, 60.0, 60.5, 60.67, 61.25, 65.0, 66.0, 66.5, 66.67, 66.92, 67.25, 68.0, 70.0, and 72.0 h. Bactericidal activity was assessed from samples obtained during the last dosing interval at times 66.5 (peak), 68.0 and 70.0 (two midpoints), and 72.0 (trough) h. Blood samples for pharmacokinetic analysis were obtained at the following times during the administration of piperacillin-tazobactam at 4.5 g q8h: 0 (prior to administration), 48.0, 48.5, 48.67, 48.92, 49.25, 50.0, 52.0, 54.0, 56.0, 56.5, 56.67, 56.92, 57.25, 59.0, 61.0, 64.0, 64.5, 64.67, 64.92, 65.25, 66.0, 68.0, 70.0, and 72.0 h. Bactericidal activity was assessed from samples obtained during the last dosing interval at times 64.5 (peak), 68.0 and 70.0 (two midpoints), and 72.0 (trough) h. All samples were collected in heparinized tubes and centrifuged immediately. Plasma was transferred and stored in two aliquots in sterile glass tubes at −70°C until analysis.

A baseline urine sample was obtained prior to the administration of piperacillin-tazobactam during both phases of the study. Urine was collected at the following intervals during the administration of piperacillin-tazobactam at 3.375 g q6h: 48 to 54, 54 to 60, 60 to 66, and 66 to 72 h; it was collected at 48 to 56, 56 to 64, and 64 to 72 h during the administration of piperacillin-tazobactam at 4.5 g q8h. The total volume of urine was recorded following each interval collection, and a 15-ml aliquot was removed. All urine samples were stored in sterile polypropylene tubes and frozen at −70°C until analysis.

Piperacillin and tazobactam analytical procedure. Piperacillin and tazobactam concentrations in plasma or urine were analyzed simultaneously by a reversed-phase high-performance liquid chromatographic (HPLC) assay at the University of Illinois Clinical Research Laboratory. Analytical powders of tazobactam sodium (lot no. 6818b46) and piperacillin sodium (lot no. 317-704) were obtained from Lederle Laboratories (Division of American Cyanamid Company, Pearl River, N.Y.). The HPLC procedure was based on the method reported by Ocampo et al. (24) and on bioanalytical method no. M298741.6, Medical Research Division, Bioanalytical Support Department, American Cyanamid Laboratory.

Separation was achieved on a Hypersil C_{18} column (7-μm particle size, 4.6 by 250 mm) (Keystone Scientific, Bellefonte, Pa.) with a gradient elution. Mobile phase A consisted of acetonitrile-water (3:97 [vol/vol]) containing 0.01 M NaH_2PO_4, adjusted to pH 2.7. Mobile phase B was acetonitrile-water (90:10 [vol/vol]) containing 0.01 M NaH_2PO_4, adjusted to pH 2.7. The flow rate was 1.5 ml/min. The chromatograms were generated with a linear gradient program of 98% eluent A and 2% eluent B to 60% eluent A and 40% eluent B in 9 min and a final linear step to 98% eluent A and 2% eluent B in 4 min. Total run time was set to 20 min. The HPLC system consisted of a Waters 600E system controller and pump, a Waters 712 WISP, and a Waters 490E programmable multiwavelength detector set at 220 nm (Waters Associates, Milford, Mass.). The detector signal was quantitated to give peak heights by using an HP3359 laboratory automation system (Hewlett-Packard, Paramus, N.J.).

To 200 μl of plasma sample was added 200 μl of internal standard solution (25 μg/ml) in buffer (0.05 M NaH_2PO_4, pH 6.0). Acetonitrile (800 μl) was added to precipitate proteins. The internal standard was benzylpenicillin potassium (lot no. 12H0275; Sigma Chemical Company, St. Louis, Mo.). The sample was then vortex mixed for 30 s and centrifuged for 10 min. The resultant supernatant was removed and transferred to a conical test tube to which 2.0 ml of dichloromethane was added. Each tube was then vortex mixed for 30 s and centrifuged for 10 min. The upper aqueous layer was then transferred to an autosampler vial, and 25 μl was injected onto the column. Retention times for tazobactam, piperacillin, and the internal standard were 6, 14, and 15 min, respectively.

The assay was linear over the concentration range of 0.5 to 200 μg/ml for tazobactam and 0.5 to 200 μg/ml for piperacillin. The minimum quantifiable concentration in plasma was 0.510 μg of tazobactam per ml and 0.50 μg of piperacillin per ml. Interday percent coefficients of variation (CV) for tazobactam in plasma ($n = 3$) were as follows: 159 μg/ml, 3.66%; 84.9 μg/ml, 2.53%; 7.95 μg/ml, 1.76%. Those for piperacillin in plasma ($n = 3$) were as follows: 152 μg/ml, 0.38%; 75.8 μg/ml, 1.22%; 7.60 μg/ml, 3.16%. Intraday CV for tazobactam ($n = 7$) were as follows: 157 μg/ml, 1.63%; 83.7 μg/ml, 3.19%; 7.88 μg/ml, 3.68%. Those for piperacillin ($n = 7$) were as follows: 391 μg/ml, 1.95%; 150 μg/ml, 1.85%; 75.2 μg/ml, 2.56%; 7.50 μg/ml, 1.53%.

To 40 μl of urine sample, 50 μl of internal standard solution, benzylpenicillin potassium (4.0 mg/ml in 0.05 M NaH_2PO_4, pH 6.0), and 3.91 ml of buffer (0.05 M NaH_2PO_4, pH 6.0) were added. The sample was vortex mixed for 10 s and transferred to an autosampler vial, and 25 μl was injected onto the HPLC column. Compounds were eluted by using the same gradient as that described for the plasma assays.

The urine assay was linear over the concentration range of 0.05 to 10 mg/ml for both tazobactam and piperacillin. The minimum quantifiable concentration in urine was 0.05 mg of both tazobactam and piperacillin per ml. Interday CV for urinary tazobactam ($n = 7$) were as follows: 7.41 mg/ml, 2.47%; 1.98 mg/ml, 2.69%; 0.148 mg/ml, 5.34%. Those for urinary piperacillin ($n = 7$) were as follows: 7.58 mg/ml, 2.76%; 2.02 mg/ml, 2.94%; 0.152 mg/ml, 2.92%. Intraday CV for urinary tazobactam ($n = 7$) were as follows: 7.41 mg/ml, 2.53%; 1.98 mg/ml, 3.43%; 0.148 mg/ml, 1.61%. Those for piperacillin ($n = 7$) were as follows: 7.58 mg/ml, 2.58%; 2.02 mg/ml, 3.26%; 0.152 mg/ml, 3.46%.

Pharmacokinetic analysis. Compartmental and noncompartmental pharmacokinetic methods were used to estimate pharmacokinetic parameters for both piperacillin and tazobactam. Initial parameter estimates (e.g., R, S, α, and β) were obtained with the microcomputer program RSTRIP (Micromath, Salt Lake City, Utah). Final estimates of these parameters were calculated by a nonlinear iterative least-squares method with a weighting factor of 1/y (PCNONLIN; SCI Software, Lexington, Ky.). The model fit was evaluated by the Akaike information criterion, plots of observed versus weighted predicted concentrations, and the sum of the squared residuals. The plasma concentration-versus-time data were best analyzed with a two-compartment open infusion model. The maximum concentration (C_{max}) was determined by visual inspection of the observed concentration-versus-time curve for each subject.

The area under the plasma concentration-time curve during the 24-h sampling period (AUC_{0-24}) and area under the first-moment curves were calculated by the trapezoidal method. The volume of distribution at steady state (V_{SS}) was corrected for steady-state dosing according to the method of Bauer and Gibaldi (3). CL was calculated from the equation $CL = dose/AUC_{0-24}$. The elimination half-life ($t_{1/2\beta}$) was calculated by dividing the natural logarithm of 2 by β. Renal clearance (CL_R) was calculated from the total quantity of drug appearing in the urine during the 24-h period divided by AUC_{0-24}. Nonrenal clearance (CL_{NR}) was estimated by subtracting the CL_R from the CL.

Microbiologic procedures. The MIC and MBC of piperacillin-tazobactam were determined for six quality control organisms by the microdilution method recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (22). The following American Type Culture Collection (ATCC) strains were tested: *S. aureus* 25923, *E. coli* 25922, *E. coli* 35218 (β-lactamase$^+$), *K. pneumoniae* 13882, *P. aeruginosa* 27853, and *B. fragilis* 25285. All organisms underwent three passages on nonselective medium prior to testing.

A stock solution of piperacillin was prepared according to NCCLS guidelines and stored at −70°C in polyethylene vials until used. Serial twofold dilutions of piperacillin were prepared in cation-supplemented (Ca^{2+}, 50 mg/liter; Mg^{2+}, 25 mg/liter) Mueller-Hinton broth (Oxoid Unipath, Ogdensburg, N.Y.). A stock solution of tazobactam was prepared according to NCCLS guidelines for sulbactam. An equal volume of tazobactam (concentration, 16 μg/ml) was added to each piperacillin dilution. A 50-μl sample of each dilution of the piperacillin-tazobactam combination was added to a 96-well microtiter plate via an eight-channel multipipetter (EDP-Plus M8; Rainin, Woburn, Mass.). A growth well containing no antibiotic was included in the assay. Final antibiotic concentrations

following the addition of the bacterial inoculum ranged from 0.0625 and 4 to 64 and 4 μg/ml for the piperacillin-tazobactam combination, respectively. The inoculum was prepared by adding isolated colonies from 24-h cultures to Trypticase soy broth (Micro Diagnostics, Lombard, Ill.), which was incubated at 35°C on a platform shaker for 3 to 5 h to obtain log-phase growth. The bacterial suspensions were diluted to match a 0.5 McFarland turbidity standard and then further diluted 1:100 with normal saline. A 50-μl sample was added to each antibiotic dilution, resulting in a final inoculum of approximately 5×10^5 CFU/ml. Plate counts were performed to determine the exact inoculum density.

MICs were determined for the aerobic organisms after 24 h of incubation at 35°C. The MIC for *B. fragilis* was read after 48 h of incubation at 35°C in an anaerobic pouch (BBL GasPakPouch; Becton Dickinson, Cockeysville, Md.). The MIC was read as the lowest antibiotic concentration showing no visible turbidity in the microtiter plate wells. For MBC determinations, a 25-μl sample from each clear well was removed with an EDP-Plus micropipetter and inoculated onto a whole-blood agar plate (aerobes) or Centers for Disease Control and Prevention anaerobic blood agar plate (*B. fragilis*). After the sample dried, the plates were streaked in three planes and incubated at 35°C. Colonies were counted at 24 and 48 h for the aerobic organisms. Colony counts were determined for *B. fragilis* after 48 and 72 h of anaerobic incubation. The MBC endpoint was defined as the plate showing >99.9% killing of the inoculum.

Bactericidal activity for the two regimens was determined in duplicate by the microdilution method recommended by the NCCLS (21). Bactericidal titers ranging from 1:2 to 1:512 were determined with serial twofold dilutions of human plasma and cation-supplemented Mueller-Hinton broth (50:50). Bacterial suspensions were prepared as described above for MICs. All serum samples from a given subject were assayed simultaneously, with the same inoculum used for both regimens. A total of 576 bactericidal titers were determined. All microtiter plates were covered to prevent evaporation, stacked in rows of four or fewer plates, and incubated at 35°C. Microtiter plates used for testing *B. fragilis* were incubated at 35°C in an anaerobic pouch. Inhibitory endpoints were read as described above for MICs. The bactericidal titer was determined by the same methods as used for the MBC. All assays were performed at the University of Illinois College of Pharmacy Microbiology Research Laboratory.

The percentage of time that concentrations in plasma remained above the MIC ($T > \text{MIC}$) for a 24-h dosing period was calculated for each dosage regimen between 48 and 72 h. Mean bactericidal titers at each time point were determined by assigning an ordinal number to each reciprocal titer (e.g., < 1:2, 0; 1:2, 1; 1:4, 2;. . .1:512, 10). These ordinal numbers were averaged for each subject, organism, regimen, and sampling time and rounded to the nearest whole number. Mean values were then reconverted to the corresponding reciprocal bactericidal or inhibitory titer (10).

The measured area under the bactericidal activity-versus-time curve ($AUBC_{0-T}$) and the area under the inhibitory activity-versus-time curve ($AUIC_{0-T}$) were determined by using the trapezoidal rule and the inverse plasma bactericidal or inhibitory titers obtained during the last dosing interval of each regimen (e.g., 66 to 72 h for the q6h regimen and 64 to 72 h for the q8h regimen). $AUBC_{0-24}$ and $AUIC_{0-24}$ were calculated by multiplying the number of doses given per day by $AUBC_{0-T}$ and $AUIC_{0-T}$. Predicted AUC_{0-T}/MBC and AUC_{0-T}/MIC values were calculated by dividing AUC of piperacillin concentrations in plasma obtained during the last dosing interval at the same time points as used for bactericidal analysis by the MBC and MIC for each organism. The AUC for the last dosing interval of each regimen was calculated by the trapezoidal rule. Predicted AUC_{0-24}/MBC and AUC_{0-24}/MIC values were calculated by multiplying the AUC_{0-T}/MBC and AUC_{0-T}/MIC by the number of doses administered per day.

Statistical analysis. Differences in mean pharmacokinetic parameters were determined by analysis of variance (ANOVA) methods with treatment period, sequence, and subject within sequence as factors (5). Sequence effects were analyzed by using the subject-within-sequence mean squares as the error term. Treatment means were compared by a two-sided test with an alpha level of 0.05. The power to detect 20% differences between the treatments was calculated by a two-sided test with an alpha level of 0.05 (32). Differences in bactericidal ($AUBC_{0-24}$) and inhibitory ($AUIC_{0-24}$) activity between the two multiple-dose regimens were determined by a paired *t* test. Differences between measured ($AUBC_{0-24}$) and predicted (AUC_{0-24}/MBC) bactericidal activity and measured ($AUIC_{0-24}$) and predicted (AUC_{0-24}/MIC) inhibitory activity for the two regimens were also determined by a paired *t* test. A *P* value of <0.05 was considered statistically significant.

RESULTS

The subjects ranged in age from 23 to 30 years (mean, 25 years) and in weight from 60.4 to 96.3 kg (mean, 78.4 kg). Creatinine clearance values ranged from 94.1 to 134.1 ml/min/1.73 m^2 for the 12 subjects studied. Subjects tolerated both regimens well, with the exception of mild diarrhea noted for two subjects following the administration of piperacillin-tazobactam at 4.5 g q8h. The plasma concentration-versus-time profiles for both dosage regimens of piperacillin and tazobactam are presented in Fig. 1 and 2, respectively. Trough concentrations of piperacillin were not significantly different from each other during the 24-h sampling period, indicating that steady state had been achieved during both dosing regimens. This was also true for tazobactam.

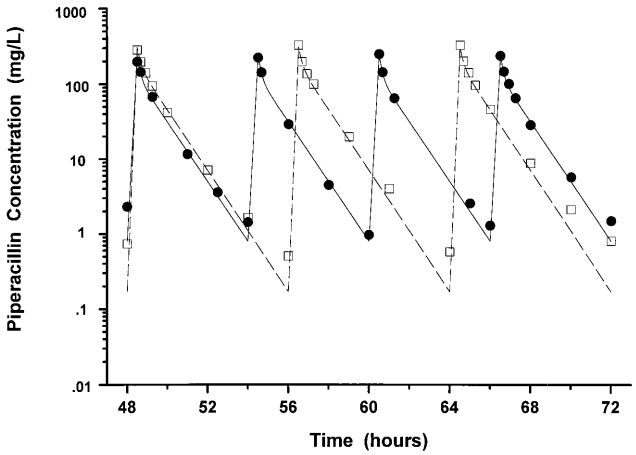

FIG. 1. Mean piperacillin plasma concentration-versus-time curves at steady state for both regimens. ●, 3.375 g q6h; □, 4.5 g q8h. The solid (3.375 g q6h) and dashed (4.5 g q8h) lines represent the computer-fitted nonlinear least-squares regression analysis of plasma concentration-time data.

Mean pharmacokinetic parameters (± standard deviation) for piperacillin and tazobactam for each dosing regimen are presented in Tables 1 and 2, respectively. No sequence or period effects for the pharmacokinetic parameters were observed. The power to detect a 20% difference for all pharmacokinetic parameters between the two regimens was 0.9 or greater.

Comparison of AUC_{0-24} for piperacillin (967.74 ± 135.56 μg · h/ml versus 978.88 ± 140.96 μg · h/ml) and tazobactam (120.14 ± 15.78 μg · h/ml versus 120.01 ± 16.22 μg · h/ml) revealed no significant differences ($P > 0.05$) between the 3.375-g q6h and 4.5-g q8h regimens, respectively. Percent differences (90% confidence intervals) for AUC_{0-24} between the two regimens were 1.15 (−3.08 to 5.38) and −0.11 (−4.01 to

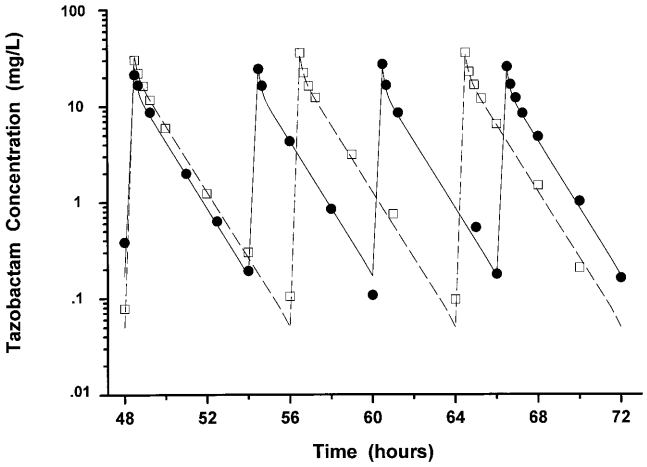

FIG. 2. Mean tazobactam plasma concentration-versus-time curves at steady state for both regimens. ●, 3.375 g q6h; □, 4.5 g q8h. The solid (3.375 g q6h) and dashed (4.5 g q8h) lines represent the computer-fitted nonlinear least-squares regression analysis of plasma concentration-time data.

TABLE 1. Mean pharmacokinetic parameters for piperacillin at steady state

Multiple-dose regimen or statistical variable	C_{max} (μg/ml)	AUC_{0-24} (μg · h/ml)	CL (ml/min/1.73 m^2)	CL_R (ml/min/1.73 m^2)	CL_{NR} (ml/min/1.73 m^2)	V_{SS} (liters/kg)	k (h^{-1})[a]	$t_{1/2\beta}$ (h)
Regimen								
4.5 g q8h	264.44 ± 50.54	978.88 ± 140.96	181.72 ± 19.54	102.58 ± 9.24	74.80 ± 17.42	0.152 ± 0.021	0.934 ± 0.107	0.75 ± 0.10
3.375 g q6h	262.67 ± 42.61	967.74 ± 135.56	183.96 ± 22.66	103.81 ± 11.17	80.15 ± 15.99	0.153 ± 0.023	0.930 ± 0.130	0.76 ± 0.11
ANOVA for crossover design[b]								
% Difference[c]	0.67	1.15	−1.22	−1.18	−6.67	−0.65	0.43	−0.92
90% confidence limit	−9.27, 10.62	−3.08, 5.38	−5.19, 2.75	−6.76, 4.39	−12.31, −1.04	−5.53, 4.23	−6.69, 7.55	−8.66, 6.81

[a] k, elimination rate constant.
[b] No values were significant.
[c] Percent difference of treatment means, 4.5 g q8h compared to 3.375 g q6h. Negative values indicate decreases.

TABLE 2. Mean pharmacokinetic parameters for tazobactam at steady state

Multiple-dose regimen or statistical variable	C_{max} (μg/ml)	AUC_{0-24} (μg · h/ml)	CL (ml/min/1.73 m^2)	CL_R (ml/min/1.73 m^2)	CL_{NR} (ml/min/1.73 m^2)	V_{SS} (liters/kg)	k (h^{-1})[a]	$t_{1/2\beta}$ (h)
Regimen								
4.5 g q8h	29.12 ± 5.59	120.01 ± 16.22	184.87 ± 18.35	125.44 ± 11.21	59.43 ± 11.82	0.170 ± 0.027	0.795 ± 0.117	0.89 ± 0.15
3.375 g q6h	28.68 ± 4.27	120.14 ± 15.78	184.71 ± 19.89	129.27 ± 12.45	55.45 ± 13.78	0.174 ± 0.028	0.780 ± 0.160	0.93 ± 0.21
ANOVA for crossover design[b]								
% Difference[c]	1.55	−0.11	0.09	−2.96	7.18	−2.30	1.92	−4.19
90% confidence limit	−8.26, 11.36	−4.01, 3.79	−3.85, 4.02	−8.59, 2.67	−2.11, 16.46	−7.93, 3.33	−7.35, 11.19	−15.84, 7.45

[a] k, elimination rate constant.
[b] No values were significant.
[c] Percent difference of treatment means, 4.5 g q8h compared to 3.375 g q6h. Negative values indicate decreases.

TABLE 3. Percentage of time above the MIC for a 24-h period for each organism

Organism	% Time above MIC of piperacillin-tazobactam at:	
	4.5 g q8h	3.375 g q6h
E. coli 25922	60	72
P. aeruginosa 27853	60	72
S. aureus 25923	88	97
E. coli 35218[a]	88	97
K. pneumoniae 13882	100	100

[a] β-Lactamase-producing strain.

3.79) for piperacillin and tazobactam, respectively. There were no statistically significant differences between $t_{1/2\beta}$ V_{SS}, CL, CL_{NR}, and CL_R for either piperacillin or tazobactam during the administration of the two regimens.

Pharmacodynamics. The MICs and MBCs of piperacillin-tazobactam against the organisms tested were as follows: *S. aureus* 25923 (1.0 and 1.0 μg/ml), *E. coli* 25922 (4.0 and 4.0 μg/ml), *E. coli* 35218, β-lactamase positive (1.0 and 1.0 μg/ml), *K. pneumoniae* 13882 (0.25 and 0.25 μg/ml), and *P. aeruginosa* 27853 (4.0 and 8.0 μg/ml, respectively). The MIC of piperacillin-tazobactam for *B. fragilis* could not be reported due to the inability to read inhibitory titers for this organism. The MBC of piperacillin-tazobactam for *B. fragilis* was 0.125 μg/ml.

The percentages of the time during a 24-h period at which piperacillin concentrations remained above the MIC for each organism during both regimens are shown in Table 3. Piperacillin concentrations remained above the MIC for 60 to 100% of the 24-h period for all organisms and regimens studied. Piperacillin-tazobactam at 3.375 g q6h provided a longer duration of inhibitory activity against both *E. coli* strains, *S. aureus*, and *P. aeruginosa.*

Mean reciprocal bactericidal titers at each time point and mean (± standard deviation) values of measured ($AUBC_{0-24}$) and predicted (AUC_{0-24}/MBC) bactericidal activity for both regimens are reported in Table 4. Mean reciprocal inhibitory titers at each time point and mean (± standard deviation) values of measured ($AUIC_{0-24}$) and predicted (AUC_{0-24}/MIC) inhibitory activity for both regimens are reported in Table 5.

Mean $AUBC_{0-24}$ and $AUIC_{0-24}$ values were significantly higher following the administration of piperacillin-tazobactam at 4.5 g q8h for all organisms with the exception of $AUBC_{0-24}$ values for *B. fragilis*. Measured and predicted values of bactericidal and inhibitory activity were significantly different ($P < 0.05$) for nearly all organisms and regimens studied, with the exception of bactericidal activity for *P. aeruginosa* and *S. aureus* determined during the administration of piperacillin-tazobactam at 3.375 g q6h. Measured values of bactericidal and inhibitory activity were not consistently higher or lower than predicted values for the organisms tested.

DISCUSSION

Saturable elimination pharmacokinetics have been described for the ureidopenicillins, for which decreases in clearance have reflected both renal and nonrenal saturation mechanisms (2, 13). Bergan and Williams reported decreases in CL of piperacillin and disproportionate increases in AUC following the administration of piperacillin as 3-min bolus injections and 2-h infusions of 15, 30, or 60 mg/kg of body weight to 12 healthy male volunteers (4). The AUCs per gram for the 15-, 30-, or 60-mg/kg regimens were 57.1, 75.0, and 79.6 μg · h/ml, respectively, for the bolus injection and 59.5, 72.7, and 77 μg · h/ml, respectively, for the 2-h infusion. The most marked increases in AUC were noted in comparing the low (15 mg/kg) dose to the intermediate and high (30 and 60 mg/kg) doses, as pharmacokinetic changes were less evident between the intermediate and high doses. Subjects in this study were not crossed over to receive all piperacillin dosage regimens. Consequently, comparison of the different regimens should consider the limited number of subjects in each arm (four per group) and the variability in results when different individuals are studied.

Batra et al. assessed the pharmacokinetics of two multiple-dose regimens of piperacillin (4 g q8h [12 g/24 h] and 6 g q6h [24 g/24 h]) and reported decreases in CL and CL_R with the higher dosage regimen (2). This protocol was not designed as a randomized crossover study, and interindividual variability, evidenced by large differences in concentrations in serum following the administration of both regimens, may have contributed to these results.

Tjandramaga et al. reported decreases in CL, CL_{NR}, and CL_R values following an intravenous dose escalation study (31). CL_{NR} values decreased from 105 ml/min/1.73 m^2 to 50.5 and 22.7 ml/min/1.73 m^2 following the administration of 1-, 4-, and 6-g intravenous bolus doses of piperacillin, respectively.

TABLE 4. Mean measured and predicted values of bactericidal activity at steady state ($n = 12$)[a]

Organism	Value for piperacillin-tazobactam at:											
	4.5 g q8h						3.375 g q6h					
	Mean reciprocal bactericidal titer at h:				$AUBC_{0-24}$	AUC_{0-24}/MBC	Mean reciprocal bactericidal titer at h:				$AUBC_{0-24}$	AUC_{0-24}/MBC
	0.5	4	6	8			0.5	2	4	6		
E. coli	128	8	0	0	799.1 ± 112.3	513.7 ± 70.0	64	16	4	0	505.3 ± 149.0	299.6 ± 42.19
P. aeruginosa	64	0	0	0	352.0 ± 74.7	256.9 ± 35.0	32	0	0	0	154.7 ± 79.4	131.4 ± 19.12
S. aureus[b]	512	8	2	0	2,461.4 ± 800.2	2,069.7 ± 288.4	256	32	8	2	1,214.5 ± 167.9	1,189.8 ± 174.1
E. coli[c]	128	8	0	0	668.3 ± 195.5	2,054.8 ± 279.8	64	16	4	0	390.7 ± 43.3	1,198.6 ± 168.8
K. pneumoniae	512	32	8	4	3,379.0 ± 81.6	8,219.2 ± 1,119.3	512	64	16	8	2,722.7 ± 587.6	4,794.3 ± 675.1
B. fragilis[d]	128	8	4	2	997.1 ± 427.5	16,438.4 ± 2,238.5	128	32	8	4	796.0 ± 306.1	9,588.5 ± 1,350.2

[a] Measured values of $AUBC_{0-24}$ were significantly higher ($P < 0.05$) following the administration of the 4.5-g q8h regimen for all organisms except *B. fragilis*. Significant differences ($P < 0.05$) existed between measured ($AUBC_{0-24}$) and predicted (AUC_{0-24}/MBC) values of bactericidal activity for all organisms except *P. aeruginosa* and *S. aureus* following the 3.375-g q6h regimen.
[b] $n = 11$.
[c] β-Lactamase-producing strain.
[d] $n = 10$.

TABLE 5. Mean measured and predicted inhibitory activity at steady state ($n = 12$)[a]

Organism	Value for piperacillin-tazobactam at:											
	4.5 g q8h						3.375 g q6h					
	Mean reciprocal inhibitory titer at h:				$AUIC_{0-24}$	AUC_{0-24}/MIC	Mean reciprocal inhibitory titer at h:				$AUIC_{0-24}$	AUC_{0-24}/MIC
	0.5	4	6	8			0.5	2	4	6		
E. coli	128	8	2	0	906.8 ± 219.5	513.7 ± 70.0	128	16	8	2	537.3 ± 151.0	299.6 ± 42.19
P. aeruginosa	64	0	0	0	416.8 ± 122.5	513.7 ± 70.0	64	2	0	0	244.0 ± 92.5	299.6 ± 42.19
S. aureus[b]	512	8	2	2	2,773.6 ± 695.5	2,069.7 ± 288.4	256	32	8	2	1,417.5 ± 397.0	1,189.8 ± 174.1
E. coli[c]	128	8	2	0	716.8 ± 179.9	2,054.8 ± 279.8	64	16	8	2	407.3 ± 48.5	1,198.6 ± 168.8
K. pneumoniae	512	32	8	4	3,407.0 ± 142.5	8,219.2 ± 1,119.3	512	64	16	8	2,744.0 ± 580.4	4,794.3 ± 675.1

[a] Measured values of $AUIC_{0-24}$ were significantly higher ($P < 0.05$) following the administration of the 4.5-g q8h regimen for all organisms. Significant differences ($P < 0.05$) existed between measured ($AUIC_{0-24}$) and predicted (AUC_{0-24}/MIC) values of inhibitory activity for all organisms.
[b] $n = 11$.
[c] β-Lactamase-producing strain.

Decreases in CL_R were most notable following the administration of 4- and 6-g intravenous doses of piperacillin. Mean CL_R values decreased from 303.6 ml/min/1.73 m^2 following the administration of a 1-g piperacillin dose to 203.7 and 186.9 ml/min/1.73 m^2 following the administration of 4- and 6-g intravenous doses of piperacillin. Decreases in CL following the administration of the four doses administered in this study were reflected in disproportionately higher AUC values, which were 36, 102, 250, and 438 μg · h/ml after doses of 1, 2, 4, and 6 g, respectively.

Saturable nonrenal elimination has been reported to influence CL values to a greater extent than saturation of renal tubular secretion mechanisms for the ureidopenicillins (4). Decreases in CL, CL_{NR}, and CL_R may not have been observed because of the smaller difference in doses of piperacillin administered to our subjects. Similarly, Tjandramaga et al. reported a more modest reduction in CL_R when smaller incremental changes in dose were evaluated (31). Additionally, no significant differences in CL, CL_{NR}, or CL_R were noted for tazobactam following administration of the two regimens ($P > 0.05$ [Table 2]). AUC_{0-T} values per gram of piperacillin and tazobactam administered were equivalent for the two regimens studied in our trial. This resulted in nearly identical AUC_{0-24} values ($P > 0.05$) for both piperacillin and tazobactam.

The pharmacokinetic parameters for both piperacillin and tazobactam reported following multiple-dose administration in this study are similar to those found after single-dose administration. Similar to Kinzig et al. (17), we found clearance values for both piperacillin and tazobactam to be significantly higher than that reported for healthy volunteers by Wise et al. (34). Additionally, CL values reported by Wise et al. for piperacillin were significantly lower than those reported in the literature for a single 4-g piperacillin dose (31, 33). Our CL values are in close agreement with those for healthy subjects reported by Johnson et al. (16), although our CL_R values appeared to be slightly lower for piperacillin. CL values for tazobactam in our report were almost identical to those reported for healthy volunteers by Cheung et al. (7), although piperacillin clearance values were approximately 20% lower for our subjects.

Pharmacodynamic analysis was performed to compare pharmacokinetic results with inhibitory and bactericidal activity provided by the two regimens. Although the piperacillin-tazobactam 3.375-g q6h regimen provided a longer duration of antimicrobial activity for both *E. coli* strains, *S. aureus*, and *P. aeruginosa*, both multiple-dose regimens provided concentrations above the MIC for 60 to 100% of the 24-h dosing period. Maximal efficacy has been demonstrated to plateau when time above the MIC approaches 60 to 70% of the dosing interval for β-lactam antimicrobials (9).

Predicted measures of $AUBC_{0-24}$ and $AUIC_{0-24}$, calculated by dividing the area under the plasma concentration-time curve by the MIC and MBC (AUC_{0-24}/MBC and AUC_{0-24}/MIC) have been shown to correlate with measured $AUBC_{0-24}$ and $AUIC_{0-24}$ values for ciprofloxacin (14). In contrast to these data, measured ($AUBC_{0-24}$ and $AUIC_{0-24}$) and predicted (AUC_{0-24}/MBC and AUC_{0-24}/MIC) values of bactericidal and inhibitory activity were significantly different for nearly all organisms and piperacillin-tazobactam regimens that we studied. Additionally, measured values were not consistently higher or lower than predicted values of bactericidal and inhibitory activity. Reasons for this variability are unclear.

Although there did appear to be some correlation between $AUBC_{0-24}$ and $AUIC_{0-24}$ values and MBC and MIC results (these values were the highest for *K. pneumoniae* and *S. aureus* and the lowest for *P. aeruginosa*), MBC did not correlate with $AUBC_{0-24}$ values for *B. fragilis*. The MBC of piperacillin-tazobactam for *B. fragilis* was actually the lowest reported for all organisms tested. Additionally, ATCC organisms that possessed the same MICs and MBCs (*S. aureus* and *E. coli* 35218 and *P. aeruginosa* and *E. coli* 25922) exhibited great differences in $AUBC_{0-24}$ and $AUIC_{0-24}$ values. Nicolau et al. also found that $AUBC_{0-24}$ values for ceftazidime were different for two isolates of *P. aeruginosa* possessing identical MICs (23). These differences may be attributed to inherent differences in organism and/or isolate specific susceptibility.

ACKNOWLEDGMENTS

This study was supported in part by a research grant from Lederle Laboratories, Division of American Cyanamid Company.

We acknowledge the assistance of Ken Fang and thank all of the postdoctoral research fellows and pharmacy students who assisted in the collection of data.

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