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# Single-Dose Pharmacokinetics of Piperacillin and Tazobactam in Infants and Children

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**The pharmacokinetics of piperacillin and tazobactam were assessed after single-dose administration to 47 infants and children. Study subjects ranging in age from 2 months to 12 years were randomized to receive one of two different doses of a piperacillin-tazobactam combination (8:1): a low dose ($n$ = 23) of 50 and 6.25 mg of piperacillin and tazobactam per kg of body weight, respectively, or a high dose ($n$ = 24) of 100 and 12.5 mg, respectively. The pharmacokinetic behavior of tazobactam was very similar to that observed for piperacillin, supporting the use of these two agents in a fixed-dose combination. No differences in the pharmacokinetics of piperacillin or tazobactam were observed between the two doses administered. The elimination parameters half-life and total body clearance decreased and increased, respectively, with increasing age, whereas volume parameters (volume of distribution and steady-state volume of distribution) remained relatively constant for both compounds. The primary metabolite of tazobactam, metabolite M1, was measurable in the plasma of 18 of the 47 study subjects; 17 of these 18 subjects received the high doses. More than 70% of the administered piperacillin and tazobactam doses were excreted unchanged in the urine over a 6-h collection period. These data combined with the known in vitro susceptibilities of a broad range of pediatric bacterial pathogens indicate that a dose of 100 mg of piperacillin and 12.5 of mg tazobactam per kg of body weight administered as a fixed-dose combination every 6 to 8 h would be appropriate to initiate clinical efficacy studies in infants and children for the treatment of systemic infections arising outside of the central nervous system.**

The beta-lactam antibiotics are among the most widely prescribed classes of drugs for infants and children. For decades these drugs have been used successfully for the treatment of most bacterial infections arising in childhood, particularly for those infections involving skin and soft tissues, the genitourinary tract, the upper and lower respiratory tracts, and the central nervous system (30, 31). Unfortunately, over the last decade, the number of infections caused by penicillin- and cephalosporin-resistant bacteria has increased dramatically, reducing the clinical utilities of these safe and previously very effective antibiotics (22, 29). By 1975 nearly 85% of all isolates of *Staphylococcus aureus* were resistant to penicillin (22), and a similar trend has been observed for *Haemophilus influenzae* and *Moraxella catarrhalis*, in which nearly 40% of all *H. influenzae* type B strains and more than 80% of *M. catarrhalis* isolates are resistant to ampicillin (6, 29). Moreover, variable and changing susceptibility patterns to a wide range of penicillin and cephalosporin antibiotics are observed for other gram-negative pathogens (6, 22, 29).

Bacterial resistance to beta-lactam antibiotics is most often mediated via one of three primary mechanisms; alterations in drug binding to their cellular targets, the penicillin-binding proteins; alterations in cell membrane permeation of gram-negative bacteria, preventing the drug from penetrating the outer cell membrane and reaching its molecular target; and the expression of drug-inactivating enzymes, the β-lactamases (6, 29). The most common mechanism by which clinical isolates of bacteria are resistant to antibiotics is through the production of inactivating enzymes (29). Although many different pharmacologic and clinical strategies have been attempted to overcome this challenge of increasing bacterial resistance, including the use of antibacterial combinations and the development of new β-lactamase-stable drugs, the most promising may be the development of β-lactamase inhibitors (22, 29, 30).

Tazobactam, like sulbactam, is a beta-lactam sulfone which possesses little if any intrinsic antibacterial activity but which has a high affinity for many nonchromosomally mediated β-lactamases. Like clavulanic acid, these β-lactamase inhibitors are often described as suicide enzyme inhibitors because they bind irreversibly to susceptible enzyme substrate. All three of these narrow-spectrum inhibitors irreversibly react with β-lactamases by an acylation reaction analogous to the interaction between beta-lactam antibiotics and targeted penicillin-binding proteins (6, 22).

The use of a combination of a β-lactamase inhibitor with a β-lactamase-labile drug is a rational approach to expanding the clinical usefulness of a drug used extensively clinically and with a known safety profile (6, 22, 25, 29). A number of drugs meet these criteria and have been combined with a β-lactamase inhibitor, enhancing their spectra of antibacterial activity; these include amoxicillin and ticarcillin with clavulanic acid, ampicillin and cefoperazone with sulbactam, and more recently, piperacillin with tazobactam (6, 11, 15, 17, 22, 25). The purpose of the present investigation was to assess the disposition characteristics of piperacillin and tazobactam when coadministered to infants and children. These pharmacokinetic data were used to define age-appropriate piperacillin-tazobactam dosing recommendations for use in controlled clinical

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efficacy evaluations of this drug combination for the treatment of pediatric infections.

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## MATERIALS AND METHODS

**Patient selection.** Infants and children between the ages of 2 months and 12 years with a suspected or proven bacterial infection arising outside of the central nervous system were eligible for enrollment in the study. All study subjects received conventional antibiotic therapy selected by their attending physicians during the conduct of the study. Subject recruitment was directed via an open enrollment scheme to establish subpopulations which were stratified into the following age groups: 2 months through 5 months, 6 months through 23 months, 2 years through 5 years, and 6 years through 12 years. The study was approved by the Institutional Review Board for Human Subjects Investigation of the University Hospitals of Cleveland. Written consent was obtained from a parent or a legal guardian, and when appropriate (i.e., for those older than 6 years), patient assent was obtained prior to drug dosing.

Prior to piperacillin-tazobactam administration, each subject provided a complete history (i.e., medical, dietary, and medication) and underwent a physical examination. Blood was obtained for the determination of glucose, serum electrolytes, creatinine, urea nitrogen, calcium, phosphorus, alkaline phosphatase, alanine aminotransferase (ALT), asparate aminotransferase (AST), gamma glutamyltransaminase, total and direct bilirubin, total protein, albumin, complete blood count with differential, and platelet count. A urine sample was collected for macro - and microscopic urinalyses. These laboratory evaluations were performed prior to and were repeated within 48 h of study drug administration. Laboratory determinations were performed by the clinical laboratories of the University Hospitals of Cleveland.

Subjects were excluded from enrollment in the study if they had (i) a history of hypersensitivity to beta-lactam antibiotics (e.g., penicillins, cephalosporins, or β-lactamase inhibitors) or (ii) evidence of renal dysfunction (i.e., creatinine level in serum >2 standard deviations [SDs] above the upper limit of normal for age), evidence of hepatic dysfunction (i.e., ALT or AST levels in serum >2 SDs above the upper limit of normal for age), cystic fibrosis, or bacterial meningitis, were immunocompromised, were receiving cancer chemotherapy, or had received an investigational drug within the preceding 14 days.

**Drug administration.** Piperacillin-tazobactam was provided in glass vials as sterile colyophilized powder equivalent to 3 g of piperacillin sodium and 0.375 g of tazobactam sodium (American Cyanamid Co., Medical Research Division, Pearl River, N.Y.). The drug was reconstituted with 0.9% sodium chloride for injection and was further diluted to a total volume of 20 to 50 ml in either normal saline or 5% glucose in water. Study drug was infused intravenously over 30 min by a research nurse by using a calibrated autosyringe. Immediately following infusion of the study drug, the intravenous infusion tubing was flushed with 3 to 10 ml of normal saline to ensure administration of the total dose.

This single-dose study was an open-label, ascending evaluation of two different piperacillin-tazobactam doses, i.e., 50 and 6.25 mg (low dose) or 100 and 12.5 mg of piperacillin and tazobactam (high dose) per kg of body weight, respectively. Since each subject enrolled in the study was already receiving conventional antibiotic therapy, a single dose of piperacillin-tazobactam was substituted for a single dose of the patient's therapeutic antibiotic. As a safety precaution, lower-dose piperacillin-tazobactam was first administered to the subjects in each age group. In the absence of any drug-associated side effects, subjects were randomized to receive high-dose piperacillin-tazobactam after 50% of the age group had received the low dose.

**Specimen collection.** Venous or arterial blood samples (<1.5 ml) were obtained from an indwelling catheter immediately prior to piperacillin-tazobactam administration and at approximately 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, and 4 h after the beginning of the intravenous infusion. Blood was collected in disposable plastic syringes and was transferred immediately into heparinized glass tubes. After gentle inversion, blood samples were placed on ice for 20 to 60 min prior to centrifugation. Samples were maintained at 4°C and were centrifuged at 2,000 × *g* for approximately 10 min; the plasma was aspirated and was immediately placed on ice prior to storage at −70°C. Before drug administration a urine sample was obtained and then all urine excreted during the next 6 h was collected as timed aliquots from 0 to 2, 2 to 4, and 4 to 6 h after the start of the infusion.

Plasma and urine samples were shipped on dry ice to American Cyanamid Company within 3 weeks of collection for the quantification of piperacillin, tazobactam, and the M1 metabolite.

**Determination of piperacillin and tazobactam in plasma and urine and the tazobactam M1 metabolite. (i) Equipment and conditions.** Analyses were performed in the Pharmacodynamic Section of the American Cyanamid Lederle Laboratories by using two Waters model 510 pumps and a Waters 680 gradient controller equipped with a WISP 710B autosampler. Chromatography was performed on a Brownlee RP-18 precolumn (15 by 3.2 mm; 7 μm), and Supelcosil LC-18-DB column (250 by 4.6 mm; 5 μm) at ambient temperature. A gradient was run at 1.5 ml/min by using the following two solutions: solution A, 3:97 (vol/vol) acetonitrile–0.01 M sodium dihydrogen phosphate adjusted to pH 2.7 with phosphoric acid; and solutin B, 90:10 (vol/vol) acetonitrile–0.01 M sodium dyhydrogen phosphate adjusted to pH 2.7 with phosphoric acid. Solutions A and B were degassed and filtered prior to use. The gradient was performed as follows: 0 to 9 min from 5% solution B to 50% solution B; return for 9 to 10 min to 5% B; remain at 5% solution B for 10 to 25 min; 25 to 30 min from 5 to 50% solution B at 0.2 ml/min. Under these conditions tazobactam eluted at 5.1 min, piperacillin eluted at 11.7 min, and the internal standard benzylpenicillin eluted at 12.3 min.

Peaks were detected with a Kratos 783 UV spectrophotometer at 220 nm (0.01 absorbance units, full scale) and were collected and recorded on a Hewlett-Packard 3350S instrument. Peak height ratios to internal standard were determined, and concentrations were calculated from a linear least-squares regression line of the natural logarithm of the known concentration versus the natural logarithm of the peak height ratios.

Quantitation of metabolite M1 was performed with equipment identical to that used for quantitation of piperacillin and tazobactam with the exception of the autosampler, which was set at 5°C to minimize conversion of tazobactam to M1. The mobile phase consisted of 2:98 (vol/vol) acetonitrile–0.005 M low UV tetrabutyl ammonium phosphate. The mobile phase was degassed and was filtered prior to use at a flow rate of 1.0 ml/min.

**(ii) Sample extraction.** For the determination of piperacillin and tazobactam, plasma and urine were stored at −70°C.

Plasma (0.2 ml) was combined with 0.2 ml of internal standard (25 μg of benzylpenicillin per ml in water) and 0.8 ml of acetonitrile in a tube (13 by 100 mm). The mixture was vortexed for 30 s and was centrifuged at 3,000 rpm for 10 min. The supernatant solution was decanted into a second tube (13 by 100 mm) and combined with 2 ml of methylene chloride, and the mixture was vortexed for 30 s and centrifuged for 10 min. The upper aqueous layer was transferred to a WISP autosampler vial, and 25 μl was injected for analysis.

Urine samples were handled in the same manner except that the internal standard was prepared in a solution of 0.05 M sodium phosphate (pH 6.0).

For the determination of metabolite M1, plasma was kept on ice throughout the procedure. A C18 Sep-Pak (Waters 51910) was activated by rinsing with 5 ml of methanol, 5 ml of water, and 5 ml of 0.05 M potassium phosphate (pH 2). Then a solution containing 0.25 ml of sample and 0.5 ml of 0.1 M potassium phosphate (pH 2) was passed through the Sep-Pak and was collected in a tube (16 by 100 mm). The Sep-Pak was washed with 1 ml of chilled water, the solution that was collected was combined with the sample eluate, and the mixture was vortexed for 10 s. A 0.1-ml chilled, niacin-containing internal standard was added to the eluate directly. The mixture was vortexed for 10 s and placed in a WISP vial, and 40 μl was injected for analysis. If the sample was cloudy only 20 μl was injected owing to high column pressures.

**(iii) Assay statistics.** The plasma and urine assays were accurate over the range of 0.5 to 200 and 0.01 to 200 μg/ml, respectively, for both piperacillin and tazobactam. The mean coefficients of variation (CVs) for calibration standards in plasma were 4.41 and 5.86% for piperacillin and tazobactam, respectively; in urine, they were 3.95 and 5.05%, respectively. The mean CVs for quality control samples in plasma were 5.17 and 8.56% for piperacillin and tazobactam, respectively; in urine they were 2.77 and 4.75%, respectively.

The plasma assay for metabolite M1 was accurate over the range of 0.5 to 100 μg/ml. The mean CVs for calibration standards and quality control samples were 6.9 and 9.2%, respectively.

**Pharmacokinetic analysis.** The dispositions of piperacillin and tazobactam were characterized by using standard noncompartmental pharmacokinetic techniques (13). Plasma piperacillin and tazobactam concentrations were plotted against time on a semilogarithmic scale. The area under the plasma drug concentration-time curve (AUC) was obtained by using the linear trapezoidal rule up to the final measured concentration and was extrapolated to infinity ($AUC_{0-\infty}$). The terminal elimination rate constant ($K_d$) and elimination half-life ($t_{1/2}$) were determined from linear regression analysis of the post-distributive terminal portion of the plasma concentration-versus-time curve. Total body clearance (CL) was determined by using the formula dose/$AUC_{0-\infty}$. The apparent steady-state volume of distribution ($V_{ss}$) was determined by the equation $V_{ss} = [(\text{dose})(\text{AUMC})/\text{AUC}^2] - [(\text{dose})(T)/(\text{AUC} \times 2)]$, where AUMC is the area under the first moment of the concentration time curve, and $T$ is the infusion duration. The volume of distribution ($V$) by the area method was calculated as $CL/K_d$, and mean residence time (MRT) was calculated as AUMC/AUC. The renal clearance ($CL_R$) of piperacillin and tazobactam for each patient was calculated as $CL_R = A/AUC$, where $A$ is the cumulative amount of drug excreted within the sampling interval, and AUC is the AUC of the drug in plasma during the same sampling interval.

**Statistical evaluation.** Statistical analysis was performed by using multiple analysis of covariance, analysis of variance, the Student $t$ test, Pearson correlation, and linear regression analysis. All statistical analyses were performed by standard methods, with an accepted level of significance of $P < 0.05$. Data are presented as the mean, SD, and range.

TABLE 1. Study subject characteristics

| Characteristic | Mean (±SD) | Range |
|---|---|---|
| No. of subjects studied | 47 | |
| Subject age (yr) | 3.4 (3.4) | 0.17–12 |
| Low dose ($n$ = 23)[a] | 3.3 (3.5) | 0.25–11 |
| High dose ($n$ = 24)[b] | 3.4 (3.4) | 0.10–12 |
| Body wt (kg) | 14.4 (10.2) | 3.8–51 |
| Serum creatinine level (mg/dl) | 0.3 (0.1) | 0.1–0.7 |
| Serum albumin level (g/dl) | 3.2 (0.6) | 2.1–4.4 |
| ALT (IU/liter) | 77 (60) | 18–297 |
| AST (IU/liter) | 30 (25) | 9–130 |
| Subject age for study group: | | |
| 2–5 mo ($n$ = 12) | 3.4 (1) | 2–5 |
| 6–23 mo ($n$ = 12) | 14 (5) | 8–23 |
| 2–5 yr ($n$ = 12) | 4.1 (1) | 2–5 |
| 6–12 yr ($n$ = 11) | 8.5 (2.4) | 6–12 |

[a] Low dose, 50 and 6.25 mg of piperacillin and tazobactam, respectively.
[b] High dose, 100 and 12.5 mg of piperacillin and tazobactam, respectively.

## RESULTS

A total of 48 subjects were enrolled in the study; complete samples for pharmacokinetic analyses were available from 47 of the subjects. The clinical and demographic characteristics of the 47 study subjects are given in Table 1. Study subjects ranged in age from 0.17 to 12 years, and all had normal renal function for age as determined by serum creatinine levels. Elevations in baseline AST and ALT levels were observed in 11 and 2 subjects, respectively (Table 1). These initial abnormal laboratory values were normalized over the study period. No subject experienced any adverse clinical effect associated with single-dose piperacillin-tazobactam administration.

The overall mean ( ± SD ) piperacillin and tazobactam plasma concentration-time curves after administration of both doses are shown in Fig. 1. Peak concentrations in plasma were observed at the first 30-min sampling time; peak and trough concentrations in plasma averaged 168 and 6 mg of piperacillin per liter and 21 and 1.2 mg of tazobactam per liter, respectively, after low-dose administration and 360 and 19 mg of piperacillin per liter and 39 and 3 mg of tazobactam per liter, respectively, after high-dose administration. The piperacillin:tazobactam plasma concentration ratio averaged 9.5:1 (±1.7:1) for the peak and 7.3:1 (±1.9:1) for the trough after high-dose drug administration and 8.1:1 (±0.8:1) for the peak and 4.9:1 (±2.2:1) for the trough after low-dose drug administration.

With the expected exceptions of AUC and peak and trough drug concentrations in plasma, statistical analysis revealed no differences in pharmacokinetic parameter estimates for either piperacillin or tazobactam relative to dose; thus, the data were pooled for presentation and further analysis. These observed differences in AUC and peak and trough drug concentrations in plasma are abolished when they are normalized to the dose administered. The pharmacokinetic parameter estimates determined for piperacillin and tazobactam subdivided by patient age are shown in Tables 2 and 3, respectively. Overall, the pharmacokinetic characteristics of piperacillin (Table 2) were very similar to those observed for tazobactam (Table 3), supporting the use of a combination of these two agents in a fixed-dose formulation. The piperacillin $t_{1/2}$ and CL ranged from 0.7 to 1.4 h and 3.3 to 5.9 ml/min/kg, respectively, with changes in drug elimination reflecting increasing age. In con-

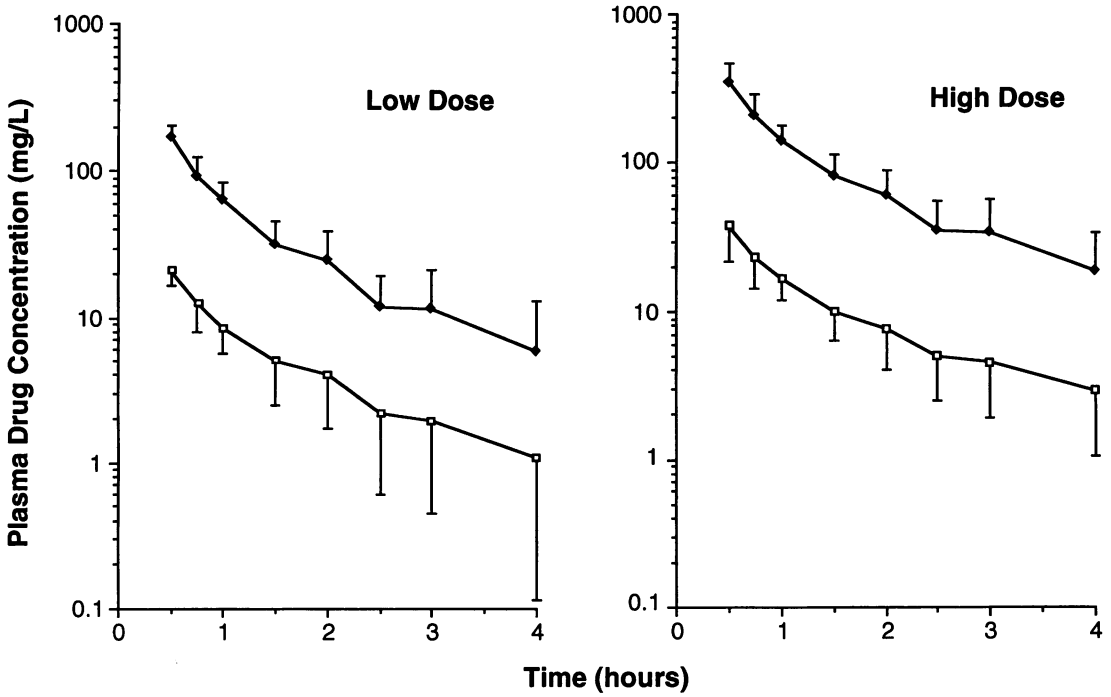


FIG. 1. Overall mean (±SD) plasma concentration-time curve for piperacillin and tazobactam after intravenous administration of two different single doses. ◆, piperacillin; □, tazobactam.

trast, the volume parameters for piperacillin (V, $V_{ss}$) remained relatively constant over the age range studied. Similarly, tazobactam elimination increased with increasing age, whereas the volume parameters remained relatively constant (Table 3).

To perform a further assessment for a possible age dependence on the disposition of piperacillin and tazobactam, the primary pharmacokinetic parameter estimates $V_{ss}$, CL, and $CL_R$ were plotted against age (Fig. 2 and 3). A linear relationship was observed between the non-weight-corrected values for $V_{ss}$ (in liters) and CL and $CL_R$ (in milliliters per minute) for both compounds. In contrast, when these parameter estimates are "normalized" to body weight, i.e., $V_{ss}$ as liters per kilogram and CL and $CL_R$ as milliliters per minute per kilogram, the observed linear relationship diminishes (Fig. 2 and 3).

Cleavage of the beta-lactam and sulfone rings of tazobactam produces the primary tazobactam metabolite, metabolite M1. Metabolite M1 was measurable in the plasma of 18 of the 47 study subjects. All but one of these subjects received high-dose piperacillin-tazobactam. Peak M1 concentrations in plasma after high-dose administration averaged 1.4 mg/liter (range, 0.5 to 2.5 mg/liter). Four-hour trough concentrations of M1 in plasma were measurable in 14 of the 17 subjects receiving high-dose piperacillin-tazobactam and averaged 1.2 mg/liter. The peak M1 concentration in plasma in the one subject who received low-dose piperacillin-tazobactam was 0.83 mg/liter, and at 2 h it declined to 0.5 mg/liter; no M1 was measurable in the remaining plasma samples.

The urinary recoveries of piperacillin and tazobactam stratified for age and presented as a percentage of the drug dose administered are shown in Fig. 4 and 5, respectively. The majority of drug excretion occurred during the first 2-h sampling period for both compounds. The overall amounts of drug excreted declined over the next 4 h. The cumulative amount of drug excreted over the 6-h sampling period and pooled as composite data is also shown in Fig. 4 and 5 for each drug, respectively. The expected dependence of piperacillin and tazobactam CL on $CL_R$ is reflected by the CLR:CL ratio in Tables 2 and 3, respectively.

## DISCUSSION

For many years, piperacillin has been a very useful antibiotic for the treatment of a variety of infections occurring in infants and children (26, 28, 30). Nevertheless, the drug's susceptibility

TABLE 2. Pharmacokinetics of piperacillin as a function of age

| Subject age | Piperacillin pharmacokinetic parameter estimates (mean [±SD])[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $t_{1/2}$ (h) | $V$ (liter/kg) | $V_{ss}$ (liter/kg) | MRT (h) | CL (ml/min/kg) | $CL_R$ (ml/min/kg) | $CL_R$:CL | Fe (0–6 h) (% dose) |
| 2–5 months ($n$ = 12) | 1.4 (0.5) | 0.37 (0.1) | 0.33 (0.1) | 2.0 (0.7) | 3.3 (0.8) | 2.6 (0.9) | 0.72 (0.2) | 71 (21) |
| 6–23 months ($n$ = 12) | 0.9 (0.3) | 0.36 (0.1) | 0.30 (0.1) | 1.4 (0.3) | 4.7 (1.8) | 2.0 (0.6) | 0.46 (0.2) | 68 (34) |
| 2–5 years ($n$ = 12) | 0.7 (0.1) | 0.36 (0.1) | 0.28 (0.1) | 1.1 (0.2) | 5.5 (1.5) | 3.4 (1.1) | 0.66 (0.2) | 74 (15) |
| 6–12 years ($n$ = 11) | 0.7 (0.2) | 0.36 (0.2) | 0.28 (0.1) | 1.1 (0.3) | 5.9 (4.7) | 3.6 (0.7) | 0.73 (0.2) | 72 (18) |

[a] $t_{1/2}$, elimination half-life; $V$, volume of distribution; $V_{ss}$, steady-state volume of distribution; MRT, mean residence time; CL, clearance; $CL_R$, renal clearance; Fe, amount of drug recovered in urine.

TABLE 3. Pharmacokinetics of tazobactam as a function of age

| Subject age | Tazobactam pharmacokinetic parameter estimates (mean [±SD])[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $t_{1/2}$ (h) | $V$ (liter/kg) | $V_{ss}$ (liter/kg) | MRT (h) | CL (ml/min/kg) | $CL_R$ (ml/min/kg) | $CL_R$:CL | Fe (0–6 h) (% dose) |
| 2–5 mo ($n$ = 12) | 1.6 (0.5) | 0.43 (0.1) | 0.39 (0.1) | 2.3 (0.7) | 3.3 (0.7) | 2.7 (0.8) | 0.8 (0.17) | 73 (17) |
| 6–23 mo ($n$ = 12) | 1.0 (0.4) | 0.42 (0.1) | 0.37 (0.1) | 1.6 (0.5) | 4.9 (1.3) | 3.4 (1.9) | 0.65 (0.24) | 69 (22) |
| 2–5 yr ($n$ = 12) | 0.8 (0.2) | 0.38 (0.1) | 0.31 (0.1) | 1.2 (0.3) | 5.5 (1.7) | 4.6 (1.5) | 0.78 (0.19) | 92 (11) |
| 6–12 yr ($n$ = 11) | 0.9 (0.4) | 0.40 (0.2) | 0.35 (0.1) | 1.3 (0.5) | 6.2 (4.5) | 3.4 (1.4) | 0.75 (0.14) | 82 (17) |

[a] $t_{1/2}$, elimination half-life; $V$, volume of distribution; $V_{ss}$, steady-state volume of distribution; MRT, mean residence time; CL, clearance; $CL_R$, renal clearance; Fe, amount of drug recovered in urine.

to degradation by bacterial β-lactamases, particularly those elaborated by *S. aureus*, *H. influenzae*, *M. catarrhalis*, and members of the family *Enterobacteriaceae*, has limited the clinical usefulness of piperacillin monotherapy for many infections, including infections occurring in pediatric patients (1, 2, 12). To circumvent this important limitation, the β-lactamase inhibitor tazobactam has been combined with piperacillin, enhancing the drug's stability to enzymatic degradation and thus extending its antibacterial spectrum of activity (6, 11, 15, 17, 21). The present study was designed to assess the pharmacokinetics of both piperacillin and tazobactam after single-dose administration in order to define appropriate dosing recommendations for the treatment of infections in pediatric patients. Two different doses of the piperacillin-tazobactam combination were administered to a group of infants and children reflecting a wide age range. Study subjects were randomized to receive either low-dose, i.e., 50 mg of piperacillin and 6.25 mg of tazobactam per kg of body weight, or high dose, i.e., 100 mg of piperacillin and 12.5 mg of tazobactam per kg of body weight. The observed similarities in the pharmacokinetic characteristics for piperacillin and tazobactam (Tables 2 and 3; Fig. 1 to 5) supports the use of the combination of the two compounds in an 8:1 piperacillin-tazobactam fixed-dose formulation.

The biodisposition of piperacillin and the derived pharmacokinetic parameter estimates described in this report are similar to those reported previously in small groups of pediatric patients (26, 28, 32, 35). The piperacillin elimination $t_{1/2}$ was prolonged and CL and $CL_R$ were reduced in the youngest study group compared with the values in older infants and children. Piperacillin elimination increased with increasing age, plateauing by essentially 2 years of age (Table 2 and Fig. 2). This pattern of increasing elimination rate with increasing age has been observed with other penicillin and cephalosporin analogs (19, 26, 32, 35). Comparison of the pharmacokinetic data derived for the older infants and children in our study with data obtained from healthy adult volunteers (16, 18, 33) reveals very similar disposition characteristics. These data suggest that the pharmacokinetic behavior of piperacillin is similar to that in adults by the age of 2 years.

The elimination of piperacillin is very dependent on renal function. The piperacillin $CL_R$ accounted for the majority of the drug's CL, as reflected by the $CL_R$:CL ratio, which ranged from 46 to 73% (Table 2). Moreover, approximately 70% of the administered piperacillin dose was recovered as parent drug over the 6-h collection period (Fig. 4). This dependence of piperacillin elimination on renal function has been described previously, and the values observed in the present study closely approximate those reported for adults (16). Presumably, the primary nonrenal route for piperacillin elimination is biliary excretion because high biliary concentrations of the drug have been described (14, 16, 24).

Although not directly assessed in the present investigation, the route of renal excretion of piperacillin in infants and children would appear to involve a combination of both glomerular filtration and tubular secretion. The primary route for piperacillin elimination in our study was the urine (Fig. 4), with the rates of both piperacillin CL and $CL_R$ exceeding the expected glomerular filtration rate. Previous studies have clearly described the importance of renal tubular secretion in the overall $CL_R$ for piperacillin as well as other amino-, carboxy-, and ureidopenicillins (16, 24, 33). This active proximal tubular secretion is antagonized by probenecid (16, 18, 33). Furthermore, the elimination of piperacillin and other ureidopenicillins has been shown to be dose dependent, as reflected by decreasing CL with increasing individual doses (3–5). Although incompletely defined, it appears that saturation of the tubular secretion process is primarily responsible for this observed dose dependency in piperacillin elimination (3–5). In the present study only two different piperacillin doses were administered, and these drug doses were administered to different subjects, precluding a critical assessment of dose-dependent pharmacokinetics. Furthermore, the coadministration of piperacillin with tazobactam has been shown to reduce the plasma CL and 24-h urinary recovery of tazobactam (36), presumably by competitive antagonism of renal tubular secretion.

It is possible that the piperacillin concentrations achieved in the plasma and urine after the administration of the two different doses to our study subjects exceeded those necessary to saturate renal excretory pathways and could account for the lack of statistical difference observed between piperacillin dose and pharmacokinetic parameter estimates. This conjecture is supported by the data of Bergan and Williams (5), who described dose-dependent piperacillin pharmacokinetics as individual doses increased from 15 to 30 and 60 mg of piperacillin per kg, dose ranges within and below the two doses used in our study.

The disposition characteristics defined for tazobactam were very similar to the values observed for piperacillin (Table 2), suggesting a compatible match for this fixed-dose combination. The tazobactam elimination $t_{1/2}$ was prolonged and the CL was reduced in the younger infants compared with the values in older infants and children, and both improved with increasing age. This similarity in drug disposition was reflected in the relatively constant ratio of piperacillin to tazobactam observed in the plasma of our study subjects. Such relative uniformity in the concentration ratio is not always apparent with fixed-dose combinations. In a pharmacokinetic evaluation of the fixed-dose combination of trimethoprim-sulfamethoxazole in patients with cystic fibrosis (27), we found the ratio of the two components to fluctuate greatly in plasma and other body fluids. In the present study, the ratio of piperacillin to tazobactam remained relatively constant over the 4-h study period

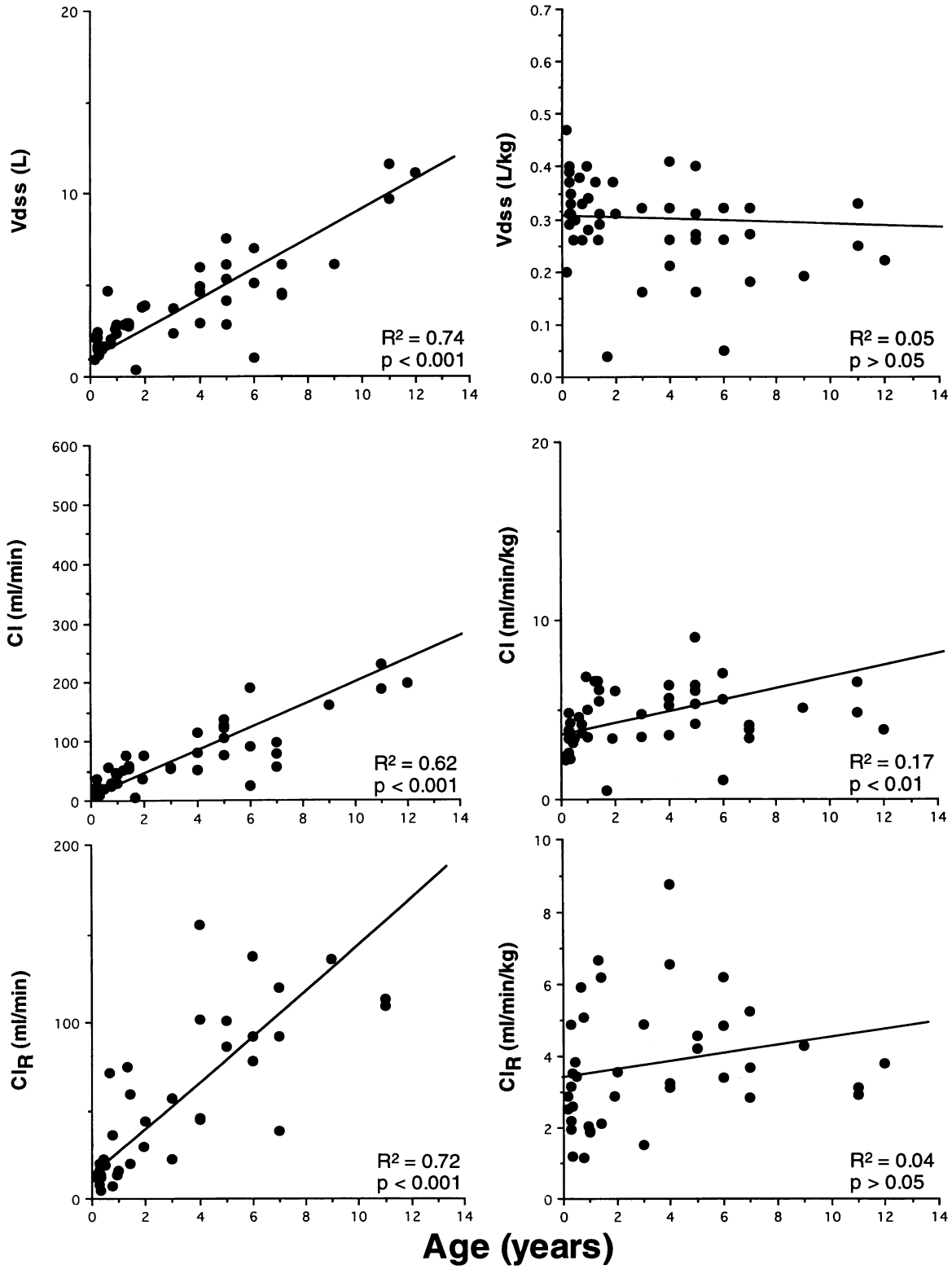


FIG. 2. Developmental characteristics of piperacillin disposition relative to age. The piperacillin pharmacokinetic parameter estimates $V_{ss}$, CL, and $CL_R$ are plotted versus subject age. The observed linear relationship between age and these parameter estimates are diminished when they are normalized for subject weight.

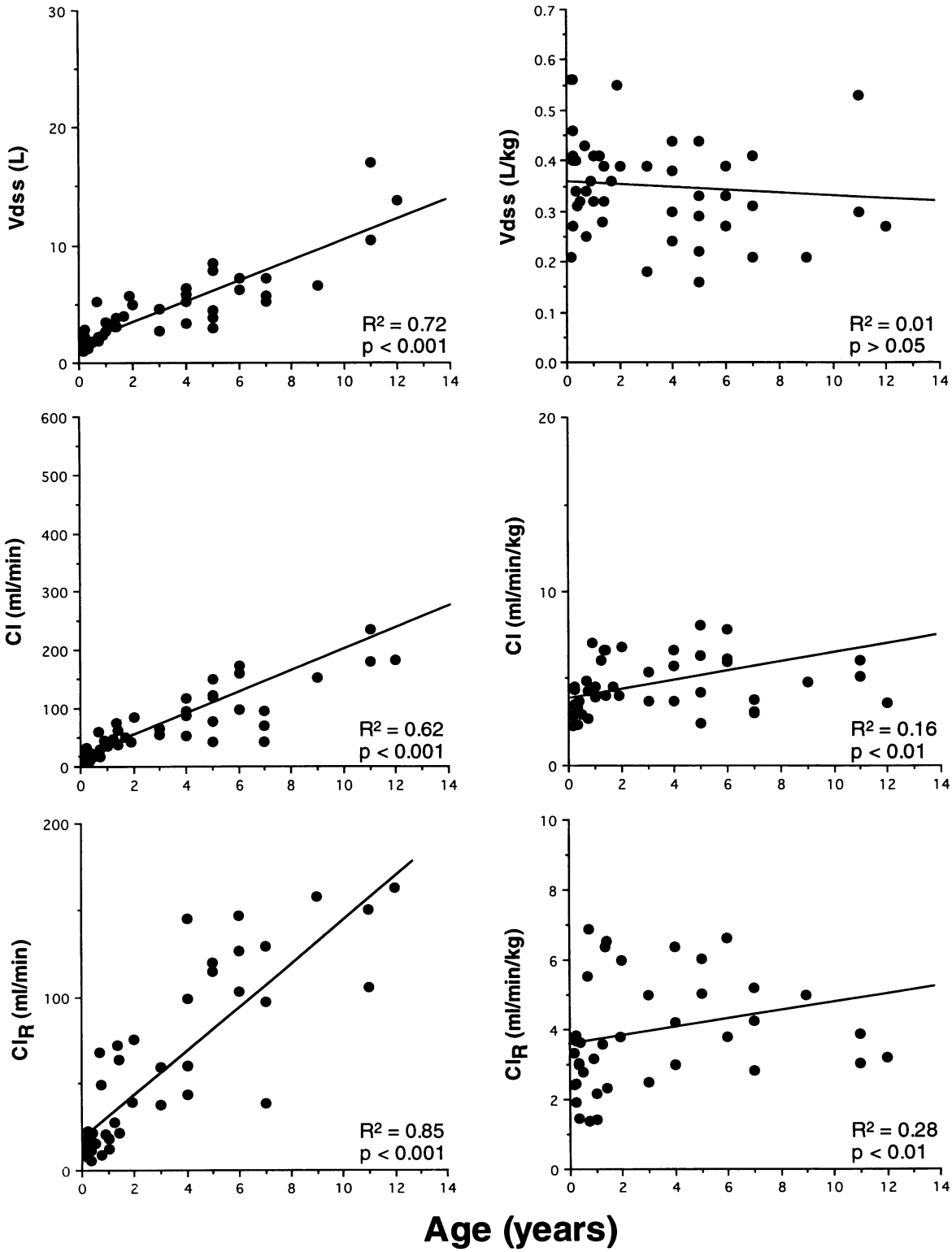


FIG. 3. Developmental characteristics of tazobactam disposition relative to age. The tazobactam pharmacokinetic parameter estimates $V_{ss}$, CL, and $CL_R$ are plotted versus subject age. The observed linear relationship between age and these parameter estimates are diminished when they are normalized for subject weight.

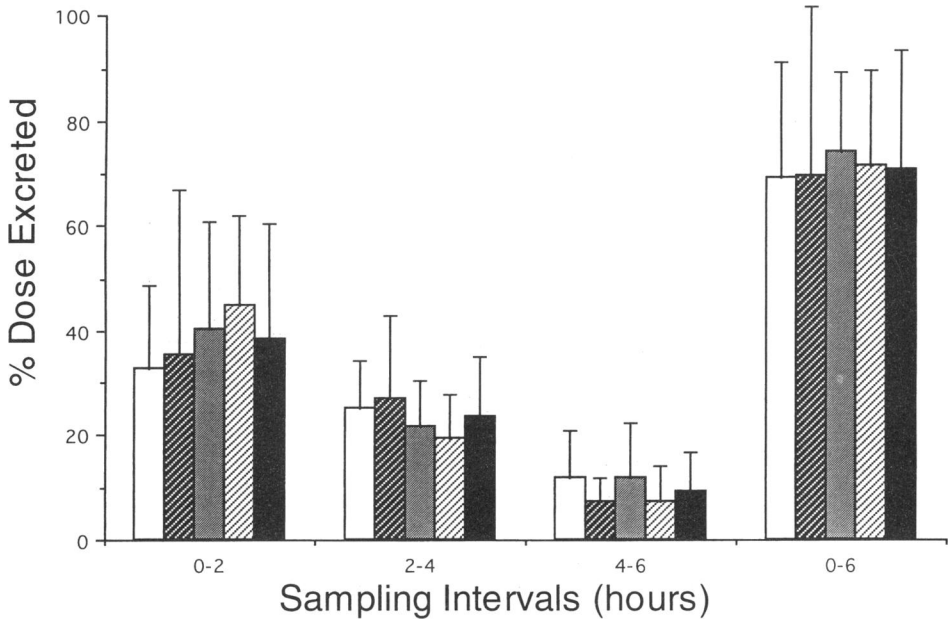


FIG. 4. Urinary recovery of piperacillin. Each bar represents the mean (±SD) for the percentage of the dose excreted during the indicated sampling intervals. □, 2 to 5 months of age; , 5 to 23 months of age; ▨ 2 to 5 years of age; ▨, 6 to 12 years; ■, overall.

after high-dose administration (9.5:1 at the peak and 7.3:1 at the trough), although greater disparity was observed in this ratio after low-dose administration (8.1:1 at the peak, declining steadily to 4.9:1 at the trough).

Tazobactam concentrations of between 1 and 4 mg/liter appear to be required to reduce the observed piperacillin MIC for the majority of clinically relevant pathogens (21). Tazobactam concentrations of 4 mg/liter or less have been shown to markedly reduced the piperacillin MIC for resistant strains of *Escherichia coli*, *Bacteroides fragilis*, and *Proteus* spp., whereas 1 mg of tazobactam per liter or less reduced the piperacillin MIC for *S. aureus*, *H. influenzae*, and *M. catarrhalis* isolates (21). The concentration of tazobactam in plasma was greater than 1 mg/liter for the majority of the 4-h study period after both high- and low-dose drug administration (Fig. 1).

The concentration of tazobactam metabolite M1 was detectable in the plasma of 18 of the 47 study subjects. The appearance rate of this antibacterially inactive metabolite was highly variable, precluding any assessment of its formation or elimination characteristics. These preliminary data would sug-

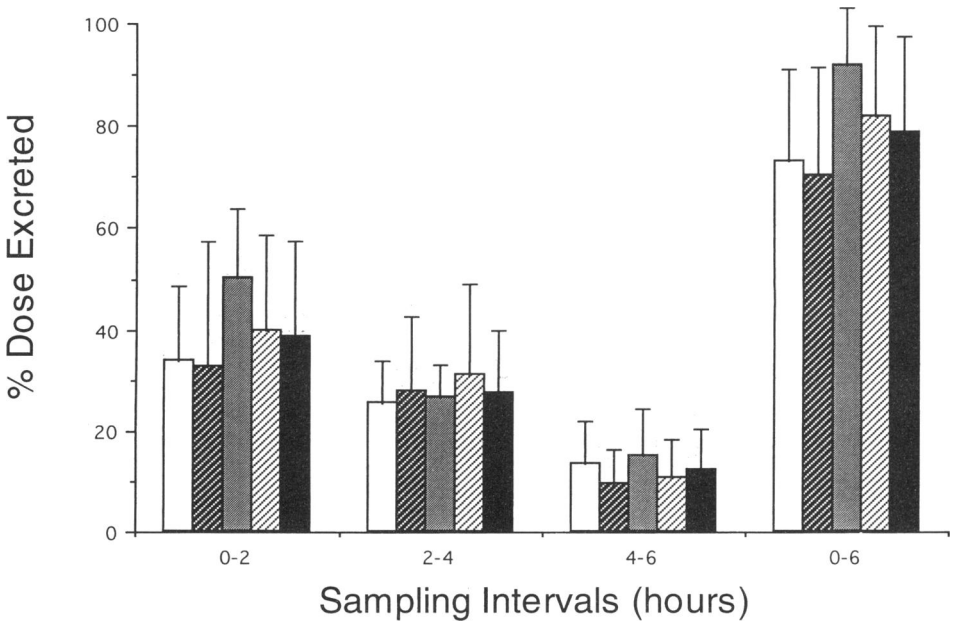


FIG. 5. Urinary recovery of tazobactam. Each bar represents the mean (±SD) for the percentage of the dose excreted during the indicated sampling intervals. □, 2 to 5 months of age; , 5 to 23 months of age; ▨, 2 to 5 years of age; ▨, 6 to 12 years; ■, overall.

TABLE 4. Predicted pharmacodynamic relationships for doses of 100 mg of piperacillin and 12.5 mg of Tazobactam per kg in infants and children

| $MIC_{90}$ (mg/liter)[a] | $T >$ MIC (h)[b] | Representative pathogen[c] |
|---|---|---|
| ≤0.5 | 9.5 | *Moraxella catarrhalis*[d], *Haemophilus influenzae*[d] *Streptococcus pneumoniae*[e], beta-hemolytic streptococci[e] |
| 1.0 | 8.5 | *Proteus vulgaris* |
| 2.0 | 7.6 | *Bacteroides fragilis* |
| 4.0 | 6.6 | *Streptococcus faecalis*[e], *Staphylococcus aureus*[d], *Escherichia coli*, *Morganella morganii* |
| 8.0 | 5.7 | |
| 16.0 | 4.7 | *Klebsiella pneumoniae* |
| ≥32 | | *Enterobacter aerogenes*, *Enterobacter cloacae*, *Pseudomonas aeruginosa* |

[a] $MIC_{90}$, MIC at which 90% of strains are inhibited.
[b] $T >$ MIC, the time during which the piperacillin concentration in plasma exceeded the corresponding MIC.
[c] Unless indicated otherwise, MICs at which 90% of strains are inhibited were obtained from reference 23.
[d] β-Lactamase-positive strains.
[e] MICs at which 90% of strains are inhibited were obtained from reference 9.

gest minimal to no accumulation of M1 in patients receiving 12.5 mg of tazobactam per kg intermittently every 6 to 8 h.

Many authorities have advocated the time that the drug concentration exceeds the MIC for the pathogen as the primary determinant of antimicrobial efficacy for beta-lactam antibiotics, whereas the peak drug concentration or AUC has been proposed as the more important parameter for aminoglycosides and quinolones (8, 9). Integrating the concept of time above the MIC with the single-dose piperacillin and tazobactam pharmacokinetic data generated in the present study provides a rational basis for the development of preliminary dosing guidelines for the administration of this drug combination to infants and children for the treatment of systemic infections. By using the mean pharmacokinetic parameter estimates for both piperacillin and tazobactam derived in our study, the representative times that plasma piperacillin concentrations exceeded the MICs for various pathogens were determined and are given in Table 4. This analysis would support the use of a dose of 100 mg of piperacillin coadministered with 12.5 mg of tazobactam per kg of body weight administered every 8 h to achieve effective antibacterial drug concentrations in plasma and tissue (6, 11, 34, 36) against pathogens for which piperacillin MICs are ≤2 mg/liter. This dosing recommendation is in agreement with preliminary piperacillin-tazobactam time-kill curve studies in serum (34), tissue distribution-concentration-time data (20, 36), and clinical efficacy studies (10, 23, 31). A more frequent dosing regimen, i.e., every 6 h rather than every 8 h, may be necessary for the successful treatment of infections caused by pathogens for which piperacillin MICs are 4 to 8 mg/liter, in which the time above the MIC ranges from 6.6 to 5.7 h, respectively (Table 4). Thus, our data would support a proposed dose of 100 mg of piperacillin and 12.5 mg of tazobactam administered per kg of body weight every 8 h in infants and children for the treatment of infections caused by pathogens for which piperacillin MICs are ≤2 mg/liter and every 6 h for pathogens for which MICs are between 4 and 8 mg/liter. Controlled clinical efficacy trials of 100 mg of piperacillin plus 12.5 of tazobactam per kg of body weight administered every 6 to 8 h should be undertaken to assess the accuracies of these dose recommendations.

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