Piperacillin and Tazobactam Exhibit Linear Pharmacokinetics after Multiple Standard Clinical Doses

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A population pharmacokinetic (PK) analysis was conducted to determine if piperacillin and tazobactam exhibited linear or nonlinear PKs and if incremental changes in the daily dosage of piperacillin affected tazobactam PKs. Four dosage groups were evaluated after multiple dosing regimens. Concentrations of drug in plasma and amounts in urine were best fitted by using a linear two-compartment PK model. No significant difference between dosing groups was seen for any piperacillin or tazobactam PK parameters. Both drugs exhibited linear PKs when given at usual clinical doses. Tazobactam PKs did not appear to be affected by the different dosing regimens of piperacillin.

Piperacillin-tazobactam is currently recommended for the treatment of intra-abdominal, lower respiratory tract, skin and skin structure, and gynecologic infections. This β-lactamase inhibitor-antibiotic combination has been developed to overcome the ongoing problem of enzymatic degradation by β-lactamase enzymes (19, 27). There are some controversial reports in the literature concerning the pharmacokinetic (PK) behavior of these two drugs. During the past 2 decades, several authors have proposed that piperacillin exhibits nonlinear PKs, i.e., that its total clearance (CL) decreases or that its terminal elimination half-life (t1/2) increases with rising plasma drug concentrations (2, 3, 4, 15, 24), while others have proposed that the drug follows linear PKs (7, 8, 10, 13, 17, 18, 21, 22, 28–30). Results suggesting nonlinear elimination of piperacillin are, however, controversial. In essence, the basic principles that need to be met to conclude that the drug’s PKs is nonlinear were not completely fulfilled. Despite these existing contradictions, no attempts to reach a consensus on the PK behavior of piperacillin have been conducted.

Some authors have suggested that the concomitant administration of piperacillin influences the elimination of tazobactam (17, 21, 29). Although the PKs of tazobactam might be different when used alone, it is never used this way clinically. Because it is currently always administered concomitantly with piperacillin, it is relevant to determine if the PKs of tazobactam is different when administered with clinically used low or high dosages of piperacillin. The objectives of this study were therefore to determine if piperacillin and tazobactam exhibited linear or nonlinear PKs and if incremental changes in doses of piperacillin affected tazobactam PKs when we administer these two drugs at usual clinical dosages.

Data were obtained from previous PK studies (17) involving 27 healthy adult male volunteers (Wyeth Ayerst Inc.). Exclusion criteria included abnormalities in baseline chemistries, histories or clinical evidence of renal or hepatic diseases, and histories of hypersensitivity to β-lactam antibiotics or β-lactamase inhibitors. The subjects did not take any other medications for 7 days before and during the study period. All subjects were within 15% of their ideal weights for their ages and heights according to the standards established by the Metropolitan Life Insurance Company. We evaluated four dosage groups after 3 to 5 days of multiple dosing (8 to 18 g of piperacillin/day and 1 to 2.25 g of tazobactam/day). Piperacillin-tazobactam was administered intravenously at dosages of 2.25 g every 6 h to 5 subjects (group 1), 3.375 g every 6 h and 4.5 g every 8 h to 12 subjects (group 2), 4.5 g every 6 hours to 5 subjects (group 3), and 3.375 g every 4 hours to 5 subjects (group 4). Doses were given by 5 (groups 1 and 3) or 30 (groups 2 and 4)-min infusion rates. Concentrations and amounts of piperacillin and tazobactam in plasma and urine, respectively, were determined by using previously validated high-performance liquid chromatography assays (unpublished data). Schedules for plasma and urine sampling were variable among the four dosage groups. The average number of plasma samples per subject was 30 (range, 24 to 39), while a mean of 11 (range, 9 to 12) urine collections were performed for each individual. All plasma and urine samples were stored at −70°C until analysis.

PK analyses were performed by using compartmental PK techniques (9). No evidence of a nonlinear PK elimination (i.e., elimination exhibiting the classic “hockey stick” effect, whereby concentrations fall very slowly at first [the handle of the hockey stick] and then very rapidly) (26) was seen by visual inspection of any individual subject’s concentration in plasma (logarithmic scale) versus time curves following piperacillin-tazobactam administrations. We therefore investigated linear PK models for the quality of fitting, which was assessed by visual inspection of graphs (concentrations versus time, weighted residuals versus observed concentrations) and computation of Akaike’s information criterion test (1). All concentrations and amounts of piperacillin or tazobactam in plasma and urine, respectively, were best fitted by using a linear two-compartment PK model. Individual PK parameter estimates (ADAPT-II) were used as priors for each dosing group, and population PK analyses were performed by using an iterative two-stage methodology (5, 6). All concentrations were fitted with a weighting factor of \( W_i = 1/S_i^2 \) where the variance \( S_i^2 \) was calculated for each observation by using the equation \( S_i^2 = (a \times Y_i) + (b)^2 \). The slope (a) is related to the sum of all errors associated with each concentration, and the intercept (b) is related to the limit of detection of the analytical assay. The following series of differential equations describes the PK model:
\[
\frac{dX(1)}{dt} = \frac{R(1)}{V_c \cdot ABW} \cdot X(1) + \frac{CL_{NR} + CL_D}{V_c \cdot ABW} \cdot X(1) + \frac{CL_D}{V_p \cdot ABW} \cdot X(2)
\]
\[
\frac{dX(2)}{dt} = \frac{CL_D}{V_c \cdot ABW} \cdot X(1) - \frac{CL_D}{V_p \cdot ABW} \cdot X(2)
\]
\[
\frac{dX(3)}{dt} = \frac{CL_R}{V_c \cdot ABW} \cdot X(1)
\]

where \( R(1) \) is the zero-order infusion rate of either piperacillin or tazobactam (mg/h); \( X(1), X(2), \) and \( X(3) \) are the amounts of drug in the central, peripheral, and urinary compartments, respectively; \( V_c \) and \( V_p \) are the central and peripheral volumes of distribution (liters/kg), respectively; \( CL_{NR} \), \( CL_D, \) and \( CL_R \) are the distributional, nonrenal, and renal clearances of piperacillin or tazobactam, respectively; and \( ABW \) is the actual body weight. The observed concentrations \( [Y(1)] \) and amounts \( [Y(2)] \) of piperacillin or tazobactam in plasma and urine, respectively, were simultaneously fitted by the model by using the following output equations:

\[
Y(1) = \frac{X(1)}{V_c \cdot ABW}
\]
\[
Y(2) = X(3) - \text{store}[R(2), 3]
\]

\( X(3) - \text{store}[R(2), 3] \) is the amount of tazobactam or piperacillin that was excreted unchanged in the urine during each specified collection interval to be fitted. Total volumes of distribution (\( V_{SS} \)) were calculated as the sum of \( V_c \) and \( V_p \). CL was calculated by adding \( CL_{NR} \) and \( CL_R \). Maximum concentrations of drug in plasma (\( C_{max} \)) were obtained directly from the observed concentrations versus time points. We calculated the estimated areas under the plasma drug concentration-time curve (AUC) of either compound during a dosing interval at steady state by using the linear trapezoidal rule.

Piperacillin and tazobactam PK parameters of the different dosage groups were compared by using a one-way analysis of variance (ANOVA) for unbalanced designs. The relationships between the AUC/dose, the CL, the \( V_{SS} \), and elimination \( t_{1/2} \) versus the administered doses of piperacillin and tazobactam were determined by linear regression. We stipulated a priori that a \( P \) value of less than 0.05 would be associated with statistical significance.

The proposed linear PK model predicted the concentrations of piperacillin and tazobactam in plasma and the amounts in urine very well, without any evidence of accumulation in each of the individual concentration-time data sets. The relationships between the dose and the estimated mean AUC/dose, the calculated individual CL, \( V_{SS} \), and \( t_{1/2} \) versus the doses of piperacillin and tazobactam were determined by linear regression. We stipulated a priori that a \( P \) value of less than 0.05 would be associated with statistical significance.
parameters of piperacillin and tazobactam were 11 and 6%, respectively. Mean values for the different estimated PK parameters are presented for the four dosage groups for piperacillin and tazobactam in Table 1.

Previous investigators have postulated that piperacillin exhibited a nonlinear PK behavior, inferring that its elimination does not follow first-order processes (2, 3, 4, 15, 24). Tjandra-maga et al. (24) reported disproportionate AUCs, prolonged terminal elimination $t_{1/2}$, and reduced CL and CLR with increasing doses of piperacillin when they administered 1 to 6 g as single-dose boluses to healthy volunteers. Batra et al. (3) observed similar trends after the administration of two multiple-dosing regimens (4 g intravenously q8h and 6 g intravenously q6h) of piperacillin. The data obtained by Morrison and Batra (15) also suggested a dose-dependent effect on the PKs of piperacillin when they administered 1 to 6 g of a single dose (g/day) and to see if using different doses of piperacillin modifies the PK profile of tazobactam. From this analysis, we conclude that the PKs of tazobactam is linear and unaffected by the coadministration of different doses of piperacillin. The results of the present study agree with those obtained by several other investigators (7, 8, 10, 13, 17, 18, 21, 22, 28, 29, 30).

Analogous to piperacillin, controversial information suggesting a slower elimination for tazobactam with dose escalation (20, 21) or when coadministered with piperacillin (17, 21, 29) has been published. The mechanism involved in this potential dose-dependent elimination for tazobactam is not yet defined, but saturation of its tubular secretion process has been proposed (20, 21, 29). Sorgel and Kinzig (20) have evaluated the PKs of tazobactam alone over the dose range of 0.1 to 1 g in healthy volunteers. They reported considerable reductions in tazobactam CL and CLR with increasing doses while the terminal elimination $t_{1/2}$ was prolonged. The differences in the PK parameter values were, however, essentially observed at the lower range of doses studied. Plasma tazobactam concentrations at 0.1- and 0.25-g doses were very close to the detection limit, which may have prevented the accurate calculations of the PK parameters for these dose levels compared with the higher doses administered. Zaghloul et al. (30) compared the PKs of tazobactam given alone (40 mg/kg) to the PKs of tazobactam when coadministered with piperacillin (320 mg/kg) in dogs. They concluded that piperacillin significantly reduced the elimination of tazobactam. The absence of a crossover design in the protocol and the small number of dogs in each arm (three per group) limit their comparison. Similarly, Wise et al. (29) reported decreases in tazobactam elimination when administered with piperacillin to healthy volunteers. As pointed out by different authors (13, 17), their PK parameter values were lower compared with the ones reported in similar healthy populations, making their interpretation difficult.

We designed the present study to assess if the PKs of tazobactam was linear between the dose range studied (1 to 2.25 g/day) and to see if using different doses of piperacillin modifies the PK profile of tazobactam. From this analysis, we conclude that the PKs of tazobactam is linear and unaffected by the coadministration of different doses of piperacillin. The results of the study conducted by Reed et al. (18) in a pediatric

<table>
<thead>
<tr>
<th>Piperacillin/ tazobactam dose (g/day)</th>
<th>Parameter estimate for piperacillin [% CV]/estimate for tazobactam [% CV]*a</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CL_{NR} (liters/h)</td>
</tr>
<tr>
<td>8/1</td>
<td>8.4 [30]/6.4 [28]</td>
</tr>
<tr>
<td>12/1.5</td>
<td>6.6 [14]/4.8 [9]</td>
</tr>
<tr>
<td>16/2</td>
<td>7.0 [17]/6.3 [13]</td>
</tr>
<tr>
<td>18/2.25</td>
<td>7.4 [15]/4.8 [10]</td>
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</tbody>
</table>

*CV, interindividual variation.
population, as well as those reported by Occhipinti et al. (17), support our conclusions.

Contrary to what has been proposed, neither piperacillin (8 to 18 g/day) nor tazobactam (1 to 2.25 g/day) exhibited non-linear PKs with usual clinical dosing regimens. The different dosing regimens of piperacillin did not affect tazobactam PKs.

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REFERENCES