

## Infectious Diseases

## Comparative Pharmacodynamics of Intermittent and Prolonged Infusions of Piperacillin/Tazobactam Using Monte Carlo Simulations and Steady-State Pharmacokinetic Data from Hospitalized Patients

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Piperacillin/tazobactam is a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination with in vitro activity against a broad range of gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*.<sup>1,2</sup> Because of its antibacterial spectrum, favorable adverse event profile, and extensive clinical experience, piperacillin/tazobactam is frequently recommended and used for the empiric treatment of serious infections, such as complicated intraabdominal infections and nosocomial pneumonia, in hospitalized patients.<sup>3,4</sup> In patients with creatinine clearances (CrCl) greater than or equal to 40 mL/min, the usual dose of piperacillin/tazobactam is 3.375 g every 6 hours for indications other than nosocomial pneumonia.<sup>5</sup> The most common organism isolated from the respiratory tract of patients in an intensive care unit is *P. aeruginosa*.<sup>6</sup> Because this organism tends to be less susceptible to piperacillin/tazobactam than are Enterobacteriaceae, a larger dose of 4.5 g every 6 hours is recommended for the empiric treatment of nosocomial pneumonia.<sup>5</sup> Based on the manufacturer's recommendations, doses are administered by intravenous infusion over 30 minutes.<sup>5</sup>

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**BACKGROUND:** Prolonging the infusion of a  $\beta$ -lactam antibiotic enhances the time in which unbound drug concentrations remain above the minimum inhibitory concentration ( $fT > MIC$ ).

**OBJECTIVE:** To compare the pharmacodynamics of several dosing regimens of piperacillin/tazobactam administered by intermittent and prolonged infusion using pharmacokinetic data from hospitalized patients.

**METHODS:** Steady-state pharmacokinetic data were obtained from 13 patients who received piperacillin/tazobactam 4.5 g every 8 hours, infused over 4 hours. Monte Carlo simulations (10,000 pts.) were performed to calculate pharmacodynamic exposures at 50%  $fT > MIC$  for 4 intermittent-infusion regimens (3.375 g every 4 and 6 h, 4.5 g every 6 and 8 h) and 4 prolonged-infusion regimens (2.25 g, 3.375 g, 4.5 g, and 6.75 g every 8 h [4-h infusion]) of piperacillin/tazobactam using pharmacokinetic data for piperacillin. Cumulative fraction of response (CFR) was calculated using MIC data for 6 gram-negative pathogens (Meropenem Yearly Susceptibility Test Information Collection, 2004–2007), and probability of target attainment (PTA) was calculated at MICs ranging from 1  $\mu$ g/mL to 64  $\mu$ g/mL.

**RESULTS:** The CFR for 3.375 g every 4 hours (intermittent infusion) and 3.375–4.5 g every 8 hours (prolonged infusion) greater than or equal to 90.3% for *Escherichia coli*, *Serratia marcescens*, and *Citrobacter* spp. Increasing the prolonged-infusion dose to 6.75 g improved the CFR to greater than 90% for *Enterobacter* spp. For every regimen evaluated, the CFR was less than 90% for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. At an MIC of 16  $\mu$ g/mL, PTA was greater than 90% for one intermittent-infusion regimen (3.375 g every 4 h) and 3 prolonged-infusion regimens ( $\geq$ 3.375 g every 8 h), but no regimen achieved a PTA greater than 90% at an MIC of 64  $\mu$ g/mL.

**CONCLUSIONS:** At doses greater than or equal to 3.375 g every 8 hours, 4-hour infusions of piperacillin/tazobactam achieved excellent target attainment with lower daily doses compared with standard regimens at MICs less than or equal to 16  $\mu$ g/mL.

**KEY WORDS:** Monte Carlo, pharmacodynamics, piperacillin, prolonged infusion, tazobactam.

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The time in which unbound drug concentrations remain above the minimum inhibitory concentration ( $fT > MIC$ ) of an infecting pathogen is the pharmacodynamic parameter that predicts clinical and microbiologic efficacy for  $\beta$ -lactam antibiotics.<sup>7-9</sup> Near-maximal bactericidal activity for penicillins is achieved when the  $fT > MIC$  is 50% of the dosing interval or longer.<sup>7-10</sup> However, most Food and Drug Administration (FDA)-approved dosing regimens for  $\beta$ -lactams commonly used today were designed prior to our current knowledge of antimicrobial pharmacodynamics. Previous reports have demonstrated that conventional dosing regimens of certain  $\beta$ -lactams may not reliably achieve the desirable pharmacodynamic targets required to maximize bactericidal activity, especially for isolates with MICs close to or at the susceptibility breakpoint of the drug.<sup>8,10-14</sup> In addition, resistance among gram-negative pathogens continues to be a major public health problem, as the prevalence of multidrug resistance has increased while the development of novel agents with activity against these pathogens has decreased.<sup>6,15-17</sup> Therefore, it is important to evaluate alternative doses and dosing strategies for currently available  $\beta$ -lactams, with the goal of optimizing the pharmacodynamic profiles of these drugs against gram-negative bacteria.

Dose optimization for  $\beta$ -lactams may be accomplished by increasing the dose while keeping the dosing interval the same, by administering the same dose more frequently, or by prolonging the duration of the intravenous infusion.<sup>12,18,19</sup> Previous analyses have shown that increasing the dose is an ineffective strategy to enhance  $fT > MIC$  for drugs with short half-lives, such as piperacillin/tazobactam.<sup>8</sup> Some potential drawbacks to administering the same dose more frequently are increased acquisition and preparation costs for pharmacy and increased administration times and costs for nursing. Prolonging the duration of the intravenous infusion has been shown to be an effective strategy for improving pharmacodynamic exposures,<sup>8,12</sup> but continuous infusion of the daily dose is less practical because a dedicated intravenous catheter is required for drug administration. Prolonging the length of the infusion to half of the dosing interval, for example, enhances drug exposure while allowing time for other drugs to be administered through the same intravenous catheter. This approach has the added benefit of requiring lower daily doses than are required by the other dose optimization strategies, thereby decreasing drug expenditures.<sup>8,12</sup>

Although previous studies have evaluated the pharmacodynamics of prolonged infusions of piperacillin/tazobactam, the pharmacokinetic data used in those studies were derived from select patient populations (primarily surgery patients), and the majority of the patients received a single dose infused over 30 minutes.<sup>12,20</sup> However, the pharmacokinetic characteristics of piperacillin/tazobactam may be different in nonsurgery patients who receive multiple doses

administered by prolonged infusion. In addition, the previous studies evaluated only 2 doses of piperacillin/tazobactam (3.375 g, 4.5 g) against 3 gram-negative pathogens (*P. aeruginosa*, *Escherichia coli*, *Klebsiella* spp.).<sup>12,20</sup> Therefore, the clinical utility of other doses should be evaluated against a broader range of bacteria. We recently reported the steady-state pharmacokinetics of piperacillin/tazobactam administered by prolonged infusion in hospitalized patients with a suspected or documented bacterial infection.<sup>21</sup> Patients received 4.5 g every 8 hours, infused over 4 hours, and the mean maximum concentration ( $C_{max}$ ) and minimum concentration ( $C_{min}$ ) were mean  $\pm$  SD,  $108.2 \pm 31.7$   $\mu$ g/mL and  $27.6 \pm 26.3$   $\mu$ g/mL, respectively.<sup>21</sup> Using the pharmacokinetic data from this study, the objective of the present study was to compare the pharmacodynamics of 4 intermittent-infusion and 4 prolonged-infusion regimens (including 2.25-g and 6.75-g doses) of piperacillin/tazobactam against 6 common gram-negative pathogens and at specific MICs.

## Methods

### PHARMACOKINETIC DATA

Steady-state pharmacokinetic data for piperacillin were obtained from a study conducted in 13 hospitalized patients ( $\geq 18$  y of age) who received piperacillin/tazobactam 4.5 g every 8 hours, infused over 4 hours.<sup>21</sup> All patients had an estimated CrCl greater than or equal to 40 mL/min and required antimicrobial therapy for a suspected or documented bacterial infection. The mean  $\pm$  SD age, weight, and estimated CrCl for the patient population were  $53.2 \pm 13.2$  years,  $79.6 \pm 13.8$  kg, and  $91 \pm 52$  mL/min, respectively. Seven patients were hospitalized in an intensive care unit, and 6 patients were hospitalized on a general ward. Nine patients were treated for pneumonia, 2 were treated for urinary tract infection/sepsis, 1 for a scrotal abscess, and 1 for fever of unknown origin. The following piperacillin pharmacokinetic parameters were used in the pharmacodynamic analysis (mean  $\pm$  SD): systemic clearance ( $Cl_s$ )  $8.6 \pm 3.0$  L/h; apparent volume of distribution during the  $\beta$  elimination phase ( $V_\beta$ )  $21.8 \pm 5.1$  L; and terminal elimination half-life ( $t_{1/2}$ )  $2.1 \pm 1.2$  h.

### MICROBIOLOGY

MIC data were obtained for 6 gram-negative pathogens from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) database for 2004–2007.<sup>22-25</sup> Bacterial isolates were collected from 15 medical centers in the US, and MICs were determined by broth microdilution as described by the Clinical and Laboratory Standards Institute (CLSI).<sup>26</sup> The organisms and the number of isolates included in the analysis were as follows: *E. coli* ( $n =$

2320), *Klebsiella pneumoniae* (n = 1454), *Enterobacter* spp. (n = 479), *Serratia marcescens* (n = 360), *Citrobacter* spp. (n = 385), and *P. aeruginosa* (n = 2338). Isolates were categorized as susceptible, intermediate, or resistant to piperacillin/tazobactam using CLSI interpretive criteria.<sup>27</sup> The MIC data are shown in Table 1.

### PHARMACODYNAMIC ANALYSIS

Pharmacodynamic exposures, as measured by the  $fT > MIC$ , were calculated by performing 10,000-patient Monte Carlo simulations (Crystal Ball 2000.2.2 software, Decisioneering, Inc., Denver, CO) for 4 intermittent-infusion and 4 prolonged-infusion regimens of piperacillin/tazobactam. The intermittent-infusion regimens were 3.375 g every 6 hours, 4.5 g every 8 hours, 4.5 g every 6 hours, and 3.375 g every 4 hours. The prolonged-infusion (4 h) regimens were 2.25 g, 3.375 g, 4.5 g, and 6.75 g every 8 hours. The  $fT > MIC$  (%) for the intermittent-infusion regimens was calculated using the following equation:

$$fT > MIC (\%) = \ln \left[ \frac{(\text{dose} \times f) / (V_{\beta} \times MIC)}{100/DI} \right] \times (t_{1/2} / 0.693) \times$$

where  $f$  is the fraction of unbound drug,  $\ln$  is the natural logarithm,  $V_{\beta}$  is the apparent volume of distribution during the  $\beta$  elimination phase,  $t_{1/2}$  is the terminal elimination half-life, and  $DI$  is the dosing interval.<sup>19,28,29</sup> The  $fT > MIC$  (%) for the prolonged infusion regimens was calculated using the following equation:

$$fT > MIC (\%) = \left( T_{INF} - \left( \ln \frac{R_0/CL_s}{R_0/CL_s - MIC} \times \frac{t_{1/2}}{0.693} \right) \right) + \left( \left( \ln \frac{R_0}{CL_s} - \ln (MIC) \right) \times \frac{t_{1/2}}{0.693} \right) \times \frac{100}{DI}$$

where  $f$  is the fraction of unbound drug,  $T_{INF}$  is the infusion time (4 h),  $\ln$  is the natural logarithm,  $R_0$  is the infusion rate calculated as (piperacillin dose in mg  $\times$  fraction un-

bound/ $T_{INF}$ ),  $CL_s$  is systemic clearance (L/h),  $t_{1/2}$  is the terminal elimination half-life, and  $DI$  is the dosing interval.<sup>19</sup> The fraction of unbound piperacillin used in the analyses was 0.65–0.75.<sup>12</sup> For both equations, pharmacokinetic input parameters were assumed to follow log-Gaussian distribution, except for fraction unbound, which was assumed to follow a uniform distribution.

The cumulative fraction of response (CFR) was calculated for each organism, using the pharmacodynamic target of 50%  $fT > MIC$ .<sup>7–10</sup> The CFR is the probability of attaining the pharmacodynamic target for a specific population of microorganisms, based on the MIC distribution within the population.<sup>30</sup> In addition, the probability of target attainment (PTA) of 50%  $fT > MIC$  was calculated at specific MIC values ranging from 1  $\mu\text{g/mL}$  to 64  $\mu\text{g/mL}$ . Dosing regimens were considered optimum if the CFR and PTA were 90% or greater.<sup>31</sup>

### Results

The CFR results at 50%  $fT > MIC$  for the intermittent- and prolonged-infusion regimens of piperacillin/tazobactam for the gram-negative pathogens are shown in Table 2. The prolonged-infusion regimen of 6.75 g every 8 hours had the highest CFR for each organism, followed by 4.5 g every 8 hours as a prolonged infusion and 3.375 g every 4 hours as an intermittent infusion. All of the regimens evaluated were optimum for *E. coli* and *S. marcescens*, but none of the regimens was optimum for *K. pneumoniae* and *P. aeruginosa*. For *Enterobacter* spp., only the 6.75 g prolonged-infusion regimen was optimum. Prolonged-infusion regimens greater than or equal to 3.375 g every 8 hours and the intermittent-infusion regimen of 3.375 g every 4 hours were optimum for *Citrobacter* spp. Although the daily doses of the intermittent-infusion regimens were identical, the CFR for 3.375 g every 6 hours was higher than that for 4.5 g every 8 hours for every organism evaluated.

The CFR for each organism increased as the daily dose increased, but the increases in CFR were relatively small for each incremental increase in dose. For the Enterobacteriaceae, the CFR increased 4.6–6.3% as the intermittent-infusion dose increased from 4.5 g every 8 hours to 3.375 g every 4 hours. For the prolonged-infusion regimens, the CFR increased 2.2–7.9% as the dose increased from 2.25 g to 6.75 g every 8 hours. For *P. aeruginosa*, the CFR increased 9.1% for the intermittent-infusion regimens and 8.1% for the prolonged-infusion regimens. For the Enterobacteriaceae, the CFR for the intermittent-infusion regimens of 4.5 g every 6 hours and 3.375 g every 4 hours was comparable to the

**Table 1.** Piperacillin/Tazobactam MIC Data<sup>a</sup>

Organism	Susceptibility					
	MIC <sub>50</sub> ( $\mu\text{g/mL}$ )	MIC <sub>90</sub> ( $\mu\text{g/mL}$ )	Range ( $\mu\text{g/mL}$ )	S (%)	I (%)	R (%)
<i>Escherichia coli</i>	4	4	0.5 to >128	96.2	1.5	2.3
<i>Klebsiella pneumoniae</i>	4	128	0.5 to >128	86.3	1.5	12.2
<i>Enterobacter</i> spp.	4	64	0.5 to >128	83.3	9.2	7.5
<i>Serratia marcescens</i>	2	4	0.5 to 128	95.0	4.2	0.8
<i>Citrobacter</i> spp.	2	32	0.5 to >128	88.1	6.5	5.4
<i>Pseudomonas aeruginosa</i>	4	128	0.5 to >128	89.1		10.9

I = intermediate; MIC<sub>50</sub> and MIC<sub>90</sub> = minimum inhibitory concentration for 50% and 90%, respectively, of strains tested; R = resistant; S = susceptible.  
<sup>a</sup>From the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC), US, 2004–2007.

percent susceptibility displayed in Table 1 for the respective organisms. The CFR for the 3.375-g prolonged-infusion regimen was comparable to or slightly higher than the percent susceptibility for each enteric organism. For *P. aeruginosa*, the percent susceptibility was higher than the CFR for every regimen evaluated.

The PTA results for piperacillin/tazobactam at specific MIC values are shown in Figure 1. All of the regimens evaluated were optimum at MICs less than or equal to 4 µg/mL, and only the 4.5 g every 8 hour intermittent-infusion regimen was not optimum at an MIC of 8 µg/mL. At the susceptibility breakpoint for Enterobacteriaceae (16 µg/mL),<sup>27</sup> only one intermittent-infusion regimen (3.375 g every 4 h) was optimum, while prolonged-infusion regimens greater than or equal to 3.375 g every 8 hours were optimum at this MIC. Only 6.75 g every 8 hours as a prolonged infusion was optimum at an MIC of 32 µg/mL, but none of the regimens was optimum at an MIC of 64 µg/mL, which is the susceptibility breakpoint for *P. aeruginosa*.<sup>27</sup>

**Discussion**

With the constant concerns for bacterial resistance and the decline in antibacterial drug discovery and development, it is imperative that dosing regimens of available antibiotics achieve appropriate pharmacodynamic exposures to maximize clinical efficacy and minimize the potential for further resistance. Alternative dosing strategies may need to be considered if the FDA-approved dosing regimens of a drug do not achieve the necessary pharmacodynamic exposures. Although continuous infusion of a β-lactam antibiotic is effective for optimizing *fT*>MIC, prolonging the length of the infusion to 3–4 hours is a more practical strategy and has been shown to provide bacteri-

dal exposures similar to those of continuous infusions of the same daily dosage.<sup>12</sup> However, if the alternative dosing strategies cannot achieve the necessary pharmacodynamic exposures, combination therapy or a different antimicrobial agent should be considered.

In the present study, we evaluated the pharmacodynamics of several intermittent- and prolonged-infusion regimens of piperacillin/tazobactam using pharmacokinetic data from hospitalized patients who required antibacterial therapy and had estimated CrCl<sub>s</sub> of 40 mL/min or greater.<sup>21</sup> Normally, these patients would receive 3.375 g or 4.5 g every 6 hours, administered over 30 minutes, for empiric treatment of a given infection.<sup>5</sup> However, the CFR for these 2 intermittent-infusion regimens was optimum only for *E. coli* and *S. marcescens*, and neither regimen was optimum at the susceptibility breakpoint for Enterobacteriaceae (16 µg/mL).<sup>27</sup> The PTA for these 2 regimens was optimum only at MICs greater than or equal to 8 µg/mL (Figure 1). These data are in agreement with a previous study suggesting that the susceptibility breakpoint for these piperacillin/tazobactam regimens, based on pharmacodynamic modeling, should be 8 µg/mL.<sup>13</sup> The only intermittent-infusion regimen that was optimum at an MIC of 16 µg/mL was 3.375 g every 4 hours (Figure 1), but the daily drug cost, pharmacy preparation time, and nursing administration time may be limitations with this regimen.

In the current study, lower daily doses administered by prolonged infusion achieved comparable CFR and PTA to those achieved with higher daily dosing regimens administered by intermittent infusion (Table 2, Figure 1). The CFR for the prolonged-infusion regimen of 2.25 g every 8 hours was comparable to those with the intermittent-infusion regimens of 3.375 g every 6 hours and 4.5 g every 8 hours. The CFR for the 3.375-g prolonged-infusion regimen was

**Table 2.** Cumulative Fraction of Response at 50% *fT*>MIC for Intermittent and Prolonged Infusions of Piperacillin/Tazobactam Against Gram-Negative Pathogens<sup>a</sup>

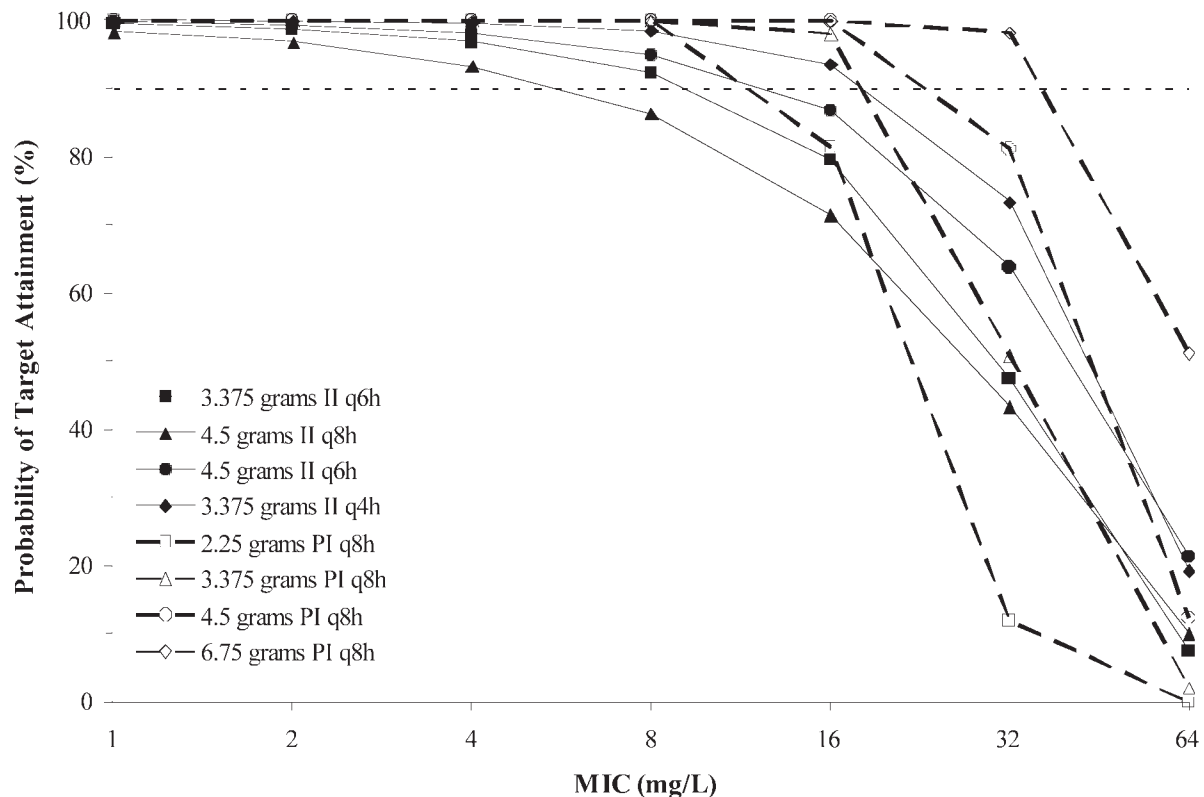
Regimen	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Enterobacter spp.</i>	<i>Serratia marcescens</i>	<i>Citrobacter spp.</i>	<i>Pseudomonas aeruginosa</i>
Intermittent infusions						
4.5 g q8h	92.2	81.8	81.5	92.4	85.4	75.8
3.375 g q6h	94.5	84.1	83.1	94.5	87.7	78.5
4.5 g q6h	95.2	85.3	85.8	95.8	89.5	82.2
3.375 g q4h	96.8	86.6	87.8	97.1	91.4	84.9
Prolonged (4-h) infusions						
2.25 g q8h	96.0	85.6	82.9	95.2	87.5	79.9
3.375 g q8h	96.4	86.9	85.9	96.3	90.3	83.5
4.5 g q8h	98.0	87.0	88.6	100.0	91.3	85.5
6.75 g q8h	100.0	87.8	90.8	100.0	93.2	88.0

*fT*>MIC = percentage of the dosing interval that unbound drug concentrations remain above the MIC; MIC = minimum inhibitory concentration.  
<sup>a</sup>Data are percentages.

comparable to that for 4.5 g every 6 hours by intermittent infusion, and the CFR for the 4.5-g prolonged-infusion regimen was comparable to the CFR for the intermittent regimen of 3.375 g every 4 hours. Based on these data, the lower-dose, prolonged-infusion regimens may be used as empiric therapy in place of higher dose intermittent-infusion regimens while providing comparable pharmacodynamic exposures. In addition, the PTA for the 2.25-g and 3.375-g prolonged-infusion regimens was optimum at MICs less than or equal to 8  $\mu\text{g/mL}$  and less than or equal to 16  $\mu\text{g/mL}$ , respectively (Figure 1). Of the 7336 isolates included in this analysis, the MIC was less than or equal to 8  $\mu\text{g/mL}$  for 6071 (82.8%) isolates. Therefore, the 2.25-g prolonged-infusion regimen may be useful for directed therapy in a substantial number of patients after the MIC is known to be less than or equal to 8  $\mu\text{g/mL}$ . De-escalation of broad-spectrum antibacterial therapy to a more tailored regimen is often encouraged, but de-escalation is usually based solely on susceptibility data without considering the antibiotic dose needed to achieve appropriate pharmacodynamic exposures.<sup>32</sup> Further de-escalation of  $\beta$ -lactam therapy may be accomplished by prolonging the infusion of lower daily doses while achieving appropriate exposures at a given MIC.

Piperacillin/tazobactam 6.75 g every 8 hours, administered as a prolonged infusion, was the only regimen evalu-

ated that achieved an optimum PTA at an MIC of 32  $\mu\text{g/mL}$  (Figure 1). The PTA was 98.3% for this prolonged-infusion regimen compared with 73.4% for the intermittent-infusion regimen of 3.375 g every 4 hours, despite the same daily dose of piperacillin (18 g). The PTA for the 4.5-g prolonged-infusion regimen was also higher than for the intermittent-infusion regimen of 3.375 g every 4 hours at this MIC. Unfortunately, none of the regimens evaluated were optimum at an MIC of 64  $\mu\text{g/mL}$ , which is the susceptibility breakpoint for *P. aeruginosa*.<sup>27</sup> As a result, patients with serious infections caused by *P. aeruginosa* with MICs of 64  $\mu\text{g/mL}$  will receive suboptimal piperacillin/tazobactam therapy, regardless of the dose and dosing strategy employed. In a retrospective cohort study, empiric treatment with piperacillin/tazobactam in patients with bacteremia caused by *P. aeruginosa* was associated with increased 30-day mortality if the isolates had MICs of 32–64  $\mu\text{g/mL}$ .<sup>11</sup> However, empiric treatment was not associated with increased mortality if the MICs were less than or equal to 16  $\mu\text{g/mL}$ .<sup>11</sup> Although this study evaluated a relatively small number of patients, it may be prudent to avoid piperacillin/tazobactam for treatment of infections outside the urinary tract caused by *P. aeruginosa* if the MIC is greater than 16  $\mu\text{g/mL}$ . In the MYSTIC database, which we used in this study, 122 (5.2%) and 65 (2.8%) of



**Figure 1.** Probability of target attainment for intermittent- and prolonged-infusion regimens of piperacillin/tazobactam at 50%  $fT > \text{MIC}$  (percentage of the dosing interval that unbound drug concentrations remain above the MIC). II = intermittent infusion; MIC = minimum inhibitory concentration; PI = prolonged infusion.

the 2338 isolates of *P. aeruginosa* had MICs of 32 and 64 µg/mL, respectively.

Most of the data supporting prolonged infusions of β-lactams are derived from Monte Carlo simulations, but there are clinical data supporting prolonged infusion of piperacillin/tazobactam in critically ill patients. In a retrospective cohort study, patients with infections caused by piperacillin/tazobactam-susceptible *P. aeruginosa* received 30-minute infusions of 3.375 g every 4 or 6 hours or 4-hour infusions of 3.375 g every 8 hours.<sup>33</sup> In patients with Acute Physiological and Chronic Health Evaluation (APACHE) II scores of 17 or greater, those who received the prolonged-infusion regimen had significantly lower 14-day mortality rates (12.2% vs 31.6%;  $p = 0.04$ ) and shorter durations of hospital stay (21 days vs 38 days;  $p = 0.02$ ) than did patients who received intermittent-infusion regimens. Although the study has limitations, the findings support the hypothesis that clinical outcomes can be improved in critically ill patients with *P. aeruginosa* infections by optimizing antimicrobial pharmacodynamics. However, it should be noted that piperacillin/tazobactam MICs for *P. aeruginosa* are typically higher than MICs for other gram-negative pathogens; therefore, the benefits of optimizing  $fT > MIC$  will likely be more apparent in patients with infections caused by *P. aeruginosa* or pathogens with higher MICs.

Potential limitations of this study are use of pharmacokinetic data derived from a relatively small number of patients and performance of Monte Carlo simulations for the 6.75-g regimen using pharmacokinetic parameters derived from a 4.5-g dose. Previous studies have demonstrated that piperacillin exhibits nonlinear pharmacokinetics when larger doses are administered.<sup>34-36</sup> In healthy volunteers, the systemic clearance of piperacillin was approximately 107 mL/min for 6.75 g and 9.0 g every 12 hours compared with 182–235 mL/min for 3.375 g every 6 hours and 184–231 mL/min for 4.5 g every 8 hours.<sup>36-38</sup> It has been suggested that the dose-dependent elimination of piperacillin is primarily due to capacity-limited renal excretion.<sup>35</sup> In subjects with normal renal function, renal clearance of lower doses of piperacillin is greater than CrCl, suggesting that tubular secretion contributes to the elimination of the drug. As the dose increases, renal clearance is similar to CrCl, suggesting saturation of tubular secretion, which may account for the slower systemic clearance at larger doses.<sup>35</sup> However, it should be noted that the larger doses in the previous studies were not administered as prolonged infusions. In healthy volunteers, the mean piperacillin  $C_{max}$  following a 1-hour infusion of 6.75 g every 12 hours was 531 µg/mL.<sup>36</sup> In hospitalized patients, the mean piperacillin  $C_{max}$  at the end of a 4-hour infusion of 4.5 g every 8 hours was 108 µg/mL.<sup>21</sup> If the pharmacokinetics of piperacillin administered by prolonged infusion was linear, the  $C_{max}$  following a 6.75-g

dose would be approximately 160 µg/mL. This concentration is still lower than the  $C_{max}$  for a 4.5-g dose infused over 30 minutes.<sup>37,38</sup> Therefore, prolonging the infusion of a 6.75-g dose will result in substantially lower peak concentrations than will intermittent infusions of the same dose, so that saturation of the tubular secretion of piperacillin may not occur and systemic clearance may not be altered. However, the pharmacokinetics of larger piperacillin doses administered by prolonged infusion has not been studied.

Prolonged-infusion regimens of piperacillin/tazobactam greater than or equal to 3.375 g every 8 hours achieved excellent target attainment at 50%  $fT > MIC$  with lower daily doses compared with intermittent-infusion regimens when the MIC was equal to or less than 16 µg/mL. Increasing the dose of the prolonged-infusion regimen to 6.75 g every 8 hours provided optimum exposure for isolates with MICs of 32 µg/mL, but no regimen reliably achieved the desirable pharmacodynamic target when the MIC was 64 µg/mL. Based on pharmacodynamic exposures and clinical experience, we conclude that piperacillin/tazobactam should be used with caution, if at all, when the MIC is greater than 16 µg/mL.

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Farmacodinámica Comparativa de Infusiones Intermitentes y Prolongadas de Piperacilina/Tazobactama Usando la Simulación Monte Carlo y Datos Farmacocinéticos en Estado Estacionario de Pacientes Hospitalizados

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EXTRACTO

**TRASFONDO:** Prolongando la infusión de un antibiótico  $\beta$ -lactámico se aumenta el tiempo en el cual las concentraciones de fármaco libre se mantienen sobre las concentraciones mínimas inhibitorias ( $fT > MIC$ ).

**OBJETIVO:** Comparar la farmacodinámica de varios regímenes de piperacilina/tazobactama administrados por infusión intermitente (II) e infusión prolongada (PI) usando datos farmacocinéticos de pacientes hospitalizados.

**MÉTODOS:** Datos farmacocinéticos en estado estacionario fueron obtenidos de 13 pacientes que recibieron 4.5 gramos cada 8 horas de piperacilina/tazobactama, infundidos por 4 horas. Las simulaciones Monte Carlo (10,000 pacientes) fueron llevadas a cabo para calcular la exposición farmacodinámica a  $50\% fT > MIC$  para 4 regímenes II (3.375 g cada 4 y 6 h, 4.5 g cada 6 y 8 h) y 4 regímenes PI (2.25 g, 3.375 g, 4.5 g, y 6.75 g cada 8 h [infusión de 4 h]) de piperacilina/tazobactama usando datos farmacocinéticos de piperacilina. Fracción acumulada de respuesta (CFR) fue calculada usando datos de MIC para 6 patógenos gram-negativos (Meropenem Yearly Susceptibility Test Information Collection, 2004–2007), y la probabilidad de alcanzar la meta (PTA) fue calculada a MIC desde 1 a 64  $\mu g/mL$ .

**RESULTADOS:** La CFR para 3.375 g cada 4 horas (II) y 3.375–4.5 g cada 8 horas (PI) fue  $>90.3\%$  para *Escherichia coli*, *Serratia marcescens*, y especies *Citrobacter*. Aumentando la dosis de PI a 6.75 g mejoró la CFR a  $>90\%$  para especies *Enterobacter*. Para cada régimen evaluado, la CFR fue  $<90\%$  para *Klebsiella pneumoniae* y *Pseudomonas aeruginosa*. A una MIC de 16  $\mu g/mL$ , PTA fue  $>90\%$  para un régimen II (3.375 g cada 4 h) y 3 regímenes PI ( $\geq 3.375$  g cada 8 h), pero ningún régimen alcanzó una PTA  $>90\%$  a una MIC de 64  $\mu g/mL$ .

**CONCLUSIONES:** A dosis  $\geq 3.375$  g cada 8 horas, infusiones de 4 horas de piperacilina/tazobactama alcanzaron la meta con dosis diarias más bajas comparadas con regímenes estándar de MICs  $\leq 16 \mu g/mL$ .

Traducido por Sonia I Lugo

Pharmacodynamique Comparative de Perfusions Intermittentes et Prolongées de Pipéracilline/Tazobactam à l'Aide de Simulations de Monte Carlo et de Données Pharmacodynamiques à l'Équilibre ("steady state") de Patients Hospitalisés

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RÉSUMÉ

**CONTEXTE:** Le fait de prolonger la perfusion d'un antibiotique de type  $\beta$ -lactam accroît le temps durant lequel la concentration de médicament libre demeure supérieure à la concentration minimale inhibitrice ( $fT > CMI$ ).

**OBJECTIF:** Comparer les pharmacodynamiques de plusieurs posologies de pipéracilline/tazobactam administrée par perfusion intermittente (PI) ou prolongée (PP) à partir de données de patients hospitalisés.

**MÉTHODES:** Des données pharmacocinétiques à l'équilibre ont été collectées sur 13 patients recevant 4.5 g de pipéracilline/tazobactam toutes les 8 heures, en perfusions de 4 heures. Des simulations de Monte Carlo (10,000 patients) ont été effectuées pour calculer les expositions pharmacodynamiques à  $50\% fT > CMI$  pour 4 PI (3.375 g toutes les 4 et 6 heures, 4.5 g toutes les 6 et 8 heures) et 4 PP (2.25 g, 3.375 g, 4.5 g, et 6.75 g toutes les 8 h [perfusions de 4 h]) de pipéracilline/tazobactam, en utilisant les données pharmacocinétiques de la pipéracilline. La fraction de réponse cumulative (FRC) a été calculée à l'aide des CMI pour 6 pathogènes à gram négatif (Meropenem Yearly Susceptibility Test Information Collection, 2004–2007) et la probabilité d'atteinte de la cible a été calculée pour des CMI variant de 1 à 64  $\mu g/mL$ .

**RÉSULTATS:** La FRC pour 3.375 g toutes les 4 heures (PI) et 3.375–4.5 g toutes les 8 heures (PP) a été  $\geq 90.3\%$  pour les espèces *Escherichia coli*, *Serratia marcescens*, et *Citrobacter*. L'accroissement de la dose PP à 6.75 g a amélioré la FRC à  $>90\%$  pour l'espèce *Enterobacter*. Pour tous les régimes de posologie évalués, la CFR a été  $<90\%$  pour *Klebsiella pneumoniae* et *Pseudomonas aeruginosa*. Pour une CMI de 16  $\mu g/mL$ , la probabilité d'atteinte de la cible a été  $>90\%$  pour un régime PI (3.375 g toutes les 4 h) et 3 PP ( $\geq 3.375$  g toutes les 8 h), mais aucun régime n'a permis d'obtenir une probabilité d'atteinte de la cible  $>90\%$  pour une CMI de 64  $\mu g/mL$ .

**CONCLUSIONS:** A des doses  $\geq 3.375$  g toutes les 8 heures, des perfusions de 4 heures de pipéracilline/tazobactam ont permis d'obtenir une excellente atteinte de cible avec des doses journalières plus faibles en comparaison des posologies standard pour des CMI  $\leq 16 \mu g/mL$ .

Traduit par Guy Berthon