J Antimicrob Chemother 2014; **69**: 176–179
doi:10.1093/jac/dkt300 Advance Access publication 18 July 2013

Journal of Antimicrobial Chemotherapy

Pharmacokinetics and pharmacodynamics of extended-infusion piperacillin/tazobactam in adult patients with cystic fibrosis-related acute pulmonary exacerbations

Jill M. Butterfield[1], Thomas P. Lodise[1], Scott Beegle[2], Jonathan Rosen[2], Joshua Farkas[2] and Manjunath P. Pai[1]*

[1]*Albany College of Pharmacy and Health Sciences, Albany, NY, USA;* [2]*Albany Medical Center, Albany, NY, USA*

*Corresponding author. Tel: +1-518-694-7146; Fax: +1-518-694-7062; E-mail: amit.pai@acphs.edu

Received 25 January 2013; returned 13 March 2013; revised 22 April 2013; accepted 26 June 2013

Objectives: Given the high frequency of acute pulmonary exacerbations due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF), piperacillin/tazobactam is commonly used in empirical regimens. While extended-infusion piperacillin/tazobactam has been employed as one strategy to optimize this agent's pharmacodynamics, this approach has not been well characterized in patients with CF. The objectives of this study were to characterize the pharmacokinetics and pharmacodynamics of extended-infusion piperacillin/tazobactam in adult patients with CF and derive optimized piperacillin/tazobactam dosing recommendations.

Methods: Six serum samples were collected from nine adult patients with CF hospitalized for acute pulmonary exacerbations who received 3/0.375 g of piperacillin/tazobactam intravenously for 4 h every 8 h. Population pharmacokinetic models were fitted to the data utilizing first-order, Michaelis–Menten (MM) and parallel first-order/MM clearance. Monte Carlo simulations were performed to determine the probability of target attainment (PTA) for regimens where free piperacillin concentrations were above the MIC for at least 50% of the dosing interval.

Results: The model incorporating MM clearance best described the data. Results of our simulation revealed that piperacillin/tazobactam dosed at 3–4 g for 30 min every 6–8 h led to <90% PTA against MIC values >4 mg/L. More intensive prolonged infusion regimens than are commonly used in practice, such as continuous infusions or 3 h infusions every 6 h, were needed to maximize the PTA for MICs ≥8 mg/L.

Conclusions: Intensive prolonged infusion regimens are the best option to ensure optimal exposures against most susceptible isolates in adult patients with CF.

Keywords: β-lactams, Monte Carlo simulation, prolonged infusions, continuous infusions

Introduction

Acute pulmonary exacerbations secondary to chronic bacterial colonization of the respiratory tract are estimated to cause 90% of deaths in patients with cystic fibrosis (CF).[1] Although there are a wide range of causative pathogens, *Pseudomonas aeruginosa* accounts for this chronic bacterial colonization in nearly 80% of adults with CF.[2] Given that eradication of *P. aeruginosa* is often not possible, antibiotic dosing should be optimized in an effort to reduce the respiratory bacterial burden and improve clinical symptomatology.[3]

A common empirical antipseudomonal antimicrobial regimen used to treat these patients consists of piperacillin/tazobactam and tobramycin. Over time, strategies have been implemented to optimize the dosage of tobramycin in this population, and guidelines now recommend higher daily doses and therapeutic drug monitoring.[3,4] In contrast, piperacillin/tazobactam is given at the same dose in patients with or without CF. This is concerning given that the probability of target attainment (PTA) for piperacillin/tazobactam has been shown to be suboptimal (<90%) using standard FDA-approved dosing in patients without CF.[5–8] Extending the duration of infusion can increase the PTA, but there are limited data on the PTA of extended-infusion piperacillin/tazobactam in patients with CF.[6,9–15] The objectives of this study were to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of extended-infusion piperacillin/tazobactam in adult patients with CF and derive optimized dosing recommendations.

Methods

The study protocol was approved by the Institutional Review Board of Albany Medical Center Hospital (AMCH) (Albany, NY, USA), and written informed consent was obtained from each patient. Adult patients (≥18 years of age) with CF who were receiving piperacillin/tazobactam for

acute pulmonary exacerbations requiring hospitalization were eligible for this study. Patients were excluded if any of the following criteria were met: (i) unable to tolerate venipuncture and multiple blood collections; (ii) female subject who was known to be pregnant; (iii) admitted to the intensive care unit; (iv) estimated creatinine clearance <50 mL/min; and (v) any known hypersensitivity to piperacillin/tazobactam.

As standard hospital protocol, patients were administered 3 g of piperacillin in combination with 0.375 g of tazobactam intravenously (iv) every 8 h for 4 h. All patients were also receiving tobramycin as part of their empirical regimen. The patient's demographic information, past medical history, history of present illness, clinical laboratory data and dosing information were reviewed and documented.

Six blood samples were collected from patients at the following timepoints: just prior to the piperacillin/tazobactam dose being studied (0 h), mid-infusion (2 h), post-infusion (4 h) and at 5, 6.5 and 8 h from the start of infusion. Serum samples were assayed as a batch by the Center for Anti-Infective Research and Development at Hartford Hospital (Hartford, CT, USA) for piperacillin concentrations by use of a validated HPLC method described previously.[8]

All data were analysed in a population PK model using BigNPAG.[9] Three two-compartment structural models were evaluated as previously described:[5,7] (i) elimination as a first-order process; (ii) Michaelis–Menten (MM) process alone; and (iii) an MM process with parallel first-order elimination. Discrimination between the models was accomplished by the rule of parsimony based on Akaike's information criterion (AIC). Upon attaining convergence, maximal *a posteriori* probability (MAP) Bayesian estimates for each patient were obtained using the 'population of one' utility in BigNPAG.[9] After the Bayesian step, goodness of fit and predictive performance were assessed.[5]

Embedded with the final PK model, a series of 5000-subject Monte Carlo simulations (MCSs) were performed using ADAPT 5.[10] Protein binding for patients with and without CF is similar for most drugs, including β-lactams,[11] and so a fixed protein binding of 30% was assumed to reflect unbound concentrations.[5] Simulations were performed for piperacillin using a standard infusion (30 min) of 3 and 4 g every 6 h and 4 g every 8 h, extended infusion (4 h) of 3 g every 8 h, extended infusion (3 h) of 3 and 4 g every 6 h and continuous infusion (24 h) of 12 and 16 g daily. Simulations were based on a 24 h dosing regimen. For each regimen examined, the fraction of simulated subjects who achieved free concentrations above the MIC for at least 50% of the dosing interval (50% $T_{>MIC}$) was calculated for piperacillin MICs ranging from 0.25 to 128 mg/L. The population simulation without process noise option was utilized and log-normal distributions of PK parameters were selected for all simulations.

Results

Nine adult patients were enrolled in the study a mean (SD) of 4.1 (2.5) days into admission. The mean (SD) age was 33.0 (12.6) years, and the majority of patients were female (88.9%) and Caucasian (100%). Average (SD) weight and body mass index were 53.6 (6.5) kg and 20.0 (2.7) kg/m^2, respectively. Mean (SD) population parameter estimates identified by BigNPAG for the linear, MM and parallel first-order/MM models are provided in Table 1. Goodness of fit and predictive performance for each structural model are also displayed in Table 1. The MM model was selected as the final model based on the AIC and goodness-of-fit statistics.

The fractions of simulated subjects who achieved 50% $T_{>MIC}$ against a range of MICs for various dosing regimens are displayed in Figure 1(a and b). For standard 30 min infusion doses, the PTA was >90% for MICs ≤2 mg/L. Against MICs of 4 mg/L, 4 g iv every 6 h for 30 min and all dosing regimens consisting of a prolonged or continuous infusion had a PTA >90%. Acceptable PTA against MICs of 8 mg/L was only seen with prolonged or continuous infusion dosing regimens, with the exception of 3 g iv for 4 h every 8 h (PTA of 87%). Against MICs of 16 mg/L, prolonged or continuous infusions of 12 g/day were estimated to provide ∼70% PTA, but a dose of 4 g iv every 6 h as a 3 h infusion and the same total daily

Table 1. PK parameters and predictive performance of population PK analyses

	Model		
	linear	MM	parallel first-order/MM
Parameter, mean (SD)			
V_{max} (mg/h)		1419.50 (436.04)	980.93 (304.88)
K_m (mg/L)		73.07 (33.72)	269.47 (270.05)
V_c (L)	13.26 (7.86)	12.27 (6.18)	12.00 (8.08)
K_{12} (h^{-1})	0.92 (1.34)	1.28 (1.65)	2.34 (3.12)
K_{21} (h^{-1})	1.73 (4.43)	0.14 (0.18)	1.87 (4.67)
CL (L/h)	16.56 (3.32)	—	9.98 (4.60)
Goodness-of-fit statistics			
AIC	217.54	209.62	217.40
regression line[a]	observed = 1.01 × predicted + 0.16	observed = 1.00 × predicted + 0.33	observed = 1.01 × predicted + 0.35
R^2[b]	0.95	0.96	0.96
mean weighted error (mg/L)	−0.04	−0.09	−0.10
bias-adjusted mean weighted square error (mg/L)^2	1.11	1.09	1.08

K_{12}, transfer rate constant from central compartment to peripheral compartment; K_{21}, transfer rate constant from peripheral compartment to central compartment; K_m, Michaelis–Menten constant; V_c, volume in the central compartment; V_{max}, maximum elimination rate.
[a]Best-fit regression line for the observed–predicted plot after the Bayesian step.
[b]Coefficient of determination for the best-fit linear regression line for the observed–predicted plot after the Bayesian step.

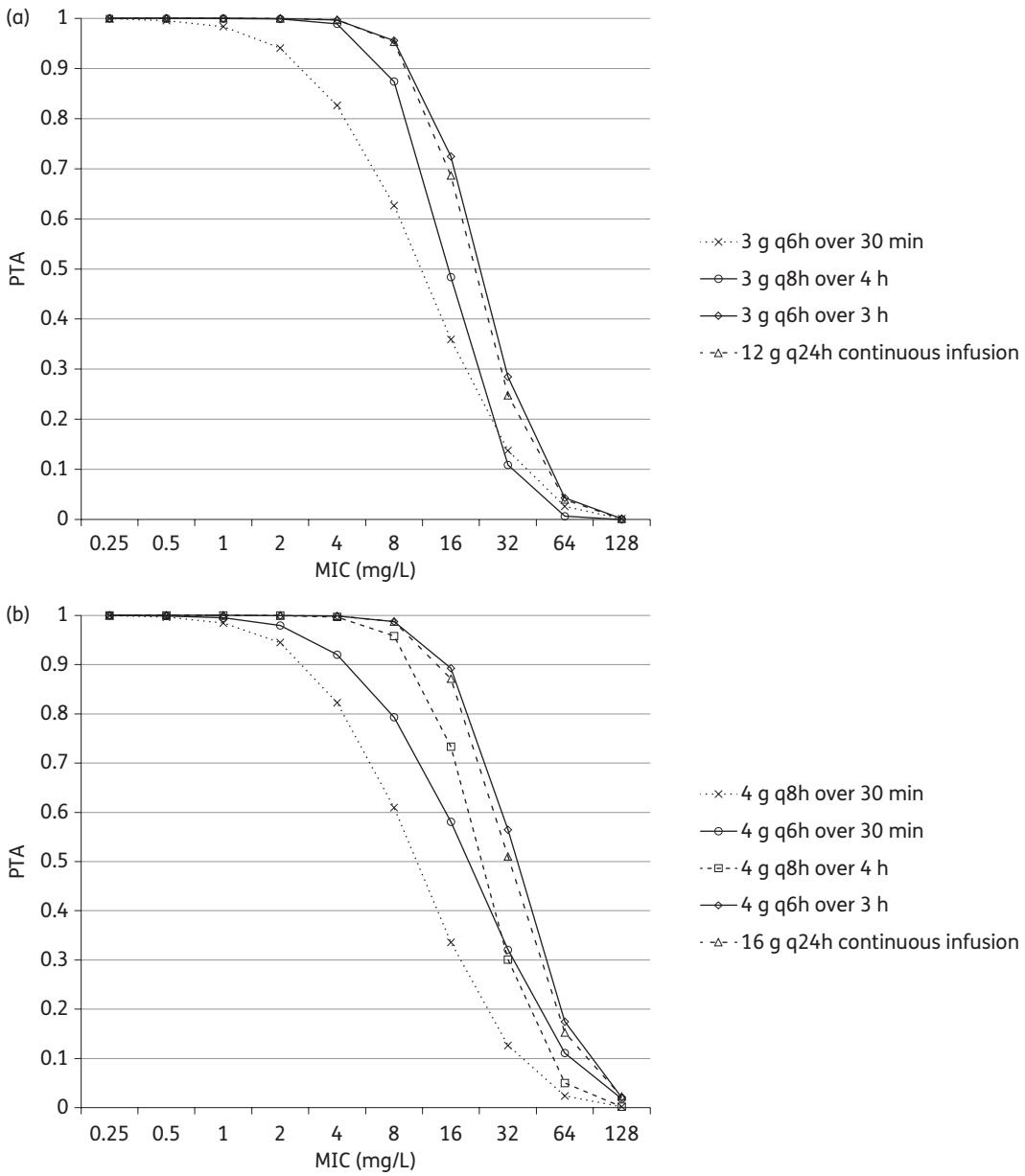

Figure 1. PTA (50% $fT_{>MIC}$) against a range of MICs for the following piperacillin regimens: 3 g iv for either 30 min or 3 h every 6 h (q6h), 3 g iv for 4 h every 8 h (q8h), and 12 g daily (q24h) as a continuous infusion (a), and 4 g iv for either 30 min or 4 h every 8 h (q8h), 4 g iv for either 30 min or 3 h every 6 h (q6h), and 16 g daily (q24h) as a continuous infusion (b).

dose (16 g) as a continuous infusion achieved a PTA of 89% and 87%, respectively. None of the regimens evaluated led to acceptable PTA for MICs >16 mg/L.

Discussion

This study sought to characterize the PK and PD of extended-infusion piperacillin/tazobactam in adult patients with CF hospitalized for acute pulmonary exacerbations. Overall, we found the serum PK of piperacillin to be best explained by an MM model. Our results match up well to previous PK analyses with methodology similar to ours. In patients with CF, Vinks *et al*.[12] also found that an MM model best fitted the data. The population estimates for V_{max} and the MM constant were 2284 mg/h and 92.3 mg/L, respectively, making their calculated intrinsic clearance (CL; V_{max}/K_m) 24.7 L/h.[12] These estimates are consistent with our observed V_{max}, K_m and calculated intrinsic CL of 19.4 L/h. Similarly, Felton *et al*.[7] also reported similar population estimates for V_{max}, K_m and calculated intrinsic CL in patients without CF (1634.7 mg/h, 78.6 mg/L and 20.8 L/h, respectively). In contrast, Bulitta *et al*.[13] demonstrated that linear elimination accounted for most of the CL of piperacillin, but this may be explained by differences in study drug administration and study population.

Despite the differences in final model selection and parameter estimates across studies, the clinical consequences of the high

intrinsic CL estimates for piperacillin/tazobactam in adult CF patients were highly apparent in our MCS analyses. Suboptimal exposure profiles were associated with all conventional intermittent infusions of piperacillin in adult patients with CF against susceptible pathogens with MICs >4 mg/L. In contrast, prolonged or continuous infusion regimens achieved nearly optimal PTA against MICs up to 16 mg/L. Although the same daily doses given as a prolonged infusion are predicted to achieve slightly better PTA than a continuous infusion, the differences were minimal. Since continuous infusion may be a preferred method of administration by patients with CF, the choice between the two regimens should be discussed individually with each patient.

While our findings demonstrate that prolonging the infusion of piperacillin/tazobactam will enhance PD exposures against pathogens with higher MICs, some analyses suggest that MIC is not predictive of outcome in patients with CF.[14,15] Furthermore, a number of studies have demonstrated that prolonged infusion reduces mortality in patients without CF,[16] but outcomes data in patients with CF are very limited. Further data are needed to better understand the clinical implications of MIC testing and prolonged infusion β-lactam therapy among patients with CF. In addition, since concentrations at the site of infection are critical for obtaining a good outcome, further analyses are needed to evaluate the penetration and PD of piperacillin/tazobactam in the lungs of patients with CF. Finally, although our MCS findings provide a good estimate of piperacillin/tazobactam exposures likely to be observed in practice among patients with CF, our analysis included a limited number of PK samples and patients. It is important that our results be validated in a larger patient population in the clinical setting.

Funding

This study was supported in part through an intramural grant from the Albany College of Pharmacy and Health Sciences, Albany, NY, USA.

Transparency declarations

None to declare.

References

1 Rogers GB, Carroll MP, Serisier DJ *et al*. Bacterial activity in cystic fibrosis lung infections. *Respir Res* 2005; **6**: 49.

2 Cystic Fibrosis Foundation Patient Registry. *2011 Annual Data Report*. Bethesda: MD, 2012.

3 Yankaskas JR, Marshall BC, Sufian B *et al*. Cystic fibrosis adult care: consensus conference report. *Chest* 2004; **125** Suppl: 1S–39S.

4 SICOR Pharmaceuticals Inc. *Package Literature for Tobramycin*. June 2005.

5 Lodise TP Jr, Lomaestro B, Rodvold KA *et al*. Pharmacodynamic profiling of piperacillin in the presence of tazobactam in patients through the use of population pharmacokinetic models and Monte Carlo simulation. *Antimicrob Agents Chemother* 2004; **48**: 4718–24.

6 Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on β-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2006; **26**: 1320–32.

7 Felton TW, Hope WW, Lomaestro BM *et al*. Population pharmacokinetics of extended-infusion piperacillin-tazobactam in hospitalized patients with nosocomial infections. *Antimicrob Agents Chemother* 2012; **56**: 4087–94.

8 Kim MK, Capitano B, Mattoes HM *et al*. Pharmacokinetic and pharmacodynamic evaluation of two dosing regimens for piperacillin-tazobactam. *Pharmacotherapy* 2002; **22**: 569–77.

9 Leary R, Jelliffe R, Schumitzky A *et al*. An adaptive grid, non-parametric approach to pharmacokinetic and dynamic (PK/PD) models. In: *Proceedings of the Fourteenth IEEE Symposium on Computer-Based Medical Systems, Bethesda, MD, USA, 2001*. p. 389–94. IEEE, Washington, DC, USA.

10 D'Argenio DZ, Schumitzky A, Wang X. *ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software*. Los Angeles, CA: Biomedical Simulations Resource, 2009.

11 Rey E, Treluyer JM, Pons G. Drug disposition in cystic fibrosis. *Clin Pharmacokinet* 1998; **35**: 313–29.

12 Vinks AA, Den Hollander JG, Overbeek SE *et al*. Population pharmacokinetic analysis of nonlinear behavior of piperacillin during intermittent or continuous infusion in patients with cystic fibrosis. *Antimicrob Agents Chemother* 2003; **47**: 541–7.

13 Bulitta JB, Duffull SB, Kinzig-Schippers M *et al*. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. *Antimicrob Agents Chemother* 2007; **51**: 2497–507.

14 Smith AL, Fiel SB, Mayer-Hamblett N *et al*. Susceptibility testing of *Pseudomonas aeruginosa* isolates and clinical response to parenteral antibiotic administration: lack of association in cystic fibrosis. *Chest* 2003; **123**: 1495–502.

15 Hurley MN, Ariff AH, Bertenshaw C *et al*. Results of antibiotic susceptibility testing do not influence clinical outcome in children with cystic fibrosis. *J Cyst Fibros* 2012; **11**: 288–92.

16 Falagas ME, Tansarli GS, Ikawa K *et al*. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Infect Dis* 2013; **56**: 272–82.