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Short Communication

Optimizing beta-lactam pharmacodynamics against *Pseudomonas aeruginosa* in adult cystic fibrosis patients

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Abstract

Background: Patients with cystic fibrosis (CF) exhibit increased clearance of beta-lactams. The purpose of this study was to predict the probability of beta-lactam target attainment (PTA) against *Pseudomonas aeruginosa* in adult CF patients based on local microbiological data.
Methods: CF-specific pharmacokinetic parameters were obtained from published data for aztreonam, cefepime, ceftazidime, meropenem and piperacillin–tazobactam. Pharmacodynamic modeling was used to determine the PTA for bolus, prolonged infusion, and continuous infusion regimens.
Results: Prolonged infusion of meropenem 2 g every 8 h performed the best among all regimens tested, with a PTA of 83%. The PTA was increased with both prolonged and continuous infusion; however, no regimen reached the target PTA of >90% against *P. aeruginosa* in CF patients at our institution.
Conclusions: Prolonged and continuous infusion provided higher PTA than bolus for all regimens. Further investigation of novel regimens in CF patients is needed.

Keywords: Beta-lactam; Pharmacokinetics; Continuous-infusion; Prolonged infusion; *Pseudomonas aeruginosa*; Pharmacodynamics

1. Introduction

As cystic fibrosis (CF) patients enter adulthood they are commonly colonized with multidrug resistant (MDR) isolates of *Pseudomonas aeruginosa*, may cause significant morbidity and mortality [1]. Most commonly, anti-pseudomonal beta-lactam antibiotics are used in combination with other agents in the treatment of acute pulmonary CF exacerbations in North America [2,3]. Since eradication of *P. aeruginosa* in CF patients is often unrealistic, the goal is to decrease the bacterial burden and improve symptoms. Based on our center's most recent CF registry report, we cared for 109 adult patients and the *P. aeruginosa* infection rate was 57.8%. Our center's rate of mucoid phenotype *P. aeruginosa* and MDR isolates were 74.6% and 11.9%, respectively [4]. The national rate during this time period for mucoid phenotype and MDR isolate were 78% and 16%, respectively [4].

Increases in total body clearance of beta-lactams and aminoglycosides in CF patients were described in the early 1990s [5]. It is not well understood why CF patients display increases in total body clearance; however, it is postulated that renal clearance of antibiotics significantly increases due to lower protein binding and increased glomerular filtration [6]. In order to maximize the efficacy of beta-lactams, pharmacodynamic parameters must be optimized and modeling should be used to predict the probability of desired clinical outcomes.

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We examined the pharmacokinetic–pharmacodynamic profile of several beta-lactams against *P. aeruginosa* isolates from our adult cystic fibrosis patients.

2. Materials and methods

All *P. aeruginosa* cultures and sensitivity results from CF patients 18 years and older were obtained from the clinical microbiology laboratory for January 1, 2013 to December 31, 2013. MICs for aztreonam, cefepime, ceftazidime, meropenem and piperacillin–tazobactam for all non-duplicate *P. aeruginosa* isolates were measured by E-test®. The following Clinical and Laboratory Standards Institute (CLSI) criteria for susceptibility were utilized: ≤16/4 mcg/mL for piperacillin–tazobactam, ≤8 mcg/mL for aztreonam, cefepime and ceftazidime, and ≤2 mcg/mL for meropenem. Only the first *P. aeruginosa* isolate per patient was evaluated in this analysis. If multiple biotypes existed in the same culture, the most resistant profile was utilized.

Pharmacokinetic data for each beta-lactam were obtained from previously published studies in CF patients [6,8–11]. Estimated protein binding was obtained from package inserts, unless reported in published studies [12–16]. The findings from five studies detailing the pharmacokinetics of the studied beta-lactams can be found in Table 1.

Pharmacodynamic exposures were measured by percent of time above the MIC (%T > MIC) for unbound drug during the given dosing interval. The antibiotic regimens tested were as follows: aztreonam, cefepime, ceftazidime and meropenem 2 g every 8 h (bolus and prolonged infusion), and piperacillin–tazobactam 4.5 g every 6 h (bolus and prolonged infusion), and the continuous infusions for each antibiotic were defined as the total daily dose of each regimen. Bolus infusion was defined as 30 min infusion and prolonged infusion was defined as an infusion over three hours. These regimens were based on current practice for dosing in adult CF patients. All dosing regimens were assumed to be a one-compartment pharmacokinetic model and the equations listed below were used to calculate %T > MIC for beta-lactams:

Intermittent Bolus.

$$\%\mathrm{T}>MIC = Ln\frac{\mathrm{Dose}\times f}{\mathrm{V}_d\times \mathrm{MIC}}\times\frac{\mathrm{V}_d}{\mathrm{CL}_T}\times\frac{100}{\mathrm{DI}.}$$

Prolonged-Infusion

$$\%\mathrm{T}>MIC = \left(T_{Inf}-\left(\left(Ln\frac{R_0/CL_T}{R_0/CL_T-MIC}\right)\times\frac{t_{1/2}}{0.693}\right)\right) + \left(\left(Ln\frac{R_0}{CL}-Ln(MIC)\right)\times\frac{t_{1/2}}{0.693}\right)\times\frac{100}{DI}$$

Continuous Infusion

$$\%\mathrm{T}>MIC = \frac{C_{ss,u}}{\mathrm{MIC}} = \frac{{}^{R_0}/_{CL_T}\times f}{\mathrm{MIC}}$$

where Ln is the natural logarithm, f is the fraction of unbound drug, V_d is the volume of distribution in liters, CL_T is the total body clearance in liters per hour, DI is the dosing interval, T_{Inf} is the infusion time, R_0 is the infusion rate, $t_{1/2}$ is the terminal elimination half-life and $C_{ss,u}$ is the steady-state concentration of unbound drug.

Crystal Ball (Oracle®, Redwood Shores, CA) was used to conduct Monte Carlo simulations of 10,000 exposures per experiment. We estimated %T > MIC for each antibiotic regimen and MIC combination. The targeted %T > MIC for bolus and prolonged-infusion regimens were 40% for meropenem, 50% for piperacillin–tazobactam and 60% for cefepime, ceftazidime and aztreonam [20]. For continuous-infusion regimens the targeted pharmacodynamic parameter was 100% T > MIC [21]. In order to predict correlation with the optimal clinical outcomes a target PTA of 90% was designated [22].

3. Results

Overall, 43 non-duplicate *P. aeruginosa* isolates were obtained. Table 2 depicts the MIC_{50}, MIC_{90}, and the percent susceptible. Meropenem was the most potent agent, with the lowest MIC_{50} and MIC_{90}. Ceftazidime had the highest percentage of the isolates susceptible (70%) and cefepime had the lowest percentage of susceptible isolates (49%).

The results for each dosing regimen can be found in Table 3. When bolus, prolonged-infusion and continuous-infusion regimens were modeled in CF patients, no regimen met the predefined goal of 90% PTA. For bolus regimens, PTA was highest with meropenem (70%) and lowest with cefepime (32%). When

Table 1
Pharmacokinetic data in CF patients.

Antibiotic	Clearance (L/h)	Volume of distribution (L)	Half-life (h)	Protein binding (f_u) [12–16]
Aztreonam [6]*	6 ± 1.1	10.95 ± 1.26	1.54 ± 0.17	0.56
Cefepime [8]*	8.47 ± 3.45	14.9 ± 5.78	1.64 ± 0.36	0.2
Ceftazidime [9]**	5.37 (3.35–12.8)	9.14 (2.77–19.9)	1.48 (0.49–1.78)	0.1
Meropenem [10]*	15.9 ± 1.9	19.6 ± 2.2	0.86 ± 0.05	0.2
Piperacillin–tazobactam [11]**	8.78 (6.39–12.1)	8.13 (5.16–10.8)	0.69 (0.34–1.19)	0.3

* Mean ± standard deviation.
** Median (range).