Case report

Ceftolozane/tazobactam for pulmonary exacerbation in a 63-year-old cystic fibrosis patient with renal insufficiency and an elevated MIC to *Pseudomonas aeruginosa*

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ABSTRACT

Cystic fibrosis (CF) is a progressive genetic disorder caused by mutations in a gene encoding the cystic fibrosis transmembrane regulator (CFTR) protein leading to persistent and difficult to treat lower airway infections. Multi-drug resistant *Pseudomonas aeruginosa* is becoming increasingly more common as a cause of pulmonary exacerbations, and newer agents such as ceftolozane/tazobactam (C/T) are being sought for treatment. There is currently little published data regarding its use in cystic fibrosis, particularly in the setting of reduced renal clearance. This report details the case of a 63-year-old female with cystic fibrosis and chronic kidney disease stage III (estimated creatinine clearance of 25 – 30 ml/min, Cockroft-Gault) who was successfully treated for a pulmonary exacerbation with C/T 3 g (2000 mg/ 1000 mg) infused intravenously every 8 h when the *P. aeruginosa* minimum inhibitory concentration (MIC) was elevated at 8 mcg/mL. Serum samples were collected to determine concentrations by a validated high-performance liquid chromatography assay. The steady state 1-hr post-infusion peak (Cmax) and trough (Cmin) concentrations for ceftolozane were 145.04 mcg/mL and 82.08 mcg/mL, and 15.93 mcg/mL and 3.20 mcg/mL for tazobactam, respectively. The patient's symptoms resolved and her lung function returned to baseline. She completed 14 days of therapy and tolerated the infusion well without any infusion-related or adverse events.

Introduction

Cystic fibrosis (CF) is a progressive genetic disorder caused by mutations in a gene encoding the cystic fibrosis transmembrane regulator (CFTR) protein. Altered protein function leads to persistent and difficult to treat lower airway infections [1,2]. In 2018, the mean age of those living with cystic fibrosis was 22.2 years. The median age at death was 30.8 years but this is predicted to increase to 47.4 years for those born in 2018 [3]. The number of adults with cystic fibrosis continues to increase as treatment advances with adults representing more than 50 % of the CF population in 2018 compared to 31.1 % in 1988 [3]. Despite the encouraging trends, the number of patients greater than 60 years of age living with cystic fibrosis remains rare and subsequently these patients are poorly represented in the available literature.

With advancing age, the prevalence of individuals with CF who are colonized with *P. aeruginosa* also increases. Last year, approximately 45 % of CF patients had respiratory cultures positive for *P. aeruginosa* and 16.9 % of those strains causing acute infection displayed multi-drug resistance (MDR) [3]. The presence of *P. aeruginosa* in respiratory cultures has been shown to be a major predictor of mortality and morbidity and is becoming progressively difficult to treat as cumulative lifetime antibiotics increase and drug resistance develops [4]. This has led to various treatment approaches including combination therapy; modified dosing strategies such as extended and continuous infusion beta-lactams to optimize pharmacokinetic/pharmacodynamic (PK/PD) parameters; as well as the development of novel antipseudomonal agents such as ceftolozane/tazobactam (C/T). C/T is effective against many gram-negative bacilli, including MDR *P. aeruginosa*. Ceftolozane, by itself, is one of the most active antipseudomonals, while the addition of tazobactam extends the coverage to include extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae [5,6]. Manufacturer's labeling recommends that C/T be dosed at 3 g (2000 mg/1000 mg) every 8 h intravenously over 60 min in patients with creatinine clearance (CrCl) > 50 mL/min with

bacterial pneumonia, with an adjustment to 1.5 mg every 8 h for CrCl 30−50 ml/min and 750 mg every 8 h for CrCl 15−29 ml/min. The manufacturer does not provide dosage adjustments for CrCl <15 mL/min in a patient not receiving dialysis [7].

While the use of C/T has been well established for urinary tract infections, nosocomial pneumonia, and complicated intra-abdominal infections [8–10], there is limited information regarding its use for acute pulmonary exacerbations in cystic fibrosis. Further, it is well known that patients with CF demonstrate altered pharmacokinetic properties from the non-CF population. Studies have reported enhanced renal and non-renal elimination, delayed absorption, and increased volume of distribution to a variety of antibiotics leading to the use of higher doses and more frequent administration times than that recommended by the manufacturer [11,12]. One small study (n = 20) and several case reports have utilized therapeutic drug monitoring to attempt to describe how C/T pharmacokinetics are altered in cystic fibrosis [6,13,14]. Another case report described the use of C/T in a 35-year-old female with CKD and a *P. aeruginosa* isolate demonstrating a low minimum inhibitory concentration (MIC) [15]. To our knowledge, there is no published data regarding the use and characterization of the pharmacokinetics of C/T in an older cystic fibrosis patient with renal insufficiency and an elevated *P. aeruginosa* MIC.

This report will review the successful use of C/T for a pulmonary exacerbation due to *P. aeruginosa* in the case of a 63-year-old female with cystic fibrosis and chronic kidney disease. Serum concentrations of C/T were collected and utilized to determine the most appropriate dose for this patient given her CrCl and in vitro susceptibility data showing an elevated MIC.

Case presentation

A 63-year-old female with cystic fibrosis presented with increased productive cough, persistent wheezing, decreased appetite, general malaise, and a significant acute decline in lung function with an FEV_1 of 0.8 L (35 % of predicted from her baseline of 45–50 % of predicted). She was diagnosed with an acute pulmonary exacerbation and it was decided to begin intravenous antibiotics. Drug allergies and intolerances include trimethoprim/sulfamethoxazole (hyperkalemia), ceftazidime (shortness of breath), ticarcillin-clavulanate (hives), and levofloxacin (muscle cramps, light-headedness). Past medical history includes cystic fibrosis-related diabetes mellitus, hypothyroidism, anemia, and chronic kidney disease stage III (estimated CrCl of 25−30 ml/min, Cockroft-Gault). She is colonized with methicillin-susceptible *Staphylococcus aureus* (MSSA) and MDR *P. aeruginosa*. Intravenous meropenem 2 g every 8 h infused over 3 h [16–18] and oral ciprofloxacin 500 mg twice daily were initiated empirically based on previous treatment success. However, after the second dose of meropenem the patient reported significant shortness of breath and tachycardia thought to be related to the meropenem infusion and as a result meropenem was discontinued.

With few options left, it was decided to initiate C/T 3 g every 8 h infused intravenously over 60 min in order to maximize exposure and ensure optimal time above the MIC. The dose of the C/T was not reduced because susceptibility of the organism was shown to be intermediate with an MIC of 8 mcg/mL on the most recent culture. Additional susceptibility data are presented in Table 1.

Two steady-state serum samples were collected, a 1-hr post-infusion peak and a trough, to perform patient-specific pharmacokinetics. The samples were sent to the Center for Anti-Infective Research and Development at Hartford Hospital where concentrations were determined by a validated high-performance liquid chromatography assay [20]. Steady state 1-hr post-infusion peak (C_{max}) and trough (C_{min}) serum concentrations for ceftolozane

were 145.04 mcg/mL and 82.08 mcg/mL, and 15.93 mcg/mL and 3.20 mcg/mL for tazobactam, respectively.

After completing 14 days of therapy with intravenous C/T and oral ciprofloxacin, the patient's symptoms resolved and lung function returned to baseline. She tolerated the infusions well without any reports of adverse events.

Discussion

This case demonstrates the usefulness of therapeutic drug monitoring (TDM) in this population and how it can be used to validate dosing, particularly with newer antimicrobials that do not have well established dosing in cystic fibrosis. Like other beta-lactams, C/T exhibits time-dependent activity, meaning it is more bactericidal the longer it is present at the site of action with an unbound concentration greater than the targeted pathogen's MIC (fT > MIC).[21] PK/PD studies have also consistently shown that beta-lactams exhibit maximum killing at concentrations 3–4 times the MIC, though effectiveness of beta-lactams ultimately depends on the duration the concentration is above the MIC more than the magnitude of the concentration (Huttner et al). Currently, standard dosing regimens of beta-lactams target approximately 50 % fT > MIC based on murine infection models from the 1980s to the 2000s [21]. Cephalosporins exhibit a fT > MIC of 30–40 %. C/T, on the other hand, has a fT > MIC similar to carbapenems, as in vitro models demonstrate a 24%–31% fT > MIC to achieve a 24 -h static effect against *P. aeruginosa* [6].

Some studies have suggested improved clinical outcomes with more aggressive PK/PD beta-lactam targets of 100 % fT > MIC and minimum trough concentrations up to 5–6 times the MIC, primarily in critically ill patients with sepsis and lower respiratory tract infections [21,22]. TDM of beta-lactam antibiotics historically has not been considered routine clinical practice since beta-lactams do not have a narrow therapeutic index. Due to the association of low antibiotic serum concentrations and increasing resistance to beta-lactams, in addition to the increasing prevalence of multi-drug resistant organisms, TDM has increased in clinical relevance to ensure target concentrations are being achieved [21]. Patients most likely to benefit from TDM include patients with altered PK, such as the critically ill, obese, elderly, and those with CF [21].

Most centers utilizing TDM target beta-lactam concentrations of 100 % fT > MIC, while some target 100 % fT>4xMIC, and a few target 50 % fT>4xMIC or 70 % fT>4x MIC [21]. For this patient, the target utilized was 100 % fT>4xMIC, or a trough of 32 mcg/mL. The specific dose of C/T 3 g every 8 h was chosen based on previous Monte Carlo simulations published by Monogue, et al. which predict a 60–70 % probability of a target attainment of 100 % fT > MIC for an MIC of 8 for this dose in adult CF patients with a mean CrCl of 117.7 mL/min. For the same dose, the reduced CrCl in this patient would increase the probability of target attainment under the assumption that CrCl is the most significant predictor of ceftolozane clearance [13]. Of note, the patient had previously tolerated non-renally-adjusted doses of other beta-lactams, including meropenem.

The serum samples tested were used to estimate unbound serum concentrations. The estimated unbound C_{max} and C_{min} were 116 mcg/mL and 66 mcg/mL, respectively, based on 20 % protein binding for ceftolozane. The estimated unbound C_{max} and C_{min} were 11 mcg/mL and 2 mcg/mL, respectively, based on 30 % protein binding for tazobactam [7]. This confirmed unbound drug concentrations of ceftolozane greater than 4 times the MIC for the entire dosing interval. As expected, the calculated half-life of ceftolozane was 7 h, which is significantly longer than that observed in adult CF patients with normal renal function (2.9 h) and healthy adults without CF (2.7 h) [13].

Table 1
Pseudomonas aeruginosa Culture and Susceptibility Data [19] [a].

	Most recent culture prior to exacerbation	2 months post-exacerbation	3 months post-exacerbation
Amikacin	S (8)	S	S
Aztreonam	–	R (>16)	R (>16)
Cefepime	R ($\geq$64)	R (>16)	R (>16)
Ceftazidime	R ($\geq$64)	R (>16)	R (>16)
Ceftazidime/Avibactam	S (8)	S (4)	S (4)
Ceftolozane/Tazobactam	I (8)	S (4)	S ($\leq$2)
Ciprofloxacin	S (1)	S	–
Colistin	–	–	S ($\leq$0.25)
Gentamicin	S (4)	S	S
Levofloxacin	I (4)	R (8)	–
Meropenem	R ($\geq$16)	R (>8)	R (>8)
Piperacillin/Tazobactam	–	R (>128)	R (>128)
Polymyxin B	–	–	S (0.5)
Tobramycin	S ($\leq$1)	S	S

[a] Susceptibility data based on CLSI Performance Standards for Antimicrobial Susceptibility Testing, 28th edition, 2018.

This patient tolerated the C/T infusion well without any infusion-related or adverse reactions despite having a documented allergy to ceftazidime in the medical chart. Ceftazidime and ceftolozane share similar side chains and potential for cross-reactivity is unknown. It is possible the previous reaction to ceftazidime was an infusion- or disease-related reaction rather than hypersensitivity

In the future, it may be reasonable to use a reduced dose of C/T 1.5 g every 8 h and still expect to achieve a target of 100 % fT>4xMIC in this patient, however given that she tolerated the high concentrations well, it would also be reasonable to utilize the same dose of C/T 3 g every 8 h in the event of future exacerbations. Of further note, subsequent respiratory culture and susceptibility data collected 2- and 3-months post-exacerbation shows *P. aeruginosa* isolates with reduced MICs to C/T (Table 1). Development of resistance has previously been shown in vitro with C/T even when 100 % fT > MIC is achieved [6]. This supports the hypothesis that higher serum concentrations and PK/PD targets may help to preserve susceptibility, but further studies are needed.

Conclusion

The use of 3 g (2000/1000 mg) of intravenous C/T infused over 60 min in a 63-year-old CF patient with renal dysfunction and *P. aeruginosa* with a high MIC to C/T was safe and effective in achieving concentrations well over PK/PD targets used for cephalosporins in centers routinely performing beta-lactam TDM.

Funding

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Meredith Tate Romano: Conceptualization, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Sasha Premraj:** Conceptualization, Writing - original draft, Writing - review & editing. **John M. Bray:** Writing - review & editing, Supervision. **Luis C. Murillo:** Writing - review & editing, Supervision.

Declaration of Competing Interest

No conflicts of interest to disclose.

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