ELSEVIER
Journal of Cystic Fibrosis xx (2017) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Ceftaroline pharmacokinetics and pharmacodynamics in patients with cystic fibrosis

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Received 23 June 2017; revised 17 October 2017; accepted 17 October 2017
Available online xxxx

Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prevalent pathogen in patients with cystic fibrosis (CF) associated with increased morbidity. Ceftaroline fosamil is an intravenous (IV) cephalosporin with activity against MRSA. There are minimal data regarding dosing in the CF population. The objective of this study was to determine the pharmacokinetic and pharmacodynamic profile of IV ceftaroline in patients with CF.
Methods: We conducted a single-center prospective study of children and young adults with CF receiving ceftaroline (15 mg/kg IV up to 600 mg every 8 h) as part of treatment for a CF pulmonary exacerbation between June 2016 and April 2017. Seven patients were enrolled for a total of 10 treatment courses. For each treatment course, up to 8 plasma samples were assayed for ceftaroline using ultra-high performance liquid chromatography with mass spectrometry. Maximum plasma concentration, systemic clearance, and elimination half-life were calculated. The area under the curve (AUC) above the minimum inhibitory concentration (MIC) and the percent time above the MIC (%fT > MIC) were determined for each subject using MICs of 0.5, 1, and 2 μg/mL and the measured MIC if available.
Results: The mean (SD) age for the 7 patients was 20.3 (8.0) years. Mean (SD) maximum plasma concentration of ceftaroline was 22.7 (9.6) μg/mL, systemic clearance 7.9 (3.3) L/h, and half-life 1.1 (0.4) hours. Using a MIC of 1 μg/mL, accepted as the MIC 90 of MRSA isolates, AUC above MIC mean (SD) was 53.6 (19.5) μg·h/mL, mean (SD) %fT > MIC was 75.7 (10.4), and all subjects had >60%fT > MIC.
Conclusions: In this cohort of CF patients, mean ceftaroline half-life was 1.1 h, which is notably lower than the general population. The dosing regimen studied, which exceeds the recommended dosing in the non-CF population, was adequate to achieve >60% time above the MIC in all patients.

Keywords: MRSA; Ceftaroline; Pharmacokinetics; Pharmacodynamics; Infection; Cystic fibrosis

1. Introduction

Despite treatment advances resulting in a steadily increasing life expectancy in patients with cystic fibrosis (CF), methicillin-resistant *Staphylococcus aureus* (MRSA) and other multi-drug resistant organisms are becoming increasingly problematic [1–4]. The prevalence of MRSA among patients with CF in the US rose from 6% to 26% from 2000 to 2010 and has remained at this high level since that time [5]. MRSA infection in CF is associated with increased morbidity, including increased rates of hospitalization, utilization of antibiotics, and lung function decline [6–9], as well as increased mortality [10]. Despite this, there are no treatment guidelines for MRSA in CF, either for chronic suppressive therapy

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https://doi.org/10.1016/j.jcf.2017.10.010

or during treatment of pulmonary exacerbations, so therapy is therefore guided by clinical consensus [11]. Furthermore, the available therapies are limited and carry significant risk profiles.

Ceftaroline was approved by the US FDA in 2010 for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. It is a bactericidal, broad-spectrum, fifth generation cephalosporin with activity against MRSA. It binds to penicillin-binding proteins and inhibits peptidoglycan synthesis [12,13]. It is formulated into a prodrug, ceftaroline fosamil, and is rapidly converted by plasma phosphatases to the active compound after intravenous administration [13,14]. It may serve as an alternative therapy for MRSA treatment in CF, however there are minimal data regarding dosing of ceftaroline in the CF population.

For adults without CF with normal renal function, the recommended intravenous (IV) ceftaroline dose is 600 mg every 12 h [13,15]. However, patients with CF are known to have accelerated clearance of beta-lactams, with increased total body clearance and larger volumes of distribution [16,17]. It remains unclear what, if any, dosage adjustment is needed for ceftaroline administration in patients with CF.

In this study, we aimed to determine the pharmacokinetic and pharmacodynamic profile of ceftaroline in children and young adults with CF and to determine if our center's current dosing regimen is adequate to achieve pharmacodynamic targets.

2. Materials and methods

2.1. Study design

We conducted a single-center prospective study of children and young adults with CF and MRSA, receiving IV ceftaroline for CF respiratory exacerbations between June 2016 and April 2017. The study was approved by the Boston Children's Hospital Institutional Review Board (Protocol P00020799). Informed consent was obtained.

2.2. Study subjects

Patients were included if they were 6 years of age or older, hospitalized on the pediatric or adult pulmonary service, and treated with ceftaroline as part of their routine clinical care. They were excluded if they were in the intensive care unit. All patients received our hospital's standard dosing regimen of 15 mg/kg every 8 h (maximum of 600 mg/dose), which exceeds the standard dosing recommended for non-CF populations of 12 mg/kg every 8 h (maximum of 400 mg/dose) or 600 mg every 12 h [12].

Individual patients could be enrolled up to two times for two discrete admissions or treatment courses. All patients had a central venous catheter in place (port-a-catheter or peripherally inserted central catheter).

2.3. Baseline data

Sociodemographic data collected included age, gender, and ethnicity. Weight, BMI, and albumin at the time of hospital admission were used as markers of nutritional status. Blood urea nitrogen (BUN) and serum creatinine were collected as measures of renal function, as well as C-reactive protein (CRP) as a measure of systemic inflammation. Medication allergies and concomitant antibiotics were also recorded. Lung function at the closest time point to ceftaroline administration and the year's best value were measured by the forced expiratory volume in 1 s (FEV_1). FEV_1 data were analyzed as percent predicted based on the Global Lung Initiative equations [18].

2.4. Blood sample collection

Each subject had up to 8 blood levels drawn around two sequential ceftaroline doses, at any time during the treatment period. This included at least one trough and two peak levels. The remaining levels were drawn at approximate times of 5 min, 15 min, 30 min, 1 h, 3 h, 6 h (which was also a trough for the following dose) following completion of the prior dose. These times were adjusted as needed to accommodate routine clinical care recording the exact time for precise population pharmacokinetic analysis. Timing was measured from completion of the saline flush which immediately followed the completion of the antibiotic infusion. All blood samples were obtained from central venous catheters. Each blood sample volume was 0.25 mL.

2.5. MRSA isolate susceptibility testing

MRSA isolates that grew from CF respiratory culture specimens (from bronchoalveoloar lavage, throat swab, or sputum) collected from the study subjects as part of routine clinical care were frozen and analyzed for susceptibility to ceftaroline using gradient diffusion testing (*E*-test), Biomerieux. Susceptibility testing was performed following the manufacturer's instructions and the Clinical and Laboratory Standards Institute guideline [19].

2.6. Drug assay

Blood samples were anticoagulated with lithium heparin and stored immediately on ice. Plasma was separated by centrifugation (1000 g × 10 min at 4 °C) and stored at −80 °C until batch analysis. Ceftaroline plasma concentrations were measured by ultra-high performance liquid chromatography in an Acquity H-Class UPLC with a Xevo TQ triple quadrupole mass spectrometer (Waters Corp., Milford MA). Data acquisition and instrument control was done by Masslynx 4.1 software (Waters Corp., Milford, MA). Both drug and internal standard (IS) aminocaproic acid were separated on an UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm) stabilized at 40 °C. The mobile phase consisted of 0.1% aqueous formic acid (A) and acetonitrile (B) with linear gradient elution from 95%A:5%B to 50%A:50%B in 4 min. The flow rate was 0.3 mL/min and the injection volume 3 mL. At the detector, the MRM modes *m/z* 604.9 → 208 for ceftaroline, and m/z 132 → 69.0 for IS were used for the quantification with cone voltages of 40 and 15 kV, respectively. All samples were analyzed in triplicate along with freshly made daily calibrators and quality control samples to determine precision and accuracy.

Please cite this article as: Barsky EE, et al, Ceftaroline pharmacokinetics and pharmacodynamics in patients with cystic fibrosis, J Cyst Fibros (2017), https://doi.org/10.1016/j.jcf.2017.10.010