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Authors

Martin, Thomas CS

Chow, Sean

Johns, Scott T

et al.

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BRIEF REPORT

Ceftaroline-associated Encephalopathy in Patients With Severe Renal Impairment

Thomas C. S. Martin,[1] Sean Chow,[2] Scott T. Johns,[2] and Sanjay R. Mehta[1,2]

[1]Division of Infectious Diseases and Global Public Health, University of California San Diego, San Diego, California; and [2]Veterans Affairs San Diego Healthcare System, San Diego, California

Encephalopathy complicates beta-lactam therapy, particularly with impaired renal function, though no studies have reported ceftaroline-associated encephalopathy. Among 28 patients with estimated glomerular filtration rates <30 mL/min who received ≥5 days of ceftaroline, 3 developed encephalopathy. Ceftaroline, when dosed supra-therapeutically for serious infections, may be a cause of antibiotic-associated encephalopathy.

Keywords. ceftaroline; encephalopathy; drug toxicity; renal failure.

Ceftaroline is an intravenous, bactericidal cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) that was licensed by the US Food and Drug Administration (FDA) in 2010 for use in skin and skin-structure tissue infections and community-acquired bacterial pneumonia [1]. Ceftaroline has also been used off-label for severe MRSA infections, including bacteremia, endocarditis, and central nervous system infections, often with an increased dosing frequency compared to the manufacturer's recommendations [2]. Ceftaroline is generally well tolerated, with side effects including gastrointestinal symptoms, elevated transaminases, hypokalemia, and rash, with postmarketing surveillance also indicating a risk of agranulocytosis [2]. Encephalopathy is a well-characterized complication of beta-lactam therapy and is often associated with renal impairment, though to date no reports have implicated ceftaroline as a cause [3, 4]. We retrospectively evaluated potential cases of encephalopathy during ceftaroline therapy in patients with severe renal impairment.

METHODS

Population

Individuals with an estimated glomerular filtration rate (eGFR) <30 ml/min that had received ≥5 days of ceftaroline in the years 2010–2018 at the Veterans Affairs Hospital San Diego, California, were included in our study. Chart reviews were performed for all participants.

Outcomes

Each patient's age, gender, ceftaroline dose and dose interval, duration of therapy, and presence of encephalopathy during therapy were recorded. For cases of encephalopathy, comorbidities, details of investigation for alternate causes, concomitant administration of medications reported to cause encephalopathy, and clinical outcomes were documented. The Naranjo Adverse Drug Reaction Probability Score (range −4 to +13) was independently calculated by 2 physicians for cases and results were categorized as definite (≥9), probable (5–8), or possible (1–4) [5].

Ethics

The local Human Subjects and Research Safety committees approved the study protocol (H180294).

RESULTS

We included 28 individuals, representing 30 courses of ceftaroline therapy. The mean age was 69.9 years and all participants were male. There were 13 (43.3%) participants on chronic dialysis, and 2 (6.7%) developed acute kidney injury (AKI) requiring renal replacement therapy (RRT) during ceftaroline therapy. Dosages of ceftaroline varied from 200 mg every 12 hours to 600 mg every 12 hours among individuals with eGFRs <30 ml/min and from 200 mg every 12 hours to 600 mg every 8 hours among individuals receiving RRT. The median duration of therapy was 21 days (interquartile range 7–41).

We identified 2 cases of probable encephalopathy and 1 case of possible encephalopathy, yielding a prevalence of 10%. The Naranjo scale results to assess causality were 6, 6, and 2 for Cases 1, 2, and 3, respectively, with concordance between physician case reviewers.

Case 1

A 61-year-old man with a history of end-stage renal disease on intermittent hemodialysis, diabetes and prior right-sided infective endocarditis presented with myalgia, fevers, diaphoresis, bilateral wrist pain, and acute loss of vision in the right eye. Blood cultures grew MRSA. A transesophageal echocardiogram revealed linear aortic valve echodensity and a computed tomography (CT) scan revealed early right psoas abscess formation. A diagnosis of acute aortic valve endocarditis was made. Ceftaroline was started at 200 mg every 8 hours and his tunnelled dialysis catheter was removed. Blood cultures remained

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Correspondence: T. C. S. Martin, Department of Infectious Diseases and Global Public Health, 9500 Gilman Drive, La Jolla, CA 92093, USA (thm001@ucsd.edu).

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positive through Day 7, leading to a dose increase of ceftaroline to 600 mg every 12 hours. On Days 30–36, progressive lethargy and myoclonus were noted. A chart review revealed no psychotropic medications and shorter dialysis sessions than usual over the prior 7 days, due to hypotension. Investigations at encephalopathy onset included a white blood cell count (WBC) of $9.7*10^6$ cells/ml, a blood urea nitrogen (BUN) of 22 mg/dL, glucose of 96 mg/dL, sodium of 134 mmol/L, alanine aminotransferase (ALT) of 86 IU/L, aspartate aminotransferase (AST) of 24 IU/L, ammonia of 44 μg/dL, and calcium of 7.5 mg/dL. Urine, blood, and sputum bacterial cultures and fungal blood cultures showed no growth. A chest X-ray radiograph showed stable, small, bilateral pleural effusions and pulmonary edema. The cerebrospinal fluid was notable for a WBC count of <3 cells/ml, normal protein/glucose, a negative bacterial culture, and a negative *Herpes simplex virus* 1/2 polymerase chain reaction. Magnetic resonance imaging (MRI) of the brain did not show acute changes, while a CT scan demonstrated improved psoas abscess and an electroencephalograph showed rare bifrontal and generalized epileptiform discharges and triphasic waves. Ceftaroline was discontinued on Day 37 and daily dialysis was initiated on Day 39. Leviteracetam was initiated on Day 40. Repeat results on Day 41 indicated a WBC count of $9.4*10^6$ cells/ml, glucose of 87 mg/dL, BUN of 20 mg/dL, sodium of 137 mmol/L, ALT of 17 IU/L, AST of 21 IU/L and calcium of 7.5 mg/dL. Improving mental status was recorded by Day 42. The tunnelled dialysis line was exchanged on Day 44, and a tip culture showed no growth. The complete resolution of encephalopathy was recorded by Day 45, and leviteracetam was discontinued. The course was complicated by hypotension of an unknown cause that required vasopressors. No additional therapy was provided to explain the resolution of symptoms, other than ceftaroline discontinuation.

Case 2

An 87-year-old man with a history of T6 paraplegia secondary to an arteriovenous malformation, neurogenic bladder/bowel, hypothyroidism, and prior *Clostridium difficile* colitis was admitted for management of a right ischial pressure ulcer. The MRI was consistent with acute osteomyelitis and debridement was performed. Surgical cultures grew MRSA. Vancomycin was started and later switched to daptomycin due to AKI with the subsequent normalization of renal function (eGFR 99 mL/min). After 6 weeks, progression on MRI was noted and therapy was switched to ceftaroline at 600 mg every 8 hours. On Day 18 of ceftaroline, the patient became febrile, with an investigation notable for fully susceptible *Pseudomonas aeruginosa* growing from a urine culture. He received gentamicin but developed AKI, and the gentamicin was switched to aztreonam. On Day 20 he was minimally communicative and by Day 21 he required a sternal rub to elicit any response. Investigations at this time showed a WBC count of 4.6*10^6 cells/L, C-reactive protein (CRP) of 7.8 mg/dL (improved from 11.6 mg/dL), BUN of 33 mg/dL, creatinine of 1.54 mg/dL, calcium of 7.6 mg/dL, glucose of 160 mg/dL and sodium of 132 mmol/L. Arterial blood gas showed a pH of 7.30, partial pressure carbon dioxide of 39 mmHg, partial pressure of oxygen of 94 mmHg, and ionized calcium of 1.23 mmol/L. A CT of the patient's head did not show acute changes and a CT of his chest/abdomen/pelvis was suggestive of chronic aspiration. On Day 21, baclofen and gabapentin were discontinued, as they may diminish sensorium and can accumulate in renal failure. On Day 22, the ceftaroline dose was reduced to 200 mg every 12 hours, after the progressive nature of the AKI became apparent. On Day 24, dialysis was started and the ceftaroline was discontinued due to the emergence of a morbiliform rash, with a biopsy confirming erythema multiforme. By Day 26, some improvement was noted, with the patient demonstrating a limited understanding of his situation, and by Day 28 the patient was alert and answering questions. Dialysis was discontinued Day 30.

Case 3

A 61-year-old man with obesity hypoventilation syndrome, systolic heart failure, diabetes mellitus, and chronic kidney disease stage 3a was admitted with diarrhea, cellulitis, and hypotension and was subsequently found to have *Salmonella sp*. in his stool and probable left elbow septic arthritis. Ceftaroline dosed at 600 mg every 12 hours was started to cover possible MRSA and *Salmonella sp*., with a subsequent increase in frequency on Day 3 to 600 mg every 8 hours, due to suspected osteomyelitis. On Day 5 of therapy, the patient was noted to be slow to respond to questions; by Day 8, increased lethargy was noted and he was not responding to questions. No medications were identified that could have lead to impaired sensorium. At that time, he had AKI, with creatinine increased from 1.6 at ceftaroline initiation (eGFR 54 ml/min) to 2.69 mg/dL (eGFR 29 ml/min). Laboratory results showed a BUN of 37 mg/dL, sodium of 137 mmol/L, calcium of 8.6 mg/dL, WBC count of 5.2*10^6 cells/L, and CRP of 3.2 mg/dL (improved from 16.0 mg/dL). He had refused his continuous positive airway pressure ventilation since admission, with arterial blood gas notable for respiratory acidosis (pCO2 80 mmHg, ionized calcium 1.15 mmol/L). A chest X-ray radiograph indicated improved pulmonary edema. Increasing lethargy, confusion, and respiratory acidosis lead to intubation on Day 13, complicated by cardiac arrest. Continuous veno-venous RRT was started on Day 16 and ceftaroline was discontinued on Day 20. Care was complicated by further cardiac arrests and the patient died on Day 34.

DISCUSSION

We report 3 cases of encephalopathy occurring during ceftaroline therapy in the setting of severe renal impairment (eGFR <30 ml/min). Using the Naranjo scale to assess causality, the likelihood of ceftaroline-associated encephalopathy

was rated probable for Cases 1 and 2 and possible for Case 3. Several similarities in the cases suggest this is a true adverse drug reaction. Firstly, the patients were on doses higher than those approved by the FDA for impaired renal function, either due to a failure to clear blood cultures on lower doses or due to AKI without an adjustment of drug dosing. Secondly, the onset of encephalopathy coincided with a high likelihood of increasing drug levels, due to changes in renal function: in the first case, shorter dialysis sessions were noted prior to the onset of encephalopathy; in the latter 2 cases, onset was contemporaneous with an acute deterioration in GFR. The FDA-approved package insert recommends a ceftaroline dose of 300 mg every 12 hours for a GFR <30 mL/min and 200 mg every 12 hours in end-stage renal disease for the treatment of skin and skin-structure tissue infections or community-acquired bacterial pneumonia. In all 3 cases of encephalopathy, these doses were exceeded, as ceftaroline was used off-label for severe MRSA infections. Although limited by our study size, the prevalence of encephalopathy among patients receiving ceftaroline who had an eGFR <30 mL/min was 10%.

While there is substantial literature regarding the neurotoxicity of beta-lactams, our study is the first to report encephalopathy associated with ceftaroline. Notably, no cases of encephalopathy were seen among patients receiving a cumulative dose of ≤800 mg/day, including individuals on dialysis. The authors therefore suggest caution and close monitoring for encephalopathy or changes in renal function among patients with eGFRs <30 mL/min who are receiving more than a 800 mg cumulative daily dose of ceftaroline.

There were limitations to our study, including the retrospective nature and small size. Cases were not investigated systematically for alternative causes of encephalopathy and, due to other comorbidities, there were several confounders. While it is difficult to draw a definitive conclusion that ceftaroline was responsible for the cases reported above, the timing of onset and resolution of encephalopathy, in particular with regards to renal injury, is suggestive.

In conclusion, we report 3 cases of encephalopathy that occurred during supratherapeutic ceftaroline therapy for severe MRSA infections in the setting of impaired renal excretion. Clinicians should remain aware of this potential complication and discontinue ceftaroline in suspected cases.

Note

Potential conflicts of interest. T. C. S. M. is supported by the National Institutes of Health (training grant number 5T32AI007384-28). Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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