Ceftaroline Cerebrospinal Fluid Penetration in the Treatment of a Ventriculopleural Shunt Infection: A Case Report

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Pharmacokinetic data regarding ceftaroline fosamil (CPT) penetration into cerebrospinal fluid (CSF) are limited to a rabbit model (15% inflamed) and adult case reports. We describe serum and CSF CPT concentrations in a 21-year-old, 34.8 kg female, medically complex patient presented with a 4-day history of fevers (Tmax 39.2°C), tachypnea, tachycardia, fatigue, and a 1-week history of pus and blood draining from the ventriculopleural (VPL) shunt. A head CT and an ultrasound of the neck revealed septated complex fluid collection surrounding the shunt. Therapy was initiated with vancomycin and ceftriaxone. Blood and CSF cultures from hospital day (HD) 1 were positive for methicillin-resistant *Staphylococcus aureus* with a CPT MIC of 0.5 mg/L and a vancomycin MIC range of 0.5 to 1 mg/L. On HD 3, CPT was added. On HD 7, simultaneous serum (69.4, 44, and 30.2 mg/L) and CSF (1.7, 2.3, and 2.3 mg/L) concentrations were obtained at 0.25, 1.5, and 4.75 hours from the end of an infusion. Based on these concentrations, CPT CSF penetration ratio ranged from 2.4% to 7.6%. After addition of CPT, the blood and CSF cultures remained negative on a regimen of vancomycin plus CPT. On HD 14, a new left-sided VPL shunt was placed. The patient continued on CPT for a period of 7 days after the new VPL shunt placement. This case demonstrated CPT CSF penetration in a range of 2.4% to 7.6%, approximately half of the rabbit model. This allowed for CSF concentrations at least 50% free time > 4 to 6× MIC of the dosing interval with a dosing regimen of 600 mg IV every 8 hours in a 34.8 kg chronic patient and resulted in a successful clinical outcome with no identified adverse outcomes.

ABBREVIATIONS AUC, area under the curve; CNS, central nervous system; CPT, ceftaroline fosamil; CSF, cerebrospinal fluid; CT, computed tomography; EVD, external ventricular drain; FDA, US Food and Drug Administration; $fT > MIC$, free drug concentration above the MIC; HD, hospital day; IV, intravenous; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PBP, penicillin binding protein; PD, pharmacodynamic; VP, ventriculoperitoneal; VPL, ventriculopleural

KEYWORDS case report; ceftaroline fosamil; ceftaroline CSF concentrations; CSF penetration; MRSA; pediatric; pharmacokinetic; pharmacodynamics

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Introduction

Ventriculoperitoneal (VP) shunts are commonly used in the management of hydrocephalus with infection as a known complication.^{1,2} Estimates of VP shunt infections range between 4% and 20% and are associated with shunt removal, replacement, and relocation accounting for significant morbidity.^{2–5} External ventricular drains (EVDs) are often used during the acute infectious period to facilitate drainage of cerebrospinal fluid (CSF) for hydrocephalus management and the infectious process.^{3,6,7} An EVD allows for acquisition of CSF for culture and analysis, administration of drugs, in addition to acquisition of CSF to allow for measurement of drug concentrations in the CSF to facilitate drug dosing regimen optimization.⁸

Ceftaroline fosamil (CPT; Forest Labs, Inc, New York, NY) is a novel cephalosporin indicated for acute bacte-

rial skin and skin structure infections and community-acquired bacterial pneumonia in adults and children.⁹ CPT has also been used for the management of non-FDA-approved infections including osteomyelitis, endocarditis, bacteraemia, and epidural abscesses.^{10–15} CPT possesses excellent in vitro activity against common clinical isolates encountered in the adult and pediatric population.^{9,16} CPT binds to penicillin binding proteins (PBPs) with high affinity for PBP2a providing activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x providing coverage against penicillin-resistant *Streptococcus pneumoniae*.^{16,17} Although CPT does not have an FDA-approved indication for CNS infections, there is significant interest in exploring its utility for this indication.

CPT has the potential for use in CNS infections based on its penetration of ~15% into inflamed meninges in animal models.^{18,19} Although the use of CPT for CNS

infections to date is limited to case reports and small case series, there is a single case report regarding CPT CSF penetration in an adult suggesting a penetration ratio of approximately 4%.^{10,13,15} As such, we describe the serum and CSF CPT concentrations in a complicated patient with a MRSA ventriculopleural (VPL) shunt infection. This was a retrospective chart review of a single patient's medical record, and approval for the case report was obtained from the Institutional Review Board of Drexel University College of Medicine.

Case

A 21-year-old, 130-cm, 34.8 kg African American female, with static encephalopathy, cerebral palsy, diabetes insipidus, cortical blindness, scoliosis after spinal fusion, obstructive hydrocephalus after VP shunt placement with 2 revisions and conversion to a VPL shunt 3 and 2 months prior, respectively, gastrostomy-jejunosomy-tube dependence, spastic quadriplegia, Graves disease, and cataracts presented with a 4-day history of fevers (Tmax 39.2°C), tachypnea, tachycardia, fatigue, and change in behavior. She was noted to have a 1-week history of pus and blood draining from the VPL shunt incision site for which she received topical management with bacitracin and gauze. Upon presentation to the emergency department, she was tachycardic to 122 beats per minute with a white blood cell count of 17.6×10^3 cells/mcL with 4% bandemia, and a C-reactive protein of 19.51 mg/dL. The shunt was accessed for a specimen and sent for routine culture. There was interval increase in ventricular size on head CT, and an ultrasound of the neck revealed a septated complex fluid collection surrounding the shunt. Therapy was initiated with vancomycin (15 mg/kg/dose IV every 6 hours) and ceftriaxone (1 g IV every 12 hours). Blood and CSF cultures from hospital day (HD) 1 were positive for MRSA with a CPT MIC of 0.5 mg/L by Etest methodology and a vancomycin MIC range of 0.5 to 1 mg/L by Vitek methodology. On HD 2, the shunt was removed and an EVD was placed. The blood culture from HD 2 was also positive for MRSA. On HD 3, ceftriaxone was discontinued, ceftaroline was added (600 mg IV every 12 hours), and on HD 4, the dose changed to 600 mg IV every 8 hours as a 30-minute infusion. On HD 7, simultaneous serum (69.4, 44, and 30.2 mg/L) and CSF (1.7, 2.26, and 2.32 mg/L) concentrations, via the EVD, were obtained at 0.25, 1.5, and 4.75 hours from the end of an infusion. Based on these concentrations, the CPT CSF penetration ratio ranged from 2.4% to 7.6%, with the estimated AUC in serum (AUC_{serum}) of 382 mg/L·hr and an AUC_{CSF} of 32 mg/L·hr for an AUC unbound ratio of 8.4%.

Within 24 hours of adding CPT, the blood and CSF were sterilized and after addition of CPT, the blood and CSF cultures continued to remain negative on a regimen of vancomycin plus CPT. The white blood cell count trended down to 11.2×10^3 cells/mcL with no bandemia

after the addition of CPT and ultimately down to 8.6×10^3 cells/mcL at the end of treatment and similarly, the C-reactive protein trended down to 5.74 mg/dL after the addition of CPT and ultimately down to < 0.5 mg/dL at the end of treatment. During this time period, the vancomycin trough concentrations ranged from 14.2 to 20.8 mg/L with stable renal function with a serum creatinine range of 0.29 to 0.34 mg/dL. On HD 14, a new left-sided VPL shunt was placed. The patient continued on CPT for a period of 7 days after the new VPL shunt placement and was subsequently discharged from the hospital. There were no adverse events documented in the medical record as having been associated with receiving vancomycin and ceftaroline therapy during the treatment course. Our methods for determining both pharmacokinetic variables and CPT serum and CSF concentration analysis had been previously reported by our group.¹¹ Assay of CPT concentrations were determined as previously described without modification.

Discussion

By age, this patient would be considered an adult. However, considering the multiple, chronic disease states, patients such as these are usually cared for in pediatric institutions. By definition, a 130-cm, 34.8 kg, 21-year old patient is < 1% on all growth charts, and with a weight of 34.8 kg is the size of a small child. Additionally, there are few data regarding anti-infective pharmacokinetics in this population of patients.^{20,21} Based on our and other's previous work, patients are usually initiated on a CPT dose of 15 mg/kg/dose with the interval chosen based on patient age with younger patients usually receiving CPT on an every-6-hour interval and older patients on an every-8-hour regimen.^{11,15}

Interestingly, the animal models suggested a CSF penetration ratio of approximately 15%, yet, in the 2 case reports and case series to date in humans, the ratio has been < 10%.^{13,18,19,22,23} The most robust data to date regarding CPT penetration into the CSF is a 9-patient pharmacokinetic analysis of adults with EVDs with a mean weight of 77 ± 17 kg and a mean age of 63 ± 16 years.²² The ratio of the peak CPT CSF concentration to peak CPT plasma concentration from that investigation was 1.2%, and the ratio of the AUC in the CSF to the AUC in plasma was 6.4% as compared with 7.6% and 8.4% in the patient described in this report, respectively. Penetration into the CSF is known to be affected by a drug's relative lipophilicity, molecular size, protein binding affinity in addition to its ability to be actively removed from the CNS via active transporters.²⁴ CPT has the following characteristics, molecular weight of 762, log P range of -4.5 to -0.79, protein binding estimate of 20%, and pH of 4.8 to 6.5, which suggests the CPT penetration should exceed 10%.^{22,25} As a class, however, cephalosporins are not considered to penetrate the CSF well, despite their common clinical use for CNS infections and penetration relative to other anti-infectives.^{24,26}

The limited penetration of CPT into the CNS could be partly explained by an efflux mechanism due to CPTs affinity for active transport systems at the blood brain barrier.^{22,23} The adult experience in treating CNS infections with ceftaroline suggest ceftaroline dosing may need to be increased above the approved FDA doses for meningitis considering the only failure reported to date was with the 600 mg IV every-12-hour regimen. Despite Chauzy et al²² suggesting CPT may not be appropriate for the management of CNS infections, the clinical data to date suggest otherwise and could be aided by therapeutic drug monitoring with CPT.

A free CPT concentration above the MIC ($fT > MIC$) for at least 26% of the dosing interval is the proposed pharmacodynamic (PD) target for *S aureus* and at least 44% for *Streptococcus pneumoniae*, which was associated with a 1 log₁₀ colony-forming-unit reduction from baseline in community-acquired bacterial pneumonia.^{9,27} One challenge in identifying optimal dosing regimens is determining if the PD target associated with success in animal models, and community-acquired bacterial pneumonia is the same in populations such as the critically ill or in the management of CNS infections. Due to the nature of *S aureus* to create biofilms and the site of infection in this patient, we opted for a higher PD target of at least 50% $fT > 4-6 \times MIC$, which is in alignment with the expected CSF concentrations in adults if the 600 mg IV every 8-hour regimen were used.^{15,28} In this patient, the ~15 mg/kg/dose every 8 hours (600 mg IV every 8 hours) dosing regimen allowed for CSF concentrations above the MRSA MIC for at least 50% $fT > 4-6 \times MIC$ of the dosing interval and a successful clinical outcome with no identified adverse outcomes with her combination anti-infective regimen.

Conclusion

This case demonstrated CPT CSF penetration in a range of 2.4% to 7.6%, approximately half of the rabbit model. This allowed for CSF concentrations at least 50% $fT > 4-6 \times MIC$ of the dosing interval with a dosing regimen of 600 mg IV every 8 hours in a patient and resulted in a successful clinical outcome with no identified adverse outcomes.

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REFERENCES

1. Ngo QN, Ranger A, Singh RN, et al. External ventricular drains in pediatric patients. *Pediatr Crit Care Med*. 2009;10(3):346–351.
2. Simon TD, Hall M, Riva-Cambrin J, et al. Infection rates following initial cerebrospinal fluid shunt placement across pediatric hospitals in the United States. Clinical article. *J Neurosurg Pediatr*. 2009;4(2):156–165.
3. Adams DJ, Rajnik M. Microbiology and treatment of cerebrospinal fluid shunt infections in children. *Curr Infect Dis Rep*. 2014;16(10):427–428.
4. Kestle J, Drake J, Milner R, et al. Long-term follow-up data from the Shunt Design Trial. *Pediatr Neurosurg*. 2000;33(5):230–236.
5. Kestle JR, Drake JM, Cochrane DD, et al. Lack of benefit of endoscopic ventriculoperitoneal shunt insertion: a multicenter randomized trial. *J Neurosurg*. 2003;98(2):284–290.
6. James HE, Walsh JW, Wilson HD, et al. Prospective randomized study of therapy in cerebrospinal fluid shunt infection. *Neurosurgery*. 1980;7(5):459–463.
7. Schreffler RT, Schreffler AJ, Wittler RR. Treatment of cerebrospinal fluid shunt infections: a decision analysis. *Pediatr Infect Dis J*. 2002;21(7):632–636.
8. Cies JJ, Moore WS 2nd, Calaman S, et al. Pharmacokinetics of continuous-infusion meropenem for the treatment of *Serratia marcescens* ventriculitis in a pediatric patient. *Pharmacotherapy*. 2015;35(4):e32–e36.
9. Ceftaroline [package insert]. Forest Pharmaceutical IT, Italy; 2015.
10. Bucheit J, Collins R, Joshi P. Methicillin-resistant *Staphylococcus aureus* epidural abscess treated with ceftaroline fosamil salvage therapy. *Am J Health Syst Pharm*. 2014;71(2):110–113.
11. Cies JJ, Moore WS 2nd, Enache A, et al. Ceftaroline for suspected or confirmed invasive methicillin-resistant *Staphylococcus aureus*: a pharmacokinetic case series. *Pediatr Crit Care Med*. 2018;19(6):e292–e299.

12. Ho TT, Cadena J, Childs LM, et al. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. *J Antimicrob Chemother.* 2012;67(5):1267–1270.
13. Kuriakose SS, Rabbat M, Gallagher JC. Ceftaroline CSF concentrations in a patient with ventriculoperitoneal shunt-related meningitis. *J Antimicrob Chemother.* 2015;70(3):953–954.
14. Polenakovik HM, Pleiman CM. Ceftaroline for methicillin-resistant *Staphylococcus aureus* bacteraemia: case series and review of the literature. *Int J Antimicrob Agents.* 2013;42(5):450–455.
15. Sakoulas G, Nonejuie P, Kullar R, et al. Examining the use of ceftaroline in the treatment of *Streptococcus pneumoniae* meningitis with reference to human cathelicidin LL-37. *Antimicrob Agents Chemother.* 2015;59(4):2428–2431.
16. File TM Jr, Wilcox MH, Stein GE. Summary of ceftaroline fosamil clinical trial studies and clinical safety. *Clin Infect Dis.* 2012;55(suppl 3):S173–S180.
17. Sader HS, Mendes RE, Farrell DJ, et al. Ceftaroline activity tested against bacterial isolates from pediatric patients: results from the assessing worldwide antimicrobial resistance and evaluation program for the United States (2011–2012). *Pediatr Infect Dis J.* 2014;33(8):837–842.
18. Cottagnoud P, Cottagnoud M, Acosta F, et al. Efficacy of ceftaroline fosamil against penicillin-sensitive and -resistant *Streptococcus pneumoniae* in an experimental rabbit meningitis model. *Antimicrob Agents Chemother.* 2013;57(10):4653–4655.
19. Stucki A, Acosta F, Cottagnoud M, et al. Efficacy of Ceftaroline Fosamil against *Escherichia coli* and *Klebsiella pneumoniae* strains in a rabbit meningitis model. *Antimicrob Agents Chemother.* 2013;57(12):5808–5810.
20. Bravo ME, Arancibia A, Jarpa S, et al. Pharmacokinetics of gentamicin in malnourished infants. *Eur J Clin Pharmacol.* 1982;21:499–504.
21. Oshikoya KA, Sammons HM, Choonara I. A systematic review of pharmacokinetics studies in children with protein-energy malnutrition. *Eur J Clin Pharmacol.* 2010;66:1025–1035.
22. Chauzy A, Nadji A, Combes JC, et al. Cerebrospinal fluid pharmacokinetics of ceftaroline in neurosurgical patients with an external ventricular drain. *J Antimicrob Chemother.* 2019;74(3):675–681.
23. Stein GE, Yasin F, Smith C, et al. A pharmacokinetic/pharmacodynamic analysis of ceftaroline prophylaxis in patients with external ventricular drains. *Surg Infect (Larchmt).* 2015;16(2):169–173.
24. Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev.* 2010;23(4):858–883.
25. Law V, Knox C, Djoumbou Y, et al. DrugBank 4.0: shedding new light on drug metabolism. *Nucleic Acids Res.* 2014;42:D1091–D1097.
26. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39(9):1267–1284.
27. Van Wart SA, Ambrose PG, Rubino CM, et al. Pharmacokinetic-pharmacodynamic target attainment analyses to evaluate in vitro susceptibility test interpretive criteria for ceftaroline against *Staphylococcus aureus* and *Streptococcus pneumoniae*. *Antimicrob Agents Chemother.* 2014;58(2):885–891.
28. Archer NK, Mazaitis MJ, Costerton JW, et al. *Staphylococcus aureus* biofilms: properties, regulation, and roles in human disease. *Virulence.* 2011;2(5):445–459.