CASE REPORT

Pharmacokinetics of Continuous-Infusion Meropenem for the Treatment of *Serratia marcescens* Ventriculitis in a Pediatric Patient

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Neither guidelines nor best practices for the treatment of external ventricular drain (EVD) and ventriculoperitoneal shunt infections exist. An antimicrobial regimen with a broad spectrum of activity and adequate cerebrospinal fluid (CSF) penetration is vital in the management of both EVD and ventriculoperitoneal infections. In this case report, we describe the pharmacokinetics of continuous-infusion meropenem for a 2-year-old girl with *Serratia marcescens* ventriculitis. A right frontal EVD was placed for the management of a posterior fossa mass with hydrocephalus and intraventricular hemorrhage. On hospital day 6, CSF specimens were cultured, which identified a pan-sensitive *Serratia marcescens* with an initial cefotaxime minimum inhibitory concentration of 1 μg/ml or less. The patient was treated with cefotaxime monotherapy from hospital days 6 to 17, during which her CSF cultures and Gram's stain remained positive. On hospital day 26, *Serratia marcescens* was noted to be resistant to cefotaxime (minimum inhibitory concentration > 16 μg/ml), and the antimicrobial regimen was ultimately changed to meropenem and amikacin. Meropenem was dosed at 40 mg/kg/dose intravenously every 6 hours, infused over 30 minutes, during which, simultaneous serum and CSF meropenem levels were measured. Meropenem serum and CSF levels were measured at 2 and 4 hours from the end of the infusion with the intent to perform a pharmacokinetic/pharmacodynamic analysis. The resulting serum meropenem levels were 12 μg/ml at 2 hours and "undetectable" at 4 hours, with CSF levels of 1 and 0.5 μg/ml at 2 and 4 hours, respectively. On hospital day 27, the meropenem regimen was changed to a continuous infusion of 200 mg/kg/day, with repeat serum and CSF meropenem levels measured on hospital day 33. The serum and CSF levels were noted to be 13 and 0.5 μg/ml, respectively. The serum level of 13 μg/ml corresponds to an estimated meropenem clearance from the serum of 10.2 ml/kg/minute. Repeat meropenem levels from the serum and CSF on hospital day 37 were 15 and 0.5 μg/ml, respectively. After instituting the continuous-infusion meropenem regimen, only three positive CSF Gram's stains were noted, with the CSF cultures remaining negative. The continuous-infusion dosing regimen allowed for 100% probability of target attainment in the serum and CSF and a successful clinical outcome.

KEY WORDS ventriculitis, meropenem, pharmacokinetic, pharmacodynamics, pediatric, carbapenem, continuous infusion.

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An external ventricular drain (EVD) is a catheter inserted through the skull via a twist drill hole into the ventricular system and connected to a closed external drainage system. An EVD allows for the

drainage of cerebrospinal fluid (CSF) for the management of emergent hydrocephalus and as a bridge to a permanent ventriculoperitoneal (VP) shunt for continued management.[1, 2] Complications associated with VP shunts include failure, hemorrhage, and infection. The rate of VP shunt infections ranges from 4% to 20%, leading to shunt removal, replacement, and significant morbidity.[2–5] Shunt infections are typically managed with shunt removal and EVD placement.[3, 6, 7] Similarly, temporary EVDs are also subject to infection. The rate of EVD infection increases with the duration of time the EVD is in place and is estimated to range from 5% to 8%.[3, 8] Unlike a VP shunt, which is completely contained underneath the dermis, external drains must transit the skin. This break in the skin's integrity can serve as a route of entry for bacteria. EVDs are also routinely inserted at the patient's bedside in response to a neurologic crisis, rather than in the operating room.

Neither guidelines nor best practices for the treatment of EVD and VP shunt infections exist in the current body of scientific literature. Furthermore, there are no formal recommendations for antimicrobial regimens or duration of therapy, as evidenced by the varying recommendations for the treatment of *Staphylococcus aureus* and gram-negative bacilli ranging from 10 to 21 days following negative cultures.[3, 9, 10] An antimicrobial regimen with a broad spectrum of activity and adequate CSF penetration is vital in the management of both VP and EVD infections. Most antimicrobial dosing recommendations are derived from healthy volunteers and do not take into consideration the pharmacokinetic and pharmacodynamic changes known to occur in an intensive care unit (ICU) setting.[11–14]

Meropenem, a broad-spectrum carbapenem, is commonly used in the pediatric ICU for empiric and definitive therapy. The majority of pharmacokinetic data to guide dosing in children, however, are limited to healthy volunteers or non-ICU patients. The available pharmacokinetic data for pediatric ICU patients demonstrate a faster clearance and larger volume of distribution.[12, 15] The purpose of this case report is to describe the pharmacokinetics of continuous-infusion meropenem for the treatment of *Serratia marcescens* ventriculitis in a pediatric patient.

Case Report

The Drexel University College of Medicine Institutional Review Board approved this retrospective chart review for a single patient for this case report. A 2-year-old girl with no significant medical history initially presented to an outside facility with a 2-week history of vomiting that evolved from minor spit-ups to worsening nonbloody, nonbilious vomiting, with irritability, sleepiness, and decreased oral intake. On presentation to the hospital, the patient's Glasgow Coma Scale score was 7 and she was altered, nonverbal, and subsequently intubated. A computed tomography (CT) scan of the brain revealed a posterior fossa mass with hydrocephalus and intraventricular hemorrhage. As a result of the CT findings, the patient was transferred to St. Christopher's Hospital for Children (SCHC) for further management.

On arrival to SCHC, a right frontal EVD was placed emergently. On hospital day 3, she underwent craniotomy for tumor resection without complications, and on day 4, she was extubated. On day 6, she became febrile, and blood, urine, and CSF specimens were cultured. The CSF specimen was noted to have 10,000 red blood cells/mm^3, 130 white blood cells (WBCs)/mm^3 (normal range 0–20 WBCs/mm^3), with a protein level of 34 mg/dl (normal range 15–45 mg/dl) and glucose level of 52 mg/dl (normal range 40–75 mg/dl). The CSF Gram's stain had many WBCs and gram-negative rods (GNRs). The CSF culture subsequently grew GNRs for which meropenem and amikacin were initiated. The GNR was subsequently identified as pan-sensitive *S. marcescens* with an initial cefotaxime minimum inhibitory concentration (MIC) of ≤ 1 μg/ml. The antimicrobial regimen was narrowed to cefotaxime monotherapy at a dosing regimen of 50 mg/kg/dose intravenously every 4 hours infused over 30 minutes (300 mg/kg/day). On hospital day 7, the patient was taken to the operating room for removal and replacement of the EVD. Again, on day 14, due to the persistently positive cultures, the patient was taken back to the operating room for removal and replacement of her external drain.

From hospital days 6 to 17, the patient's CSF cultures and Gram's stain remained positive. Due to the persistent ventriculitis, on day 17, rifampin and amikacin were added to the cefotaxime regimen. From days 18 to 21, the CSF Gram's stain and cultures were negative. On day 24, she again experienced fevers, and the CSF cultures from days 24 and 25 grew *S. marcescens*. On day 26, she was taken back to the operating room for suboccipital wound washout with bacitracin along with removal of a dural graft with replacement with autologous fascia, removal of mesh, and

EVD replacement. At this point, the cefotaxime MIC for the *S. marcescens* was noted to be resistant (MIC > 16 μg/ml), and the antimicrobial regimen was changed to sulfamethoxazole/trimethoprim (MIC ≤ 20), meropenem (MIC ≤ 0.25), and amikacin (MIC ≤ 2). The sulfamethoxazole/trimethoprim was continued for 48 hours prior to being discontinued, and the meropenem and amikacin were both continued.

The meropenem was dosed at 40 mg/kg/dose intravenously every 6 hours, infused over 30 minutes, during which, simultaneous serum and CSF meropenem levels were measured. Random meropenem serum and CSF levels were measured at 2 and 4 hours from the end of the infusion with the intent to perform a pharmacokinetic/pharmacodynamic analysis. The resulting serum levels were 12 μg/ml at 2 hours and "undetectable" at 4 hours, with CSF levels of 1 and 0.5 μg/ml at 2 and 4 hours, respectively. Due to the undetectable 4-hour serum level, a true pharmacokinetic analysis could not be completed for the intermittent dosing regimen. The 2-hour CSF level most likely represented the peak concentration, with an estimated half-life of 2 hours for elimination from the CNS. The patient remained on the every-6-hour intermittent dosing regimen for 5 days from the time the serum, and CSF samples were sent for analysis, while they were transported, analyzed, and resulted. While on the intermittent regimen of 40 mg/kg/dose intravenously every 6 hours, the CSF Gram's stain and cultures remained positive. On hospital day 27, the meropenem regimen was changed to a continuous infusion of 200 mg/kg/day, with repeat meropenem levels measured from the serum and CSF on day 33. The serum and CSF levels were noted to be 13 and 0.5 μg/ml, respectively. The serum level of 13 μg/ml corresponds to an estimated meropenem clearance from the serum of 10.2 ml/kg/minute. Repeat meropenem levels from the serum and CSF on day 37 were 15 and 0.5 μg/ml, respectively. After instituting the continuous-infusion meropenem regimen, only three positive CSF Gram's stains were noted, with the CSF cultures remaining negative. On day 46, the EVD was removed and replaced with a permanent VP shunt. The meropenem infusion continued for 2 weeks after shunt placement.

The serum and CSF concentrations for meropenem in plasma and CSF were determined by bioassay (using *Clostridium perfringens* ATCC 13124) at ARUP Laboratories (Salt Lake City, UT). The standard curve for the meropenem bioassay ranged from 5 to 40 μg/ml with an interday assay variability that was less than 15% across all reference samples between 5 and 40 μg/ml. In the event samples were outside the upper limit of determination on the standard curve, a 1:2 or 1:5 dilution was made until the sample was within the standard curve. If samples were below the lower limit of determination on the standard curve, a value of "undetectable" was reported by the reference laboratory.

The following equation was used in determining patient-specific pharmacokinetic variables: Dose (mg/kg/hr) = C_{ss} (μg/ml) * Cl, where Cl = k_e (hr^{-1}) * V_d (L/kg), where C_{ss} = meropenem concentration at steady state, Cl = clearance, k_e = elimination rate constant, and V_d = volume of distribution. The percentage of time relative to the dosing interval that the drug concentration remains above the MIC ($fT > MIC$) for meropenem was calculated, and the probability of target attainment (PTA) was calculated using a pharmacodynamic target of ≥ 40% $fT > MIC$. A PTA of 90% or greater was defined as optimal.[16, 17] The continuous-infusion dosing regimen allowed for 100% PTA in the serum and CSF.

Discussion

The site of infection merits serious consideration when determining an optimal drug dosing regimen, which can be guided by contemporary antimicrobial pharmacokinetic and pharmacodynamic research. Bacterial eradication in the VP shunt and EVD infections is reliant on achieving and maintaining adequate drug concentrations at the site of infection, the CSF. Clinicians frequently rely on application of standard dosing regimens when treating complicated infections, risking failure, as therapeutic antimicrobial concentrations in plasma may not ensure appropriate CSF concentrations.[18, 19] The calculated meropenem clearance from our patient's serum level analysis, 10.2 ml/kg/minute, was significantly higher than the population pharmacokinetic estimates derived from both healthy volunteers and other pediatric ICU patients (range 4.88–7.5 ml/kg/min), one of whom was receiving extracorporeal life support.[12, 15, 20] Augmented renal clearance is a state of enhanced renal elimination of circulating solute, which has been previously described with antimicrobial drugs.[18, 21, 22] Enhanced antimicrobial elimination predisposes to subtherapeutic drug levels, therapeutic failure, and the selection of drug-resistant bacteria.[18]

This case highlights the value of therapeutic drug monitoring, which dictated the need for dose escalation as well as initiation of continuous-infusion meropenem to achieve optimal drug exposure, eradication of an EVD infection, and clinical success without any undue toxicity or adverse effects. For β-lactams and carbapenems, a relationship exists between the killing of bacteria and the time that free drug concentrations remain above the MIC for a pathogen.[23] Variations in drug clearance or volume of distribution can adversely affect the resultant $fT > MIC$, leading to underexposure and suboptimal response. Previous investigations utilizing meropenem doses of 20 and 40 mg/kg have been shown to produce CSF peaks of 0.1 to 2.8 and 0.3 to 6.5 μg/ml, respectively, about 2 to 4 hours after dosing.[24–26] It has been reported that in the absence of meningeal inflammation, the penetration of meropenem into the CSF is reduced. In adult patients receiving meropenem for non-CNS disease with EVDs, a 2000-mg dose infused over 30 minutes resulted in CSF peak concentrations of 0.63 ± 0.5 μg/ml, with a range of 0.13 to 1.6 μg/ml. [27] Interestingly, these values were demonstrably lower than corresponding mean plasma concentrations of 84.7 ± 23.7 μg/ml, with a time to reach the maximum concentration in the CSF of 4.1 ± 2.6 hours, suggesting a delayed distribution of meropenem into the CNS. The pharmacokinetic profile of meropenem in our patient seems to be discordant from that in the current literature. Our 3% CSF penetration ratio of meropenem is much lower than the 15% to 25% previously published in patients with CNS disease and higher than the ~0.7% in patients without CNS infections.[24–27] Faster meropenem clearance, as observed in our patient, may explain the difference in time to peak CSF levels being less than 4 hours in our patient.

Bacteria contained in biofilms are often very resistant.[28–32] Two current hypotheses for this are decreased penetration of antimicrobials into the biofilm and heterogeneity of biofilm-encased bacteria.[28–32] Medical devices colonized with biofilm-forming organisms often result in clinical infections that are very difficult to treat. Biofilms attributable to *S. marcescens* have been described and may account for the persistence of ventriculitis in our patient.[33] Difficulty eradicating biofilm-related infections frequently necessitates implant removal, ongoing antimicrobial therapy, and eventual replacement of the implant, all of which increase cost and prolong hospitalization.

This case illustrates the use of antimicrobial therapeutic drug monitoring to guarantee sufficient drug exposure to successfully treat CNS infections. Neurosurgical patients represent a vulnerable population at risk of inadequate antimicrobial dosing. With the prevalence of literature focusing on acute kidney injury and the need for antimicrobial dose reduction, scenarios where doses may, in contrast, need to be increased may not be readily recognized. The inability of current clinical estimates of renal function to identify augmented renal function could further complicate the situation, which highlights the need for the availability of real-time therapeutic drug monitoring. Therapeutic drug monitoring has the benefits of antimicrobial dosing regimen optimization to ensure the best chance for a successful clinical outcome while minimizing potential adverse effects and drug-related toxicities.

Conclusion

In this pediatric patient with *S. marcescens* ventriculitis, the use of continuous-infusion meropenem, along with simultaneous therapeutic drug monitoring of serum and CSF drug levels, allowed for a consistent CSF concentration above the MIC for 100% of the entire dosing interval, thereby avoiding trough levels below the MIC as seen with intermittent dosing and providing eradication of this persistent ventriculitis.

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