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Case Report

Pharmacokinetics of Continuous Infusion Meropenem With Concurrent Extracorporeal Life Support and Continuous Renal Replacement Therapy: A Case Report

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Pharmacokinetic parameters can be significantly altered for both extracorporeal life support (ECLS) and continuous renal replacement therapy (CRRT). This case report describes the pharmacokinetics of continuous-infusion meropenem in a patient on ECLS with concurrent CRRT. A 2.8-kg, 10-day-old, full-term neonate born via spontaneous vaginal delivery presented with hypothermia, lethargy, and a ~500-g weight loss from birth. She progressed to respiratory failure on hospital day 2 (HD 2) and developed sepsis, disseminated intravascular coagulation, and liver failure as a result of disseminated adenoviral infection. By HD 6, acute kidney injury was evident, with progressive fluid overload >1500 mL (+) for the admission. On HD 6 venoarterial ECLS was instituted for lung protection and fluid removal. On HD 7 she was initiated on CRRT. On HD 12, a blood culture returned positive and subsequently grew *Pseudomonas aeruginosa* with a minimum inhibitory concentration (MIC) for meropenem of 0.25 mg/L. She was started on vancomycin, meropenem, and amikacin. A meropenem bolus of 40 mg/kg was given, followed by a continuous infusion of 10 mg/kg/hr (240 mg/kg/day). On HD 15 (ECLS day 9) a meropenem serum concentration of 21 mcg/mL was obtained, corresponding to a clearance of 7.9 mL/kg/min. Repeat cultures from HDs 13 to 15 (ECLS days 7-9) were sterile. This meropenem regimen was successful in providing a target attainment of 100% for serum concentrations above the MIC for ≥40% of the dosing interval and was associated with a sterilization of blood in this complex patient on concurrent ECLS and CRRT circuits.

INDEX TERMS: carbapenem, CRRT, ECMO, meropenem, pediatric, pharmacodynamics, pharmacokinetic, renal

J Pediatr Pharmacol Ther 2016;21(1):92–97

INTRODUCTION

Pharmacokinetic parameters, such as the volume of distribution (Vd) and clearance (CL), can be significantly altered for individuals receiving extracorporeal life support (ECLS) in addition to continuous renal replacement therapy (CRRT). Pharmacokinetics and pharmacodynamics are important considerations when treating any infection.[1] Most antimicrobial dosing recommendations are derived from healthy volunteers and do not account for known pharmacokinetic and pharmacodynamic changes occurring in an adult or pediatric intensive care unit (ICU) setting.[2–6] Further, use of extracorporeal membrane oxygenation (ECMO) to provide ECLS can dramatically alter antimicrobial concentrations, as can CRRT.[7–10]

For β-lactam antibiotics like meropenem, there is a direct relationship between the time that free drug concentrations remain above the minimum inhibitory concentration (MIC) at the site of infection—referred to as %*f*T>MIC—and the killing of bacteria.[11–13] Ideally, the free drug concentration should be about 4 to 6 times the MIC for a duration of at least 40% of the dosing interval, depending on the specific β-lactam being used.[11–13] Most of the meropenem pharmacokinetic data in children are limited to healthy volunteers or non-ICU patients. The available pharmacokinetic data for pediatric ICU patients demonstrate a faster CL and larger volume of distribution.[3,14] Additionally, there is a single report on pharmacokinetic data

for meropenem in a pediatric patient in the setting of ECLS.[15] The purpose of this case report is to describe the pharmacokinetics of a meropenem continuous infusion in a neonate receiving concurrent ECLS and CRRT. The Drexel University College of Medicine Institutional Review Board approved this case report.

CASE REPORT

Clinical Course

A 2.8-kg, 10-day-old, full-term female neonate born via spontaneous vaginal delivery presented to her primary care physician on the day of admission for a routine visit. Her parents reported poor feeding with a 500-g weight loss. She was noted to be hypothermic and lethargic. She was transferred to St. Christopher's Hospital for Children because of a concern for a serious bacterial infection. Upon admission, a nasopharyngeal specimen sent for reverse transcriptase–polymerase chain reaction test returned positive for adenovirus. Her respiratory status worsened, with progression to respiratory failure on hospital day 2 (HD 2). She developed multiorgan dysfunction with septic shock, disseminated intravascular coagulation, acute kidney injury, and liver failure as a result of disseminated adenoviral infection. By the sixth day of hospitalization, her fluid balance was >1500 mL positive since admission. She deteriorated further that evening, requiring ECLS for lung protection. The following morning CRRT was initiated. On day 12, a blood culture returned positive, which was empirically treated with vancomycin, meropenem, and amikacin. Meropenem was started with a 40 mg/kg bolus given over 30 minutes, followed by a continuous infusion of 10 mg/kg/hr (240 mg/kg/day). The blood culture subsequently grew *Pseudomonas aeruginosa* with a meropenem MIC of 0.25 mcg/mL. Within 48 hours, after full organism identification, the vancomycin was discontinued. On day 15 of hospitalization (ECLS day 9) a meropenem serum concentration of 21 mg/L was obtained, corresponding to a CL of 7.9 mL/kg/min, which provided a 100% *f*T>MIC. At the time the meropenem serum concentration as obtained the CRRT modality was hemodiafiltration and the prescription included a dialysate flow rate of 200 mL/hr, a pre–blood pump flow rate of 250 mL/hr, a post–blood pump flow rate of 50 mL/hr, and a blood flow rate of 50 mL/min. These CRRT settings were at steady and unchanged for the 36 hours prior to the meropenem concentration being obtained, and the ECMO settings were unchanged for 22 hours prior to the meropenem concentration being obtained. For the 3 days prior to the meropenem concentration being obtained, the urine output was 0, 0, and 8 mL per day, with an ultrafiltration rate that ranged from 0 to 40 mL/hr for the 72 hours preceding the meropenem concentration. Repeat blood cultures from days 13 through 15 were sterile. There was only 1 circuit change done on day 14 for the CRRT circuitry, and the ECLS circuit was not changed for the entire duration of the ECLS run. The continuous infusion meropenem continued through day 15, when technologic support was removed as a result of a grade IV intraventricular hemorrhage.

Drug Dosing and Samples

Meropenem bolus (40 mg/kg) was infused over 30 minutes and was followed by a continuous infusion of 10 mg/kg/hr (240 mg/kg/day). The meropenem concentration was 40 mg/mL, and the diluent was normal saline. The continuous infusion was administered for 8 hours, and the syringe was changed every 8 hours due to the limited stability of meropenem at room temperature at 40 mg/mL. While on ECLS and CRRT support, a meropenem serum concentration was obtained 72 hours after the start of the continuous infusion.

Drug Serum Concentrations

Serum concentrations for meropenem (total drug) in plasma 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 mg/L, with an interday assay variability that was less than 15% across all reference samples between 5 and 40 mg/L. 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.

Pharmacokinetics

The following equation was used in determin-

ing patient-specific pharmacokinetic variables. Dose (mg/kg/hr) = Css (mg/L) * CL, where CL = k_e (hr^{-1}) * Vd (L/kg), where Css is the concentration at steady state. The %*f*T>MIC for meropenem was calculated. The probability of target attainment was calculated using a pharmacodynamic target of ≥40% *f*T>MIC,[1,13,14] and a value ≥90% was defined as optimal.[1,16,17]

ECLS Circuitry and Priming

The ECLS circuit for this patient was prepared using custom tubing with a 1/4-inch diameter and 3/32-inch thickness, made of polyvinylchloride and superTygon (Medtronic Inc., Minneapolis, MN), and a Quadrox-iD Peds oxygenator (Maquet, Rastatt, Germany). The circuit is crystalloid primed with Isolyte S pH 7.4 (B. Braun Medical Inc., Bethlehem, PA). After debubbling the circuit, 10 mL of 25% albumin was added and recirculated. The initial crystalloid/albumin prime was then displaced with the priming solution (packed red blood cells and fresh frozen plasma), tromethamine, heparin, and calcium gluconate. The circuit pH was adjusted using sodium bicarbonate or tromethamine as needed to a range of 7.35 to 7.45. The estimated priming volume for the neonatal ECLS circuit was 750 mL.

CRRT Circuitry and Priming

Dialysis was performed using the Prismaflex System (Gambro, Baxter, Deerfield, IL). The attending nephrologist prescribed the mode of dialysis (i.e., continuous venovenous hemofiltration or hemodiafiltration). The Prismaflex was initially primed with two 1-L bags of normal saline with 5000 units of heparin in each bag. The machine was then primed with a blood exchange (blood is transfused to the patient as the prime is wasted), depending on the percent extracorporeal volume of the patient, with a Duosol (B Braun Medical) dialysis solution using HF1000, AN69 dialysis filters.

DISCUSSION

Information is lacking regarding the impact of ECLS and CRRT on the pharmacokinetics and antimicrobial dosing requirements in neonatal and pediatric patients. Too commonly, typical antimicrobial dosing regimens are used for complicated, critically ill, neonatal, and pediatric patients. Adult data suggest variable vancomycin pharmacokinetics in the setting of vasoactive administration, extrarenal CL of vancomycin, CRRT intensity, CRRT circuitry, and even albumin concentrations.[8,9,18] Further, Joy and colleagues[9] demonstrated that escalation in CRRT intensity from hemofiltration to hemodiafiltration increased vancomycin CL by greater than or equal to 30%, mirroring data for other hydrophilic drugs, like β-lactams. We previously reported the first description of meropenem pharmacokinetics in the setting of ECLS in children[15] and are unaware of any meropenem pharmacokinetic estimates with concurrent ECLS and CRRT. The calculated meropenem CL in the ECLS report was larger than the population pharmacokinetic estimates derived from healthy volunteers, 4.14 to 4.8 vs. 4 mL/kg/min, a range of approximately 4% to 20% larger.[16] We have also previously demonstrated that meropenem pharmacokinetics in pediatric ICU patients not receiving ECLS are different when compared with published literature from which the standard meropenem dosing recommendations are derived.[3,14] In this report of meropenem pharmacokinetics in the setting of concurrent ECLS and CRRT, the CL was considerably larger at 7.9 mL/kg/min. A comparison of meropenem CL estimates is presented in the Table.[14,15,19] Meropenem is predominantly renally eliminated, with a range of 54% to 79% of unchanged drug recovered in the urine.[19,20] Meropenem has a small Vd estimate of ~0.4 L/kg, minimal protein binding (<2%), and low molecular weight (383 Da), which are all characteristics making meropenem readily removed by renal replacement therapies.[19,20] Data suggest extracorporeal removal of meropenem ranging from 23% to 56% in adults receiving CRRT; however, there are no estimates in children receiving CRRT.[21–27] The standard meropenem dose in a patient this age is 20 mg/kg per dose IV every 8 to 12 hours. Further, Nehus et al[28] conducted clinical trial simulations to determine dosing regimens in children that would provide for a target attainment of 40% and 75% time above the MIC. Simulations suggested that a dosing regimen of 20 mg/kg per dose IV every 8 hours would be sufficient to obtain the aforementioned target attainments for children younger than 5 years. For *Pseudomonas aeruginosa*, the susceptibility interpretive criteria for meropenem are as follows: sensitive, MIC ≤ 4 mg/L; intermediate, MIC = 8 mg/L; and resistant, MIC 16 ≥ mg/L.[19]

Table. Meropenem Pharmacokinetic Clearance Estimates for Pediatric Patients

Patient Characteristic/Data Source	Clearance, mL/kg/min
Non-ICU[19]	4
ECLS[15]	4.2-4.88
ECLS with CRRT (current report)	7.9
Pediatric ICU[14]	10.2

CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; ICU, intensive care unit

Considering the infecting pathogen and MIC are not known when empiric therapy is initiated, empiric dosing regimens should be designed to provide for appropriate exposures in case the infecting pathogen is a multidrug-resistant organism. Even though the *P aeruginosa* MIC was 0.25 mcg/mL for our patient, with the concern for dissemination to other sites, such as lung, bone, and even the central nervous system, the dosing regimen was not reduced. Further, the dosing regimen used in this scenario would have provided for an appropriate pharmacodynamics exposure up to the meropenem-resistant breakpoint of 16 mg/L. The total effluent flow rate, which estimates extracorporeal CL, used for the simulations by Nehus and colleagues[28] was 1.79 mL/kg/min. The total CL in our patient was significantly higher at 7.9 mL/kg/min, demonstrating that neither of the intermittent dosing regimens would have provided for an appropriate pharmacodynamic exposure in our patient, further strengthening the argument for real-time therapeutic drug monitoring.

Frequently, the site of infection and *ex vivo* treatment devices are rarely considered when designing drug-dosing regimens, which must be amended as ongoing antimicrobial pharmacokinetic and pharmacodynamic research is conducted. For example, in our patient the volume of blood, blood products, and drugs needed for the ECLS prime is approximately 1200 mL and for the CRRT circuit prime is approximately 2000 mL, which dramatically increases the extracorporeal volume any drug needs to distribute in. Most of the literature describing pharmacokinetic differences with ECLS and CRRT are with older equipment and devices. This area of research and literature must be revised to incorporate contemporary devices and treatment modalities. Roberts et al[5] demonstrated that current dosing recommendations in infected critically ill adult patients did not provide an appropriate % *f*T>MIC and had a negative impact on patient outcomes without ECLS or CRRT. In the setting of ECLS or CRRT, the ability to achieve the pharmacodymanic target % *f*T>MIC would be reduced, demonstrating that the "one dose fits all" theory is not appropriate. The result of insufficient antibiotic exposure can be severe. Adult data demonstrate a relationship between antibiotic underdosing and the development of antibiotic resistance.[29] The link was first established with low fluoroquinolone exposures[30] and more recently with other antimicrobials, such as β-lactams.[31,32] Considering that ICUs harbor multidrug-resistant pathogens, optimized dosing regimens that minimize resistance development should be employed to maximize patient outcomes. One strategy to optimize dosing regimens is real-time, prospective therapeutic drug monitoring. This is critical because suboptimal anti-infective therapy is associated with worse outcomes.[6,33–39] Systematic research using *ex vivo* circuits, large animal models, and population pharmacokinetic studies are indicated to improve antimicrobial dosing regimens and, therefore, patient outcomes during ECLS and CRRT.

CONCLUSION

This case report demonstrates meropenem CL is significantly increased, likely due to an increase in the Vd from ECLS and CRRT, and the elimination rate constant from CRRT in this critically ill neonate. Appropriate time above the MIC can be achieved by continuous-infusion meropenem with concurrent therapeutic drug monitoring.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Acknowledgment This work, in part, was presented at the 44th Society of Critical Care Medicine Critical Care Congress meeting, abstract 1155; January 2015; Phoenix, Arizona.

Abbreviations CL, clearance; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; HD, hospital day; ICU, intensive care unit; MIC, minimum inhibitory concentration; Vd, volume of distribution

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