CASE REPORT

Pharmacokinetics of Continuous-Infusion Meropenem in a Pediatric Patient Receiving Extracorporeal Life Support

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Meropenem, a broad-spectrum carbapenem, is commonly used for empirical and definitive therapy in the pediatric intensive care unit (ICU). Pharmacokinetic data to guide dosing in children, however, are limited to healthy volunteers or patients who are not in the ICU. Adult data demonstrate that pharmacokinetic parameters such as the volume of distribution and clearance can be significantly altered in individuals receiving extracorporeal membrane oxygenation (ECMO). Alterations in the volume of distribution and clearance of antimicrobials in patients with sepsis and septic shock have also been documented, and these patients have demonstrated lower than expected antimicrobial serum concentrations based on standard dosing regimens. Therefore, an understanding of the pharmacokinetic changes in critically ill children receiving ECMO is crucial to determining the most appropriate dose and dosing interval selection for any antimicrobial therapy. In this case report, we describe the pharmacokinetics of a continuous infusion of meropenem in a pediatric cardiac ICU patient who was receiving concurrent extracorporeal life support. The patient was an 8-month-old male infant who underwent a Glenn procedure and pulmonary artery reconstruction. Postoperatively, he required ECMO with a total run of 21 days. On day 11 of ECMO, a bronchoalveolar lavage was performed, and blood cultures from days 11 and 12 of ECMO grew *Pseudomonas aeruginosa,* with a meropenem minimum inhibitory concentration (MIC) of 0.5 μg/ml. On ECMO day 13, meropenem was initiated with a loading dose of 40 mg/kg and infused over 30 minutes, followed by a continuous infusion of 200 mg/kg/day. A meropenem serum concentration measured 8 hours after the start of the infusion was 46 μg/ml. Repeat levels were measured on days 3 and 9 of meropenem therapy and were 39 and 42 μg/ml, respectively. Repeat blood and respiratory cultures remained negative. This meropenem regimen (40-mg/kg bolus followed by a continuous infusion of 200 mg/kg/day) was successful in providing a target attainment of 100% for serum and lung concentrations above the MIC for at least 40% of the dosing interval and was associated with a successful clinical outcome.

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Early initiation of antimicrobials with a spectrum of activity that covers likely infecting pathogens is paramount in the intensive care unit (ICU). This intervention has been demonstrated to reduce morbidity and mortality across many different settings including adult and pediatric populations.[1–7] Most antimicrobial dosing recommendations are derived from healthy volunteers and do not take into consideration the

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pharmacokinetic and pharmacodynamic changes that are known to occur in an ICU setting.[4, 8–11] Augmented renal clearance is a state of enhanced renal elimination that can result in subtherapeutic concentrations of β-lactam antimicrobials and reduce the time that the free drug concentration is above the minimum inhibitory concentration (*f*T>MIC) for the infecting organism.[12, 13] Further, the use of extracorporeal membrane oxygenation (ECMO) for extracorporeal life support (ECLS) is commonly used in the ICU and can also have a dramatic effect on antimicrobial concentrations.[14, 15]

Meropenem, a broad-spectrum carbapenem, is commonly used in the pediatric ICU for empirical and definitive therapy. Most of the 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 does demonstrate a faster clearance and larger volume of distribution.[8] However, to our knowledge, pharmacokinetic data for meropenem in pediatric patients in the setting of ECLS have not been documented. In this case report, we describe the pharmacokinetics of a continuous infusion of meropenem in a pediatric cardiac ICU patient who was receiving concurrent ECLS.

Case Report

An 8-month-old male infant with heterotaxy, dextrocardia, asplenia, malrotation, mitral atresia, double outlet right ventricle, and pulmonary stenosis underwent a bidirectional cavopulmonary shunt (Glenn procedure) and pulmonary artery reconstruction. Postoperatively, he became hypoxemic due to pulmonary artery stenosis, viral bronchiolitis, and pulmonary hypertension requiring ECLS support; the total ECLS run was 21 days. On ECLS day 8, there was a concern for infection, and an empirical antimicrobial regimen of cefepime and ciprofloxacin was initiated. On day 11 of ECLS, a bronchoalveolar lavage (BAL) was performed, and the BAL cultures grew *Pseudomonas aeruginosa*. Blood cultures on days 11 and 12 of ECLS also grew *P. aeruginosa,* with a meropenem MIC of 0.5 μg/ml. The respective MICs for the isolate of *P. aeruginosa* are shown in Table 1. On ECLS day 13, cefepime and ciprofloxacin were discontinued, and meropenem and tobramycin were started.

Meropenem was initiated with a loading dose of 40 mg/kg infused over 30 minutes, followed by a continuous infusion of 200 mg/kg/day. Meropenem plasma concentrations 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 that 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

Table 1. Organism Isolates and Antimicrobial Minimum Inhibitory Concentrations on Days 11 and 12 of Extracorporeal Life Support

Day of ECLS	Source	Organism	Drug	MIC, μg/ml	Day of ECLS	Source	Organism	Drug	MIC, μg/ml
11	Blood	*Pseudomonas aeruginosa*	Amikacin	≤ 2	11	BAL	*Pseudomonas aeruginosa*	Amikacin	≤ 2
			Cefepime	8				Cefepime	8
			Ceftazidime	2				Ceftazidime	4
			Ciprofloxacin	2				Ciprofloxacin	1
			Gentamicin	≤ 1				Gentamicin	≤ 1
			Meropenem	≤ 0.25				Meropenem	0.5
			Piperacillin-tazobactam	8				Piperacillin-tazobactam	8
			Tobramycin	≤ 1				Tobramycin	≤ 1
12	Blood ECLS Circuit	*Pseudomonas aeruginosa*	Amikacin	≤ 2	12	Blood Blue port	*Pseudomonas aeruginosa*	Amikacin	≤ 2
			Cefepime	16				Cefepime	8
			Ceftazidime	2				Ceftazidime	2
			Ciprofloxacin	2				Ciprofloxacin	2
			Gentamicin	≤ 1				Gentamicin	≤ 1
			Meropenem	≤ 0.25				Meropenem	≤ 0.25
			Piperacillin-tazobactam	8				Piperacillin-tazobactam	8
			Tobramycin	≤ 1				Tobramycin	≤ 1

BAL = bronchoalveolar lavage; ECLC = extracorporeal life support; MIC = minimum inhibitory concentration.

lower limit of determination on the standard curve, a value of "undetectable" was reported by the reference laboratory.

The following equation was used to determine patient-specific pharmacokinetic variables: Dose (mg/kg/hr) = C_{ss} (μg/ml) * Cl, with Cl = k_{el} (/hr) * Vd (L/kg), where C_{ss} = meropenem concentration at steady state, Cl = clearance, k_{el} = elimination rate constant, and Vd = volume of distribution. The *f*T>MIC for meropenem was calculated, and the probability of target attainment (PTA) was calculated using a pharmacodynamic target of ≥ 40% *f*T>MIC.[16–18] A PTA of 90% or higher was defined as optimal.[16–18]

The ECMO circuit for this patient was prepared by using custom tubing with a 1/4-inch diameter and 3/32-inch thickness, made of polyvinylchloride and Super Tygon (Medtronic Inc., Minneapolis, MN) and a Quadrox-iD Pediatric oxygenator (Maquet, Wayne, NJ). The circuit is crystalloid primed with Isolyte S pH 7.4 (B. Braun Medical Inc., Woburn, MA). After debubbling the circuit, 10 ml of 25% albumin was added and recirculated. The initial crystalloid/albumin prime is then displaced with the priming solution (packed red blood cells and fresh-frozen plasma), tromethamine, heparin, and calcium gluconate. The circuit pH was adjusted as needed to a range of 7.35–7.45.

While the patient was receiving ECMO support, three blood samples were collected to determine meropenem serum concentrations. The first level, measured 8 hours after the start of the infusion, was 46 μg/ml. Repeat levels measured on days 3 (ECLS day 15) and 9 (ECLS day 21) of meropenem therapy were 39 and 42 μg/ml, respectively.

Table 2 presents the patient's meropenem clearance estimates. The 8-hour, day 3, and day 9 meropenem levels of 46, 39, and 42 μg/ml corresponded to clearances of 4.14, 4.88, and 4.54 ml/kg/minute, respectively. For each time point that a meropenem serum concentration was measured, the *f*T>MIC of 40% was achieved for 100% of the dosing interval, with a meropenem regimen consisting of a 40-mg/kg loading dose followed by a continuous infusion of 200 mg/kg/day.

Blood cultures collected on ECLS days 13–21 were all negative. Blood cultures collected for 1 week after ECLS decannulation remained negative. Repeat respiratory cultures from ECLS day 20 and from day 6 after decannulation were also negative.

Discussion

In general, there is a dearth of data describing the impact of ECLS on the pharmacokinetics and antimicrobial dosing requirements in pediatric patients. Clinicians often rely on standard dosing regimens for complicated critically ill pediatric and pediatric cardiac ICU patients, thus risking therapeutic failure. A single research letter exists describing the impact of the ECLS setting on meropenem pharmacokinetics in two adult patients.[19] The first was a patient with pneumonia and respiratory failure who was found to have a significantly increased clearance (20.4 L/hr) and a higher volume of distribution (0.56 L/kg). The second patient received venoarterial ECLS and extended daily ultrafiltration for *P. aeruginosa* pneumonia and multiorgan failure. The patient also had an elevated meropenem clearance (20.8 L/hr) from a high-dose infusion of 6.5 g infused over 24 hours. The calculated clearance for our patient was also higher than the population pharmacokinetic estimate derived from healthy volunteers—ranging from 4.14 to 4.88 ml/kg/minute for our patient versus 4 ml/kg/minute—representing ~4–20% higher than current estimates.[20] We have also shown previously that meropenem pharmacokinetics are different in pediatric ICU patients who were not receiving ECLS compared with the currently published literature.[8]

The site of infection is often not taken into account when determining a drug dosing regimen, which is a paradigm that most likely needs to change as more contemporary antimicrobial pharmacokinetic and pharmacodynamic research is conducted. The estimated epithelial lining fluid

Table 2. Meropenem Serum and Estimated Epithelial Lining Fluid Concentrations and Pharmacokinetic Parameters

Hour[a]	Meropenem serum concentration, μg/ml	ELF ratio	Estimated ELF concentration, μg/ml	40% *f*T>MIC	Clearance, ml/min/kg
8	46	0.25	11.5	Yes	4.140
72 (day 3)	39	0.25	9.75	Yes	4.880
216 (day 9)	42	0.25	10.5	Yes	4.540

ELF = epithelial lining fluid; *f*T>MIC = percentage of time relative to the dosing interval that the drug concentration remains above the minimum inhibitory concentration.
[a]After the start of the meropenem infusion.

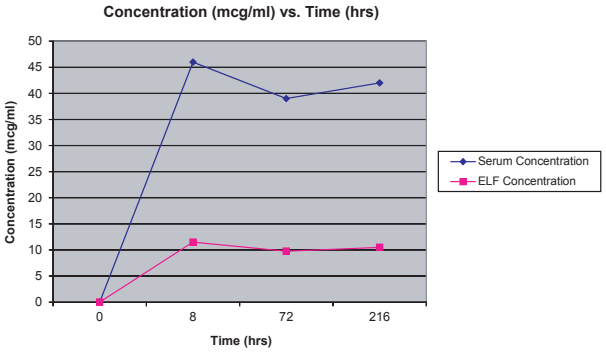

Figure 1. Meropenem serum and estimated epithelial lining fluid (ELF) concentrations over time.

(ELF) penetration ratio for meropenem is 25%.[21] Thus if the site of infection is thought to be the lungs, the dosing regimen should be adjusted to obtain a serum concentration that allows for an ELF concentration that is 4–6 times the MIC for at least 40% of the dosing interval, if possible, when using meropenem. The meropenem MIC for *P. aeruginosa* grown from the BAL culture was 0.5 μg/ml. Therefore, 6 times the MIC would require a 3-μg/ml concentration in ELF. Using the 200-mg/kg/day continuous infusion of meropenem, the estimated ELF concentration was at least 9 μg/ml, allowing for a *f*T>MIC for 100% of the dosing interval that provided rapid and sustained sterilization of the bloodstream (Figure 1). The use of a continuous infusion, monitored with drug levels, allowed for a steady ELF concentration above the MIC and avoided periods of trough levels below the MIC associated with intermittent dosing. Further, the repeat respiratory cultures while the patient was still receiving ECLS and after decannulation also remained negative with this continuous-infusion meropenem regimen (Figure 1).

Factors affecting pharmacokinetics during ECLS may include sequestration in the circuit, increased volume of distribution, and, usually, decreased clearance.[22] Most of the available pharmacokinetic data are derived from neonates regarding sedatives and select antimicrobials. However, unlike sedation, there are no real-time pharmacodynamic end points for antimicrobial therapy, and therapeutic drug monitoring is available for only a select number of antimicrobials. This is critical because suboptimal antimicrobial therapy is associated with worse outcomes.[1–7, 23] Systematic research using ex vivo circuits, large animal models, and population pharmacokinetics studies are needed to improve antimicrobial dosing regimens and, therefore, patient outcomes during ECLS.[22–24]

Conclusion

In this pediatric patient with a *P. aeruginosa* infection and who was receiving ECLS, a meropenem regimen of a 40-mg/kg bolus followed by a continuous infusion of 200 mg/kg/day was successful in providing a target attainment of 100% for serum and lung concentrations above the MIC for at least 40% of the dosing interval and was associated with a successful clinical outcome.

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