JPPT | Case Report

Therapeutic Drug Monitoring of Continuous Infusion Doripenem in a Pediatric Patient on Continuous Renal Replacement Therapy

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An 11-year-old African American male with severe combined immunodeficiency variant, non-cystic fibrosis bronchiectasis, pancreatic insufficiency, chronic mycobacterium avium-intracellulare infection, chronic sinusitis, and malnutrition presented with a 1-week history of fevers. He subsequently developed respiratory decompensation and cefepime was discontinued and doripenem was initiated. Doripenem was the carbapenem used due to a national shortage of meropenem. By day 7 the patient (24.7 kg) had a positive fluid balance of 6925 mL (28% FO), and on days 7 into 8 developed acute kidney injury evidenced by an elevated serum creatinine of 0.68 mg/dL, an increase from the baseline of 0.28 mg/dL. On day 9, the patient was initiated on continuous renal replacement therapy (CRRT) and the doripenem dosing was changed to a continuous infusion of 2.5 mg/kg/hr (60 mg/kg/day). Approximately 12.5 hours after the start of the doripenem a serum concentration was obtained, which was 4.01 mg/L corresponding to a clearance of 10.5 mL/min/kg. The pediatric dosing and pharmacokinetic data available for doripenem suggest a clearance estimate of 4.4 to 4.8 mL/min/kg, and the adult clearance estimate is 2.4 to 3.78 mL/min/kg. The calculated clearance in our patient of 10.5 mL/min/kg is over double the highest clearance estimate in the pediatric literature. This case demonstrates that doripenem clearance is significantly increased with CRRT in comparison with the published pediatric and adult data. An appropriate pharmacodynamic outcome (time that free drug concentration > minimum inhibitory concentration) can be achieved by continuous infusion doripenem with concurrent therapeutic drug monitoring.

ABBREVIATIONS CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; *f*T > MIC, time that free drug concentration > MIC; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PICU, pediatric intensive care unit

KEYWORDS carbapenem; continuous renal replacement therapy; CRRT; dialysis; Doribax; doripenem; pediatric; pharmacodynamics; pharmacokinetic; renal; therapeutic drug monitoring

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Introduction

Doripenem (Doribax, Shionogi, Inc, Florham Park, NJ) is a broad-spectrum parenteral carbapenem with activity against Gram-positive and Gram-negative organisms, including streptococci, methicillin-susceptible staphylococci, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Bacteroides fragilis*.[1-4] In comparison with other carbapenem antimicrobials, doripenem displays increased activity against *Pseudomonas aeruginosa*, making it an attractive option for the treatment of multidrug resistant Gram-negative infections.[2-4] Dosing information and clinical data related to doripenem in pediatrics are limited.[5,6] As such, information related to dosing and therapeutic drug monitoring of doripenem for pediatric intensive care unit (PICU) patients is needed.

Continuous renal replacement therapies (CRRTs) play a fundamental role in fluid management for critically ill patients experiencing acute kidney injury. The two CRRT modalities commonly used are continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis. CVVH is commonly used for acid-base stabilization in septic patients, and continuous venovenous hemodialysis is used mainly for fluid management. The use of both methods, continuous venovenous hemodiafiltration, is an increasingly employed modality. Pharmacokinetics and pharmacodynamics are essential factors when treating any infection and are known to undergo changes for patients in the PICU and with CRRT.[7-19] Therefore, the purpose of this case report is to describe the pharmacokinetics of continuous infusion doripenem in a pediatric patient receiving CRRT. The Drexel University College of Medicine Institutional Review Board approved this case report.

Case Description

Clinical Course

An 11-year-old African American male with severe combined immunodeficiency variant, non-cystic fibrosis bronchiectasis, pancreatic insufficiency, chronic mycobacterium avium-intracellulare infection, chronic sinusitis, and malnutrition presented with a 1-week history of fevers. Three days prior to presentation, he was seen by his pulmonologist and a respiratory culture was obtained and subsequently grew methicillin-resistant *Staphylococcus aureus* (MRSA). He was started on empiric sulfamethoxazole/trimethoprim for presumed MRSA pneumonia. The patient continued to be febrile and then presented to the emergency department and was subsequently admitted for management of his pneumonia with intravenous (IV) antimicrobials.

On day 1 of hospitalization, he was noted to be tachycardic and tachypneic requiring increasing oxygen support to maintain an oxygen saturation > 92%. He was transferred to the PICU for acute hypoxic respiratory failure necessitating non-invasive positive pressure ventilation with high-flow nasal cannula on day 3. Therapy was escalated to continuous positive airway pressure ventilation, bilevel positive airway pressure ventilation, and ultimately invasive mechanical ventilation and escalated to high frequency oscillatory ventilation by days 5 and 6. Upon admission, the patient was started on vancomycin for the MRSA (vancomycin minimum inhibitory concentration [MIC] of 0.5 mcg/mL) and cefepime due to a previous history of *Pseudomonas aeruginosa* pneumonia. The ongoing therapy of azithromycin, ethambutol, and rifampin was continued for treatment of the mycobacterium avium-intracellulare infection. Following the patient's respiratory decompensation, cefepime was discontinued and doripenem was initiated.

Doripenem was the carbapenem used due to a national shortage of meropenem. Doripenem was initiated at a dose of 15 mg/kg IV every 6 hours. By day 5, the patient (24.7 kg) had a positive fluid balance of 5563 mL translating to 22.5% fluid overload. By day 7 the patient had a positive fluid balance of 6925 mL (28% fluid overload), and on day 7 into 8 developed acute kidney injury evidenced by an elevated serum creatinine of 0.68 mg/dL, an increase from the baseline of 0.28 mg/dL. On the ninth day of hospitalization, the patient was initiated on CRRT for management of the fluid overload and electrolytes. The patient was started on CVVH without dialysis, using large volume replacement to control his chemical balance and creating a fluid deficit to remove fluid with a preblood pump flow rate of 900 mL/hr, a postblood pump flow rate of 100 mL/hr, and a blood flow rate of 180 mL/min. With the initiation of CRRT, the doripenem dosing was changed to a continuous infusion of 2.5 mg/kg/hr (60 mg/kg/day).

Approximately 12.5 hours after the start of the doripenem continuous infusion a doripenem serum concentration was obtained, which was 4.01 mg/L corresponding to a clearance of 10.5 mL/min/kg. At the time the doripenem serum concentration was obtained, the CRRT settings were steady and unchanged and the urine output was 0.46 mL/min/kg for the time period preceding the concentration. On day 10, the patient continued to clinically deteriorate exhibiting hypothermia, hypotension, severe respiratory and metabolic acidosis, and worsening coagulopathy. Despite increasing support on high frequency oscillatory ventilation, suctioning, and increasing inotropes the patient expired.

Drug Dosing and Samples

Prior to CRRT initiation, a 15 mg/kg dose of doripenem was given within 3 hours; therefore, a loading dose was not given prior to starting the doripenem continuous infusion. At the time of CRRT initiation, the doripenem continuous infusion was initiated at 2.5 mg/kg/hr (60 mg/kg/day). The infusion was performed by giving a 20 mg/kg dose over 8 hours via a syringe pump with changing of the syringe every 8 hours.

Drug Concentrations

Concentrations for doripenem in plasma were determined by liquid chromatography tandem mass spectrometry at Atlantic Diagnostic Laboratories (Bensalem, PA). The standard curve for the doripenem assay ranged from 5 to 40 mg/L with an interday assay variability that was < 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 measurable 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 specimens were immediately sent to the lab, spun down and stored at −80°C until they were picked up by the outside lab courier. The time from sending the sample until it reached the reference lab for analysis and results was < 24 hours.

Pharmacokinetics

The following equation was used in determining patient-specific pharmacokinetic variables. Dose (mg/kg/hr) = C_t (mg/L) *CL, where CL = k_e (hr^{-1}) * Vd (L/kg). Where CL is clearance, ke is the elimination rate constant, Vd is volume of distribution, and C_t is the concentration at time obtained. For carbapenem antibiotics like doripenem, the longer time the free drug concentration remains above the MIC at the site of infection, referred to as *f*T > MIC, there is increased killing of bacteria.[20-24] The *f*T% > MIC for doripenem and the probability of target attainment was calculated using a pharmacodynamic target of ≥ 40% *f*T > MIC.[22,23] Taking into consideration the approximate 8% protein

binding of doripenem, the 2.5 mg/kg/hr dosing regimen produced a calculated/estimated free drug concentration of about 3.69 mg/L, which allowed for a *f*T% > MIC of 100% for MICs < 4 mg/L.[1]

CRRT Circuitry and Priming

The dialysis was performed using the Prismaflex System (Gambro) machine. Mode of dialysis and CVVH was dictated by the attending nephrologist prescribing the dialysis. The Prismaflex machine was initially primed with two 1-L bags of normal saline with 5000 units of heparin. The machine was then primed with normal saline and 5% albumin; the CRRT solution was a Duosol (B Braun Medical, Bethlehem, PA) dialysis solution utilizing a HF1000, AN69 dialysis filter.

Discussion

To our knowledge, this is the first report describing doripenem pharmacokinetics in a pediatric patient receiving CRRT. The pediatric dosing and pharmacokinetic data available for doripenem are derived from pediatric patients with complicated intra-abdominal infections, urinary tract infections, and bacterial pneumonia, which suggest a clearance estimate of 4.4 to 4.8 mL/min/kg and the adult clearance estimate from the package insert is a clearance range of 2.4 to 3.78 mL/min/kg.[1,5] The calculated clearance in our patient of 10.5 mL/min/kg is over double the highest clearance estimate reported in the pediatric literature.

Literature evaluating the impact of CRRT on antimicrobial pharmacokinetics in neonatal and pediatric patients is absent. Therefore, relying on standard doses for critically ill pediatric patients on CRRT may not be appropriate. The pharmacodynamic target typically chosen for carbapenems is a *f*T% > MIC of 40% although there are data suggesting a pharmacodynamic target of *f*T% > MIC of 80%.[22-24] Using the doripenem dosing regimen evaluated in pediatric patients with intra-abdominal infections, urinary tract infections, and bacterial pneumonia of 60 mg/kg/day given as 20 mg/kg/dose IV every 8 hours would have only provided for an estimated *f*T% > MIC of 28% at the breakpoint of 4 mg/L.[5,25] Even doubling the dose to 40 mg/kg/dose given every 8 hours would have only provided for a *f*T% > MIC of 37%. One common approach to maximizing the *f*T% > MIC is to shorten the dosing interval; for example, giving a drug every 6 hours instead of every 8 hours. When evaluating regimens of 15, 20, and 40 mg/kg/dose every 6 hours, the resultant *f*T% > MIC values were 33, 38, and 49.7%. In this patient, a continuous infusion regimen of 2.5 mg/kg/hr (60 mg/kg/day) provided for a *f*T% > MIC of 100% for MICs < 4 mg/L. The continuous infusion dosing regimen of 60 mg/kg/day was chosen because the 60 mg/kg/day target is what has been investigated previously. Interestingly, the 40 mg/kg/dose every 6 hours regimen (160 mg/kg/day), which is not currently under investigation as a treatment regimen in pediatrics, required > 2.5 times the total dose to achieve *f*T% > MIC of at least 40% up to the breakpoint considering the doripenem dosing recommendation for CRRT is an every 12-hour dosing regimen.[1,26] Furthermore, a more recent adult investigation suggests that a larger dose equivalent to the 40 mg/kg/dose every 8 hours regimen is appropriate in adult patients during CRRT. However, this case report demonstrates that recommendation would not have provided for the target pharmacodynamic exposure.[27]

Contemporary extracorporeal treatment devices are rarely considered when designing drug dosing regimens, which is a paradigm in desperate need of change as ongoing antimicrobial pharmacokinetic and pharmacodynamic research is conducted. For example, in our patient, the volume of prime for the CRRT circuit was approximately 2000 mL, which dramatically increases the extracorporeal volume any drug needs to distribute in. Furthermore, most of the literature describing pharmacokinetic differences with CRRT are with older equipment and devices. While there are other potential causes that could contribute to enhance drug clearance such as drug loss via residual urine output and drug adsorption to the extracorporeal tubing, neither of these would explain the clearance estimate observed in this scenario. There can be a dramatic impact from low antimicrobial exposures. The adult data demonstrate a relationship between antibiotic underdosing and the development of antibiotic resistance.[28] The link was first established with low fluoroquinolone exposures and subsequently with β-lactams.[28-31] Optimized, individualized dosing regimens that minimize resistance development should be utilized in an effort to maximize patient outcomes, especially in the critical care setting where infections related to multidrug-resistant pathogens are more common and dose individualization has a positive impact on morbidity and mortality.[32] Real-time, prospective therapeutic drug monitoring is one approach available to assist in designing optimized dosing regimens, which can be significant as suboptimal anti-infective therapy is associated with worse outcomes.[33-39] Organized research using contemporary extracorporeal circuits utilizing *ex vivo* and animal models coupled with population pharmacokinetic studies are essential to improve upon current antimicrobial dosing regimens and, consequently, patient outcomes during CRRT.

Conclusions

This case demonstrates that doripenem clearance is significantly increased with CRRT in comparison with the published pediatric and adult data. An appropriate pharmacodynamic outcome (*f*T > MIC) can be achieved by continuous infusion doripenem with concurrent therapeutic drug monitoring.

ARTICLE INFORMATION

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