Therapeutic Drug Monitoring of Prolonged Infusion Aztreonam for Multi-Drug Resistant *Pseudomonas aeruginosa*: A Case Report

Jeffrey J. Cies, PharmD, MPH; Richard J. LaCoursiere, PharmD; Wayne S. Moore II, PharmD; and Arun Chopra, MD

Aztreonam, a broad-spectrum monobactam, is typically reserved for multidrug resistant (MDR) infections. Pharmacokinetic (PK) data to guide dosing in children, however, are limited to healthy volunteers or nonintensive care unit (ICU) patients. Impaired antibiotic delivery into tissue remains a major concern and may explain the high morbidity and mortality associated with MDR infections. Therefore, evaluating the PK changes in pediatric ICU patients is necessary to elucidate the most appropriate antimicrobial regimen. We describe the PK of prolonged infusion aztreonam in a patient with MDR *Pseudomonas aeruginosa* empyema. The 16-year-old tetraplegic male with a cervical spinal cord injury, chronic respiratory failure, and tracheostomy was admitted with a 2-day history of fever and hypoxemia. Chest x-ray revealed a left lower lobe infiltrate. On hospital day 2, computed tomography scan noted a massive collapse of the left lung with bronchiectasis and hepatization with a pneumatocele. He underwent bronchoscopy on days 2, 6, and 10 and the cultures subsequently grew *P aeruginosa* only sensitive to aztreonam (minimum inhibitory concentration [MIC] of 2–6 mg/L). A regimen of aztreonam 2 grams intravenously (IV) every 6 hours (each dose infused over 4 hours) and polymyxin B 1,000,000 units IV every 12 hours (each dose infused over 30 minutes) was initiated on day 3. On day 8, the aztreonam serum plateau concentration was 71 mg/L. Repeat respiratory and bronchoscopy cultures from days 19 to 37 remained negative. Aztreonam clearance was 2.3 mL/kg/min, which was significantly increased when compared with the 1.3 mL/kg/min suggested in the prescribing information based on adult data. A prolonged infusion of 2 grams of aztreonam every 6 hours (each dose infused over 4 hours) successfully attained 100% of the target serum and lung concentrations above the MIC for at least 40% of the dosing interval, and was associated with successful treatment of MDR *P aeruginosa* empyema.

ABBREVIATIONS ARC, augmented renal clearance; CT, computed tomography; ELF, epithelial lining fluid; ICU, intensive care unit; IV, intravenously; MDR, multidrug resistant; MIC, minimum inhibitory concentration; PK, pharmacokinetic

KEYWORDS aztreonam; monobactam; pediatric; pharmacodynamics; pharmacokinetic; prolonged infusion; therapeutic drug monitoring

J Pediatr Pharmacol Ther 2017;22(6):467–470

DOI: 10.5863/1551-6776-22.6.467

Introduction

Prompt administration of antimicrobials with an appropriate spectrum of activity for infecting pathogens is vital in the intensive care unit (ICU). Prompt and appropriate antimicrobial therapy has been shown to reduce morbidity and mortality across many different pediatric and adult settings.^{1–7} Unfortunately, many antimicrobial dosing recommendations are developed using healthy volunteers and neglect the pharmacokinetic and pharmacodynamic changes known to occur in patients in an ICU setting.^{8–11} Further, augmented renal clearance (ARC) is the state of enhanced renal drug elimination observed in critical illness, which can generate subtherapeutic antimicrobial concentrations. ARC results in a reduction in the time the free drug concentration is above the

minimum inhibitory concentration ($fT > MIC$) of the infecting organism, the primary pharmacodynamic parameter linked to efficacy for β -lactams and monobactams.^{12–17}

Aztreonam, a broad-spectrum monobactam, is typically reserved for multidrug resistant (MDR) infections.¹⁸ Aztreonam displays bactericidal activity against *Pseudomonas aeruginosa* and other Gram-negative aerobes.¹⁸ Pharmacokinetic data to guide dosing in children are limited to healthy volunteers or non-ICU patients. Currently, a single study has been conducted assessing the pharmacokinetics of aztreonam in 29 pediatric patients; however, information documenting the severity of their infections and the hospital care setting in which they were treated is excluded.¹⁹ Impaired antimicrobial distribution into affected tissues is a major concern with all infections; this is especially true

of infections caused by MDR organisms, which exhibit high morbidity and mortality.¹⁻⁵ An understanding of the pharmacokinetic changes in patients in the pediatric ICU is crucial to determine the most appropriate antimicrobial dosing regimen. The purpose of this case report is to describe the therapeutic drug monitoring of prolonged infusion aztreonam in an adolescent patient with MDR *P aeruginosa* complicated empyema. The Drexel University College of Medicine Institutional Review Board approved this case report.

Case

A 16-year-old, 51 kg, tetraplegic male with a C2 spinal cord injury secondary to a gunshot wound, chronic respiratory failure, and a tracheostomy was admitted with fever and hypoxemia for 2 days. At presentation, a chest x-ray revealed a left lower lobe lung infiltrate. On hospital day 2, a computed tomography (CT) scan was obtained demonstrating massive collapse of the left lung with bronchiectasis and hepatization with a pneumatocele and a small right lung pleural effusion. On hospital day 2, culture obtained from the first bronchoalveolar lavage (BAL) subsequently grew *P aeruginosa* susceptible only to aztreonam with a minimum inhibitory concentration (MIC) of 6 mg/L and polymyxin B with a zone of inhibition of 15 mm. On the third day of hospitalization, a regimen of 2 grams of aztreonam intravenously (IV) every 6 hours was infused over 4 hours and 1,000,000 units of polymyxin B IV every 12 hours was infused over 30 minutes. Three days later, a repeat BAL also grew *P aeruginosa*, but the aztreonam MIC for this isolate was 4 mg/L. On the eighth day of hospitalization, a serum aztreonam concentration was obtained immediately at the end of the 4-hour prolonged infusion and was 71 mg/L, corresponding to a clearance of 2.3 mL/min/kg. On the 19th day of hospitalization, a repeat CT scan with contrast showed near complete collapse of the left lung as well as decreasing size of the empyema, suggestive of improving pneumonia and bronchopleural fistula. On this same day, the respiratory culture obtained 16 days into this antimicrobial regimen was negative for the presence of any organism. Repeat BAL on day 21 also demonstrated no growth as did repeat BALs and cultures obtained on days 23 and 26 of hospitalization. His chest x-ray continued to improve and suctioning needs subsequently decreased throughout the hospitalization. A repeat CT scan on day 30 showed improved aeration of the left lung and only a small right empyema and a respiratory culture obtained on day 37 was negative. The patient was treated for a duration of 6 weeks from the first negative BAL. There were no adverse events or toxicities that developed in this patient as a result of the prolonged aztreonam infusion regimen.

Drug Levels. Aztreonam plasma concentration was determined by bioassay (utilizing *Klebsiella pneumoniae* ATCC 1296) at ARUP Laboratories (Salt Lake

City, UT). The standard curve for the aztreonam bioassay ranged from 10 to 40 mg/L with an interday assay variability that was less than 15% across all reference samples between 10 and 40 mg/L. In the event a sample was 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 a sample was 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 utilized in determining patient-specific pharmacokinetic variables: $\text{Dose (mg/kg/hr)} = C_{ss} \text{ (mg/L)} \times \text{CL}$, where $\text{CL} = k_e \text{ (hr}^{-1}\text{)} \times \text{Vd (L/kg)}$. The $tT > \text{MIC}$ for aztreonam was calculated, and the probability of target attainment was calculated using a pharmacodynamic target of $\geq 40\% tT > \text{MIC}$.¹⁴⁻¹⁷ A probability of target attainment $\geq 90\%$ was defined as optimal.¹⁴⁻¹⁷

Discussion

Standard dosing regimens are commonly utilized regardless of a patient's clinical scenario. For complicated, critically ill patients, this paradigm places patients at risk for therapeutic failure as a result of altered pharmacokinetics and pharmacodynamics commonly seen in an ICU setting. The aztreonam¹⁸ package insert suggests a clearance estimate in adults of 1.3 mL/min/kg and a pediatric estimate that closely approximates this value. To the authors knowledge, there are no published pharmacokinetic data of aztreonam in critically ill children. Data on aztreonam pharmacokinetics in critically ill adult patients suggest higher clearance estimates in the range of 1.8 to 2 mL/min/kg.^{20,21} The clearance value in this patient was 2.3 mL/min/kg, a value approximately 78% higher than suggested in the package insert and about 15% to 30% higher than adult patients in the ICU.¹⁸ Current dosing recommendations available in drug dosing references²¹⁻²³ are based on the clearance estimate of 1.3 mL/min/kg. Dosing regimens are reliant on an equation where $\text{dose} = \text{desired concentration} \times \text{clearance value}$. As can be seen with a simple manipulation of the above equation, if the clearance value changes, the desired target concentration will not be obtained following administration of a “standard dose.” For example, if a standard aztreonam dose is given and the clearance estimate is doubled, the actual concentration will be reduced in comparison to the target concentration. This relationship is rarely used when selecting and designing dosing regimens in the pediatric ICU.

Site of infection must be taken into account when determining an optimal drug dosing regimen, which is a paradigm that should change as more contemporary antimicrobial pharmacokinetic and pharmacodynamic research is conducted. The estimated epithelial lining fluid (ELF) ratio for aztreonam ranges from 36% to 80%.²³ Therefore, the dosing regimen should be

adjusted to maintain a serum concentration that allows for an ELF concentration 4 to 6 times the MIC for at least 40% of the dosing interval when using aztreonam to treat a primary lung infection. The *P aeruginosa* MIC grown from the BAL culture was 2 to 6 mg/L. Therefore, 6 times the MIC would require a range of 12 to 36 mg/L concentration in the ELF. To achieve this target ELF concentration, the serum concentration would need to be at least 35 mg/L and in our patient, it was 71 mg/L. Using the 2-gram prolonged infusion of aztreonam over 4 hours every 6 hours, the estimated ELF concentration was in the range of 25 to 57 mg/L, which allowed for a probability of target attainment of 100% for serum and presumed ELF concentrations above the MIC for at least 40% of the dosing interval. The use of a prolonged infusion regimen, monitored with drug levels, allowed for a steady ELF concentration above the MIC. This dosing regimen avoided periods of trough concentrations below the MIC seen with intermittent dosing, which is critical, as suboptimal antimicrobial therapy is associated with worse outcomes.^{1-7,25} Further, the repeat BAL and respiratory cultures also remained negative with this prolonged infusion aztreonam regimen.

This case illustrates the use of antimicrobial therapeutic drug monitoring to guarantee sufficient drug exposure to successfully treat a MDR *P aeruginosa* empyema. Pediatric ICU patients are a population at extreme risk of insufficient antimicrobial dosing. Literature focusing on acute kidney injury has many clinicians advocating for judicious decrement of antimicrobial dosing, yet clinical scenarios may necessitate increasing dosing regimens, and the inability to identify ARC can further complicate the situation. This is another case demonstrating the need for real-time therapeutic drug monitoring.²⁶⁻²⁸ Therapeutic drug monitoring can provide for optimization of antimicrobial dosing regimens to maximize the opportunity for a successful clinical outcome while minimizing potential adverse effects and drug-related toxicities. Compared with adults, children have a greater number of functioning nephrons, and therefore, have greater drug clearance (CL) via glomerular filtration.^{29,30} As a result, children between the ages of 6 months to 6 years usually have a renal elimination of drugs that is at least 2 times faster than adults 18 years of age and older.³¹⁻³³ Therefore, this finding of increased aztreonam clearance would be expected in infants and younger children as described previously with other β -lactam antimicrobials.^{8,9,26}

Conclusion

A prolonged infusion regimen of aztreonam 2 grams every 6 hours (each dose infused over 4 hours) was successful in providing a probability of target attainment of 100% for serum and presumed ELF concentrations above the MIC for at least 40% of the dosing interval and associated with a successful clinical outcome in this complex patient with MDR *P aeruginosa* empyema.

ARTICLE INFORMATION

Affiliations The Center for Pediatric Pharmacotherapy (JJC, WSM, AC), LLC, Pottstown, Pennsylvania; St. Christopher's Hospital for Children (JJC), Philadelphia, Pennsylvania; Drexel University College of Medicine (JJC), Philadelphia, Pennsylvania; Thomas Jefferson University School of Pharmacy (RJL), Philadelphia, Pennsylvania; NYU Langone Medical Center (AC), New York, New York; NYU School of Medicine (AC), New York, New York

Correspondence Jeffrey J. Cies, PharmD, MPH; jeffrey.cies@gmail.com

Disclosure Dr Cies is a consultant for Atlantic Diagnostic Laboratories and has received grants and/or honoraria from Allergan, Merck, and Thermo Fisher Scientific. 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. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Copyright Published by the Pediatric Pharmacy Advocacy Group. All rights reserved.

For permissions, email: matthew.helms@ppag.org

REFERENCES

1. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
2. Harbarth S, Garbino J, Pugin J, et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med*. 2003;115(7):529-535.
3. MacArthur RD, Miller M, Albertson T, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. *Clin Infect Dis*. 2004;38(2):284-288.
4. Udy AA, Roberts JA, Dewaele J, et al. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. *Int J Antimicrob Agents*. 2012;39(6):455-457.
5. Goncalves-Pereira J, Povoas P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. *Crit Care*. 2011;15(5):R206.
6. Surviving Sepsis Campaign. International guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2013;41(2):580-637.
7. Muszynski JA, Knatz NL, Sargel CL, et al. Timing of correct parenteral antibiotic initiation and outcomes from severe bacterial community-acquired pneumonia in children. *Pediatr Infect Dis J*. 2011;30(4):295-301.
8. Cies JJ, Shankar V, Schlichting C, Kuti JL. Population pharmacokinetics of piperacillin/tazobactam in critically ill young children. *Pediatr Infect Dis J*. 2014;33(2):168-173.
9. Cies JJ, Moore WS, Chopra A. Meropenem pharmacokinetics in critically ill children. Abstract number 938 presented at: Society of Critical Care Medicine 43rd Annual Congress; January 2014; San Francisco, CA.

10. Lipman J, Udy AA, Roberts JA. Do we understand the impact of altered physiology, consequent interventions, and resultant clinical scenarios in ICU? The antibiotic story. *Anaesth Intensive Care*. 2011;39(6):999–1000.
11. Roberts JA, Paul SK, Akova M, et al, for the DALI study. DALI: defining antibiotic levels in intensive care unit patients: are current β -lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014;58(8):1072–1083.
12. Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet*. 2010;49(1):1–16.
13. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial β -lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest*. 2012;142(1):30–39.
14. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of bug and drug. *Nat Rev Microbiol*. 2004;2(4):289–300.
15. Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis*. 2003;36(suppl 1):S42–S50.
16. Tam VH, Louie A, Lomaestro BM, Drusano GL. Integration of population pharmacokinetics, a pharmacodynamic target, and microbiologic surveillance data to generate a rational empiric dosing strategy for cefepime against *Pseudomonas aeruginosa*. *Pharmacotherapy*. 2003;23(3):291–295.
17. Courter JD, Kuti JL, Girotto JE, Nicolau DP. Optimizing bactericidal exposure for beta-lactams using prolonged and continuous infusions in the pediatric population. *Pediatr Blood Cancer*. 2009;53(3):379–385.
18. Aztreonam (Azactam) [package insert]. Bristol-Myers Squibb Company; revised May 2012.
19. Stutman HR, Marks MI, Swabb EA. Single-dose pharmacokinetics of aztreonam in pediatric patients. *Antimicrob Agents Chemother*. 1984;26(2):196–199.
20. Boccazzi A, Langer M, Mandelli M, et al. The pharmacokinetics of aztreonam and penetration into the bronchial secretions of critically ill patients. *J Antimicrob Chemother*. 1989;23(3):401–407.
21. McKindley DS, Boucher BA, Hess MM, et al. Pharmacokinetics of aztreonam and imipenem in critically ill patients with pneumonia. *Pharmacotherapy*. 1996;16(5):924–931.
22. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online. Hudson, OH: Lexi-Comp, Inc; 2015.
23. *Micromedex Healthcare Series* [intranet database]. Version 5.1. Greenwood Village, CO: Thomson Micromedex.
24. Tschudy MM, Arcara KM, eds. *The Harriet Lane Handbook: A Manual for Pediatric House Officers*. Philadelphia, PA: Mosby Elsevier; 2012.
25. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest*. 1999;115(2):462–474.
26. 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.
27. Cies JJ, Moore WS 2nd, Miller K, et al. Therapeutic drug monitoring of continuous-infusion acyclovir for disseminated herpes simplex virus infection in a neonate receiving concurrent extracorporeal life support and continuous renal replacement therapy. *Pharmacotherapy*. 2015;35(2):229–233.
28. Cies JJ, Moore WS 2nd, Dickerman MJ, et al. Pharmacokinetics of continuous-infusion meropenem in a pediatric patient receiving extracorporeal life support. *Pharmacotherapy*. 2014;34(10):e175–e179.
29. Lindeman, RD, Tobin, J, Shock, NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985;33(4):278–285.
30. Rowe JW, Andres R, Tobin JD, et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol*. 1976;31(2):155–163.
31. Reed MD, Goldfarb J, Yamashita TS, et al. Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother*. 1994;38(12):2817–2826.
32. Chien S, Wells TG, Blumer JL, et al. Levofloxacin pharmacokinetics in children. *J Clin Pharmacol*. 2005;45(2):153–160.
33. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet*. 2006;45(11):1077–1097.