Pharmacokinetics of Peramivir in an Adolescent Patient Receiving Continuous Venovenous Hemodiafiltration

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Critically ill patients requiring renal replacement therapy commonly experience pharmacokinetic alterations. This case report describes the pharmacokinetics of peramivir (Rapivab, BioCryst Pharmaceuticals, Inc, Durham, NC), the first US Food and Drug Administration–approved intravenous neuraminidase inhibitor for the treatment of influenza, in an adolescent patient receiving continuous renal replacement therapy (CRRT). A 49.5-kg, 17-year-old Caucasian female presented with fever, cough, and persistent hypoxia. She quickly progressed to acute respiratory and renal failure in the setting of viral septic shock as a result of a severe influenza H1N1 infection. On hospital day 3, therapy was switched from oseltamivir (Tamiflu, Roche Laboratories Inc, Nutley, NJ) to peramivir owing to the concern for inadequate enteral absorption. On the third day of peramivir treatment, at a dose of 200 mg daily, peramivir serum concentrations revealed a smaller peak concentration, larger volumes of distribution, similar 24-hour area under the curve, and a shorter half-life as compared to adult patients with normal renal function. This illustrated the significant differences in pharmacokinetics when administered in the setting of CRRT. The patient had resolution of viral infection as evidenced by negative respiratory viral panel polymerase chain reaction at hospital day 14 and was eventually discharged at her baseline.

ABBREVIATIONS AUC, area under the curve; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; Vd, volume of distribution; RVP, respiratory viral polymerase-chain reaction panel

KEYWORDS adolescent; case report; continuous renal replacement therapy; CRRT; influenza; pediatric peramivir; pharmacokinetics; therapeutic drug monitoring

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Introduction

Critically ill patients are known to experience alterations in their pharmacokinetics, including diminished gastrointestinal perfusion reducing absorption, reduced plasma albumin increasing volume of distribution (Vd) and free drug concentrations, altered hepatic blood flow with dynamic metabolic effects, and altered renal clearance affecting drug elimination.¹ Adding an additional level of complexity are variations produced in patients receiving extracorporeal therapies, which can have a vast array of pharmacokinetic consequences.^{2–6} In the study of infectious diseases, these variations are becoming an increasingly examined domain as further insights are gained into the concentration-effect relationships between antimicrobials and organisms. Optimizing drug concentrations in order to maximize pharmacodynamic target attainment has been shown to decrease mortality when assessing β -lactam antibiotics and Gram-negative infections.^{7–11} In the treatment of influenza with antivirals, the pharmacodynamic target has not been clearly elucidated; however, an animal model has suggested an association between total drug exposure (area under the curve [AUC]) and mor-

tality.¹² The interplay between pharmacodynamics and pharmacokinetics with extracorporeal therapies creates a unique challenge to the critical care practitioner in providing optimal care to critically ill patients.

Peramivir (Rapivab, BioCryst Pharmaceuticals, Inc, Durham, NC), the first US Food and Drug Administration–approved intravenous (IV) neuraminidase inhibitor, is a cyclopentane derivative with potent antiviral activity against both influenza A and B viruses.¹³ A recent multicenter, open-label study of pediatric patients with H1N1 influenza sought to address the efficacy, safety, and pharmacokinetics of peramivir.¹⁴ The authors concluded that standardized, weight-based dosage in pediatrics had similar efficacy and safety outcomes when compared to adult patients. Notably, the authors excluded pediatric patients with a range of comorbidities including those with renal dysfunction. Peramivir exhibits linear pharmacokinetics and possesses a small molecular weight with minimal plasma protein binding, which can predispose patients with renal dysfunction to drug accumulation.^{13,15}

There have been several case reports of peramivir use in adult patients on continuous renal replacement therapy (CRRT); however data in patients below the

age of 18 years are limited.¹⁶⁻²⁰ In 2009, the US Food and Drug Administration issued an emergency use authorization for peramivir, which subsequently acknowledged this lack of data and put forth recommendations for dosage in CRRT, based on known developmental characteristics of pediatric patients and the available adult data.¹⁵ To our knowledge, this is the first case report to describe the pharmacokinetics of peramivir in a critically ill adolescent patient receiving continuous venovenous hemodiafiltration (CVVHDF).

Case Report

A 17-year-old, 49.5-kg Caucasian female with a medical history significant for developmental delay, cerebral palsy, Lennox-Gastaut syndrome, and chronic lung disease presented to a large, urban, tertiary care, academic medical center with a 3-day history of fever, cough, increased work of breathing, and persistent hypoxemia. The patient received IV fluids and broad-spectrum antibiotics for presumed pneumonia and was started on oseltamivir (Tamiflu, Roche Laboratories Inc, Nutley, NJ) for influenza A H1N1 (2009) diagnosed by a respiratory viral polymerase-chain-reaction panel (RVP). The patient developed viral septic shock requiring vasopressor support and acute respiratory distress syndrome requiring intubation and subsequent escalation to high-frequency oscillatory ventilation. By hospital day 3, she displayed evidence of fluid overload with decreased cardiac function requiring milrinone and also developed acute kidney injury managed with CRRT.

On day 3, the patient was given a single dose of 600 mg of peramivir owing to concern for inadequate absorption of oseltamivir. In the setting of acute kidney injury and CRRT, the dosage regimen of peramivir was adjusted to 200 mg daily on the basis of package insert recommendations for creatinine clearance 30 to 49 mL/min,²¹ and serum concentrations were taken on peramivir treatment day 3 (Figure). Peramivir 200 mg daily was continued through day 8, after which doses were adjusted on the basis of renal function and extracorporeal support.

During the time course of peramivir serum concentration collection, the CRRT modality was CVVHDF and the prescription included a dialysate flow rate of 1000 mL/hr, a pre-blood replacement fluid pump flow rate of 500 mL/hr, a post-blood replacement fluid pump flow rate of 500 mL/hr, a blood flow rate of 250 mL/min, and an ultrafiltrate goal of 150 mL/hr. These settings were steady and unchanged for the 24 hours before the first serum sample with the exception of a 1-hour interruption for filter clotting approximately 11 hours before the first concentration was obtained. Dialysis was performed with the Prismaflex System (Gambro, Deerfield, IL) with a M100 filter, primed with 152 mL of heparinized sodium chloride per institutional protocol. For 24 hours before peramivir concentration being obtained, the total urine output was 108 mL (0.09 mL/kg/hr), with an ultrafiltration

Figure. Peramivir serum concentrations—between second and third dose of 200 mg.

that averaged 137 mL/hr.

Broad-spectrum antibiotics were continued for concern for bacterial superinfection for a total of 10 days despite negative cultures and were dose-adjusted for CRRT. A repeated RVP was negative for influenza on day 14, thus peramivir was discontinued after a total antiviral treatment duration of 14 days. Hemodynamic support with milrinone and dopamine was continued through hospital days 19 and 25, respectively. CRRT was stopped on day 8, but was restarted on days 11 through 14 for worsening fluid overload. Two days after stopping peramivir (day 16), the patient experienced a decreased neutrophil count from a baseline of approximately 5000 cells/mm³ to 1300 cells/mm³. The neutrophil count recovered the following day. Decreased neutrophil counts have been cited as an adverse drug reaction related to peramivir treatment, and based on an evaluation by Naranjo et al,²² this adverse drug reaction would be classified as probable.^{14,22} Ultimately, the patient's influenza infection resolved, she was subsequently extubated, had a return of normal renal function by hospital day 35, and was discharged at her baseline status.

Drug Dosage and Samples

Peramivir 200 mg in 50 mL of normal saline was infused once daily over 30 minutes (T = 0 hours, initiation of infusion). Serum samples were collected after the second 200-mg dose in a clot-activator containing silicone-coated red-top plastic tube, centrifuged, and frozen for storage. A peramivir serum peak concentration obtained at T + 0.7 hours was 12,600 ng/mL, followed by a midinterval concentration at T + 12.9 hours of 3300 ng/mL, and a T + 24.7 hours trough concentration of 1630 ng/mL (Figure). Concentrations for peramivir in serum were determined by liquid chromatography tandem mass spectrometry. The method was proven to be accurate and precise at linearity range of 1000 to 25,000 ng/mL with a correlation coefficient (r) of ≥ 0.99 . The method was rugged with 1000 ng/mL as the lower limit of quantitation. The interday assay variability was less than 10% across all reference samples between

Table. Published Pharmacokinetics of Peramivir in Continuous Renal Replacement Therapy

Parameter	Present Case	Bentley et al ¹⁶	Bazan et al ¹⁸	Bazan et al ¹⁸	Scheetz et al ¹⁹	Thomas et al ¹⁷	Thomas et al ¹⁷
Age (yr)/Sex	17/F	29/F	37/F	23/F	18/M	38/F	29/M
CRRT mode	CVVHDF	CVVHDF	CVVHDF	CVVHDF	CVVH	SLED	SLED
Daily dose (mg)	200	480	600	600	600	600	600
BFR (mL/min)	250	Unknown	150	200	200	200	200
DFR (mL/hr)	1000	1000	1000	1000	n/a	300	300
RFR (mL/hr)	1000	Unknown	1000	1000	n/a	n/a	n/a
UF (mL/hr)	150	850	981	1297	3500	n/a	n/a
$t_{1/2}$ (hr)	11.6	8.2	7.6	3.7	6.2	~5	~5
C_{peak} (ng/mL)	12,600	19,477	18,400	20,300	24,100	~27,000	~33,000
C_{min} (ng/mL)	1630	2750	2170	251	1920	~9000	~5000
CL (mL/min)	26	41	56	106	50	66	66
AUC (ng·hr/mL)	126,000	196,166	178,000	94,400	195,709	Unknown	Unknown

AUC, area under the curve; BFR, blood flow rate; CL, clearance; C_{min} , trough plasma concentration; C_{peak} , peak plasma concentration; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; DFR, dialysate flow rate; n/a, not applicable; RFR, replacement fluid rate; SLED, sustained low-efficiency dialysis; $t_{1/2}$, elimination half-life; UF, ultrafiltrate rate

1000 and 25,000 ng/mL. In the event samples were outside the upper limit of determination on the standard curve, a 1:2 or 1:10 dilution was made until the sample was within the standard curve.

Discussion

Current understanding of the pharmacokinetics of IV peramivir allows us to assess CRRT clearance, which can be used to estimate total body elimination. Based on the CVVHDF modality, this should closely parallel the sum of dialysate flow rate, ultrafiltrate rate, and residual renal function given the low protein binding and low molecular weight of peramivir. Given the severity of infection and the unknown pharmacokinetic implications combined with the patient's age and weight, the decision was made to use the dose recommended by the package insert for adult patients with a creatinine clearance of 30 to 49 mL/min for the CVVHDF dose adjustment.²¹

Scheetz et al¹⁹ reported the peramivir pharmacokinetics of an 18-year-old male who required continuous venovenous hemofiltration (CVVH). The authors' recommendations for maintenance dose calculations are based on desired concentration, ultrafiltration rate (plus residual renal function), sieving coefficient, and time between dose intervals. In practice, as plasma protein fraction unbound (F_u) approaches 1 (as is the case with peramivir) and the molecular weight of the drug is low (below 20,000 Da), a sieving coefficient (S_u) can be estimated to be 1.^{21,23} The authors were able to confirm this estimation in their measurements and calculations of the sieving coefficient of peramivir.

In CVVHDF, clearance can be calculated on the basis of ultrafiltration rate, dialysate flow rate, and residual

renal function. Understanding the pharmacokinetic profile of peramivir and our knowledge of CRRT clearance, the next important variable to consider becomes the pharmacodynamic target. Scheetz et al¹⁹ recommend targeting a steady-state concentration ($C_{average}$) of 17,078 ng/mL, which was averaged from peak (C_{peak}) and trough (C_{min}) concentrations in adult patients with normal renal function. Based on this recommendation, this patient would have required more than 800 mg given the CRRT settings. However, an *in vivo* murine study found that AUC is the covariate linked to mortality for influenza infections treated with peramivir and therefore $C_{average}$ may not be the optimal target for peramivir.¹² These different approaches demonstrate that the optimal pharmacokinetic target is not clearly elucidated for peramivir.

In the absence of pediatric data, it is a common practice in pediatric dosage studies to target adult parameters although there are significant changes in the absorption, metabolism, distribution, and elimination of medications as the child ages.^{24,25} In the present case, this dosage approach produced a serum peak of 12,600 ng/mL with estimated Vd of 15.9 L (0.32 L/kg), AUC₂₄ of 126,000 ng·hr/mL, clearance of 0.53 mL/min/kg, and a terminal half-life of 11.6 hours from the serum concentrations obtained. Compared to the package insert, this dosage scheme achieved a smaller serum peak concentration, larger Vd, similar AUC₂₄, and a shorter half-life, illustrating the significant differences in pharmacokinetics when administered in the setting of CVVHDF. However, in comparison with adult data in patients receiving CRRT, this patient experienced a similar pharmacokinetic profile when taking into account dose adjustments (Table). Ultimately, the strategy

used in this patient had a favorable outcome with RVP evidence of viral clearance by day 14 and discharge of the patient at her baseline status at the 35th day of hospitalization. It should be noted that the AUC_{24} was calculated by using 3 concentrations, which may decrease the accuracy of this value when compared to cases with more concentrations available. Additionally, the relative time of peak serum concentration obtained and the values used to determine half-life may also differ across the available reports and therefore these variations should be recognized.

Peramivir does not seem to possess any of the classic indications for therapeutic drug monitoring (i.e., narrow therapeutic index, high interpatient variability, high inpatient variability) in patients with normal organ function. However, in patients with critical illness requiring extracorporeal therapies, serum concentration monitoring may provide useful information regarding pharmacokinetic variations and pharmacodynamic target attainment.²⁶

Conclusion

There is a paucity of data in the application of pharmacokinetic alterations in pediatric patients receiving extracorporeal therapies. Based on presented pharmacokinetic calculations, this pediatric patient treated with dose-adjusted peramivir while receiving CRRT experienced pharmacokinetic alterations comparable to adult patients receiving renal replacement therapies and ultimately improved.

ARTICLE INFORMATION

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REFERENCES

- Smith BS, Yogaratnam D, Levasseur-Franklin KE, et al. Introduction to drug pharmacokinetics in the critically ill patient. *Chest*. 2012;141(5):1327-1336.

- Cies JJ, Moore WS II, Conley SB, et al. Pharmacokinetics of continuous infusion meropenem with concurrent extracorporeal life support and continuous renal replacement therapy: a case report. *J Pediatr Pharmacol Ther*. 2016;21(1):92-97.
- Uldemolins M, Martin-Loeches I, Llaurodo-Serra M, et al. Piperacillin population pharmacokinetics in critically ill patients with multiple organ dysfunction syndrome receiving continuous venovenous haemodiafiltration: effect of type of dialysis membrane on dosing requirements. *J Antimicrob Chemother*. 2016;71(6):1651-1659.
- Roger C, Wallis SC, Louart B, et al. Comparison of equal doses of continuous venovenous haemofiltration and haemodiafiltration on ciprofloxacin population pharmacokinetics in critically ill patients. *J Antimicrob Chemother*. 2016;71(6):1643-1650.
- Shekar K, Fraser JF, Smith MT, et al. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J Crit Care*. 2012;27(6):741.e9-e18.
- Pea F, Viale P, Pavan F, et al. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. *Clin Pharmacokinet*. 2007;46(12):997-1038.
- Bauer KA, West JE, O'Brien JM, et al. Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. *Antimicrob Agents Chemother*. 2013;57(7):2907-2912.
- Lee GC, Liou H, Yee R, et al. Outcomes of extended-infusion piperacillin-tazobactam: a retrospective analysis of critically ill patients. *Clin Ther*. 2012;34(12):2297-2300.
- Scaglione F, Esposito S, Leone S, et al. Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia. *Eur Respir J*. 2009;34(2):394-400.
- Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014;58(8):1072-1083.
- Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis*. 2007;44(3):357-363.
- Drusano GL, Preston SL, Smee D, et al. Pharmacodynamic evaluation of RWJ-270201, a novel neuraminidase inhibitor, in a lethal murine model of influenza predicts efficacy for once-daily dosing. *Antimicrob Agents Chemother*. 2001;45(7):2115-2118.
- Sidwell RW, Smee DF. Peramivir (BCX-1812, RWJ-270201): potential new therapy for influenza. *Expert Opin Investig Drugs*. 2002;11(6):859-869.
- Sugaya N, Kohno S, Ishibashi T, et al. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. *Antimicrob Agents Chemother*. 2012;56(1):369-377.
- FDA. Emergency use authorization of peramivir IV fact sheet for health care providers. <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187811.pdf>. Accessed December 19, 2016.
- Bentley ML, Hollister AS, Hansenb AC, et al. Peramivir pharmacokinetics in a patient receiving continuous venovenous hemodiafiltration during the 2009 H1N1 influenza A pandemic. *Int J Clin Pharmacol Ther*. 2014;52(12):1105-1111.

17. Thomas B, Hollister AS, Muczynski KA. Peramivir clearance in continuous renal replacement therapy. *Hemodial Int*. 2010;14(3):339-340.
18. Bazan JA, Bauer KA, Hollister AS, et al. Peramivir pharmacokinetics in two critically ill adults with 2009 H1N1 influenza A concurrently receiving continuous renal replacement therapy. *Pharmacotherapy*. 2010;30(10):1016-1020.
19. Scheetz MH, Griffith MM, Ghossein C, et al. Pharmacokinetic assessment of peramivir in a hospitalized adult undergoing continuous venovenous hemofiltration. *Ann Pharmacother*. 2011;45(12):e64.
20. Hernandez JE, Adiga R, Armstrong R, et al. Clinical experience in adults and children treated with intravenous peramivir for 2009 influenza A (H1N1) under an emergency IND program in the United States. *Clin Infect Dis*. 2011;52(6):695-706.
21. Bohler J, Donauer J, Keller F. Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. *Kidney Int Suppl*. 1999(72):S24-S28.
22. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.
23. Schetz M, Ferdinande P, Van den Berghe G, et al. Pharmacokinetics of continuous renal replacement therapy. *Intensive Care Med*. 1995;21(7):612-620.
24. Mulugeta Y, Barrett JS, Nelson R, et al. Exposure matching for extrapolation of efficacy in pediatric drug development. *J Clin Pharmacol*. 2016;56(11):1326-1334.
25. Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. *J Pediatr Pharmacol Ther*. 2014;19(4):262-276.
26. Winter ME. *Basic Clinical Pharmacokinetics*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.