PHARMACOTHERAPY

Peramivir for Influenza A and B Viral Infections: A Pharmacokinetic Case Series

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Objective To describe the peramivir (PRV) pharmacokinetics in critically ill children treated for influenza A or B viral infections.

Design Retrospective electronic medical record review of prospectively collected data from critically ill children receiving peramivir for influenza A or B viral infections in the pediatric intensive care unit (PICU).

Setting A 189-bed, freestanding children's tertiary care teaching hospital in Philadelphia, PA.

Patients Critically ill children admitted to the PICU who were infected with influenza between January 1, 2016 and March 31, 2018.

Interventions None.

Results Eleven patients, two females (18%) and nine males (82%), accounted for 24 peramivir samples for therapeutic drug management. The median age was 5 years (interquartile range 1.5–6.5 yrs) with a median weight of 16.4 kg (interquartile range 14–24 kg). Ten (91%) patients demonstrated a larger volume of distribution, 11 (100%) patients demonstrated an increase in clearance, and 11 (100%) patients demonstrated a shorter half-life estimate as compared with the package insert and previous pediatric trial data for peramivir. Eight (73%) patients tested positive for a strain of influenza A and 3 (27%) patients tested positive for influenza B; 4 of 11 (36%) patients tested positive for multiple viruses. All patients had adjustments made to their dosing interval to a more frequent interval. Ten (91%) patients were adjusted to an every-12-hour regimen and 1 (9%) patient was adjusted to an every-8-hour regimen. No adverse events were associated with peramivir treatment.

Conclusion The pharmacokinetics of PRV demonstrated in this PICU cohort differs in comparison to healthy pediatric and adult patients, and alterations to dosing regimens may be needed in PICU patients to achieve pharmacodynamic exposures. Additional investigations in the PICU population are needed to confirm these findings.

Key Words peramivir, pharmacokinetics, pharmacodynamic, pediatric, influenza.

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Introduction

Peramivir (PRV, Rapivab®, BioCryst Pharmaceutical, Inc, Durham, NC, U.S.A.) was the first intravenous neuraminidase (NA) inhibitor to obtain United States Food and Drug Administration approval and possesses antiviral activity against both influenza A and B viruses.[1] The optimal pharmacodynamic target for NA inhibitors has not yet been determined. Animal models suggest the area under the curve (AUC) has the closest association with improved mortality.[2] A single multicenter, open-label, uncontrolled study assessed the efficacy, safety, and pharmacokinetics of PRV in pediatric patients during the 2009 pandemic H1N1 influenza A epidemic.[3] The authors concluded that a standardized, weight-based dosing regimen in pediatric patients had similar efficacy and safety outcomes when compared with adult patients.[3, 4] However, this investigation appears to have excluded pediatric patients with a disease severity necessitating admission to the intensive care unit.[3]

Drug development programs commonly evaluate a drug's pharmacokinetic and pharmacodynamic properties in healthy adult and pediatric subjects.[5] Commonly anti-infective drugs are not widely evaluated in the population in which they are intended to be used. This is especially true in the setting of critical illness even though critical illness is a known risk factor for alterations to drug pharmacokinetics and pharmacodynamics in adult and pediatric patients.[6–15] As such, there is a lack of information regarding the pharmacokinetics and pharmacodynamics of PRV in a pediatric intensive care unit (PICU) population and the degree of these alterations in comparison to healthy volunteers. Therefore, the purpose of this investigation is to report a pharmacokinetic case series of PRV in PICU patients treated for an influenza A or B viral infection.

Materials and Methods

Patient Population and Study Design

At St. Christopher's Hospital for Children (Philadelphia, PA), critically ill patients who are prescribed anti-infectives normally receive therapeutic drug management (TDM), as has been described previously.[11, 12] Therefore, in an effort to attain pharmacokinetic and pharmacodynamic targets, dosing regimens are adjusted based on concentrations. An electronic medical record review was conducted of patients undergoing PRV TDM for clinical management between January 1, 2016, and March 31, 2018. Patients admitted to the PICU who received PRV for empiric or definitive therapy with an expected duration of $\geq$ 48 hours were eligible for inclusion. Patients who had cystic fibrosis, those with acute or chronic renal failure with an estimated creatinine clearance of $<$ 60 ml/min/1.73 m^2 using the modified Schwartz[16] equation, and those receiving extracorporeal therapies with continuous renal replacement therapy and extracorporeal membrane oxygenation were excluded from this analysis. The study was conducted in agreement with the Declaration of Helsinki, current amendment, the guideline for Good Clinical Practice, and approval of the Drexel University College of Medicine Institutional Review Board.

Demographic, clinical, and microbiological-viral data were collected. The BioFire® FilmArray® Multiplex polymerase chain reaction (PCR) respiratory panel (bioMérieux Clinical Diagnostics, Salt Lake City, UT) technique was utilized for influenza A and B detection.

Blood Sampling and Pharmacokinetic-Pharmacodynamic Analysis

Our methodology has been previously described[11, 12] but briefly, usually a minimum of two blood samples are collected per patient to facilitate determination of patient-specific pharmacokinetic parameters for subsequent dose alteration. Penetration ratios are also considered when designing dosing regimens for sites including epithelial lining fluid, for example, when available to achieve the target pharmacodynamic exposure, which primarily was an AUC of $\geq$ 100 μg/hr/ml for PRV while also attempting to maintain a trough level of approximately 10 μg/ml.[17] Peramivir samples were collected in regular red top tubes and subsequently centrifuged within 30 minutes of collection at 2000 *g* for $\geq$ 15 minutes to separate the plasma, which was then transferred to a cryovial and stored at −80°C. Samples were transported on dry ice to the reference laboratory and upon receipt, samples were thawed and analyzed. Peramivir concentrations were determined by validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) (U.S. Food and Drug Administration guidelines: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf) at Atlantic Diagnostic

Laboratories (Bensalem, PA). The LC-MS/MS method was accurate and precise at a linearity range of 1–60,000 ng/ml with a correlation coefficient (r) of ≥ 0.99 and an interday assay variability that was < 4% across all control samples.

Additionally, our pharmacokinetic analysis technique has been previously described[11, 12] for using a noncompartmental pharmacokinetic approach for each patient's concentrations to determine their respective pharmacokinetic parameters. To calculate PRV free drug concentrations, the protein binding estimate of 20% was utilized since the package insert (PI) states the protein binding estimate to be < 30%.[1] Patient's medical records were reviewed to assess for adverse events specifically related to PRV administration, with emphasis on the adverse events reported in the previous investigation of PRV in pediatric patients with an incidence of ≥ 2%.[3]

Results

A total of 11 patients, two females (18%) and nine males (82%), were included in this investigation and accounted for 24 PRV samples for TDM. All patients met inclusion criteria, and no patients received any form of extracorporeal therapy. No patients were excluded based on a creatinine clearance estimate of < 60 ml/min/1.73 m^2. A median of two samples for TDM was collected per patient (range 2–3 samples). The median age was 5 years (interquartile range (IQR) 1.5–6.5 years) with a median weight of 16.4 kg (IQR 14–24 kg). Patient demographics and PRV dosing information are presented in Table 1. The individual patient pharmacokinetic parameter estimates are presented in Table 2. Figure 1 displays the individual PRV concentration versus time profiles. The initial PRV doses ranged between 9.8 and 12.7 mg/kg/dose, and all patients were initiated on an every-24-hour dosing interval with doses infused over 30 minutes. Ten of 11 (91%) patients demonstrated a larger volume of distribution (V_d) as compared with the data from the PI and the previous pediatric PRV trial.[1, 3] Eleven (100%) patients demonstrated an increase in clearance (CL) and a shorter half-life estimate as compared with the PI and the previous pediatric PRV trial.[1, 3] All patients had adjustments made to their dosing regimens, specifically an adjustment to a more frequent dosing interval, to result in an AUC exposure closer to the AUC target described in the PI and the previous pediatric PRV trial and/or to not allow for a prolonged period with concentrations < 10 μg/ml.[1, 3] Ten (91%) patients were adjusted to an every-12-hour regimen and one (9%) patient was adjusted to an every-8-hour regimen. There were no adverse events associated with PRV treatment.

All patients tested positive for a virus via multiplex reverse transcriptase–polymerase chain reaction (RT-PCR) testing. Eight (73%) patients tested positive for a strain of influenza A and three (27%) patients tested positive for influenza B; four of 11 (36%) patients tested positive for multiple viruses. All patients had respiratory failure, with three (27%) patients requiring intubation. The median length of stay was 8 days (IQR 5.5–9 days), and there were no deaths in this cohort. The median duration of PRV treatment was 3 days (IQR 3–5.5 days). All patients were changed to oral oseltamivir to finish a 10-day total treatment course (10 days including PRV and oseltamivir).

Discussion

Currently, PRV has an FDA approved indication for the treatment of acute uncomplicated influenza in patients 2 years of age and older who have been symptomatic for no more than 2 days.[1] The current FDA recommended dose of PRV in pediatric patients 2–12 years of age with acute uncomplicated influenza is a single 12 mg/kg dose (up to a maximum dose of 600 mg), administered via intravenous infusion over 15–30 minutes.[18, 19] Additionally, during the 2009 influenza, PRV was part of an emergency use authorization in the United States for patients with pandemic A (H1N1) 2009 virus to be given every 24 hours for a period of 5 to 10 days.[20] The current FDA-approved pediatric dosing regimen is recommended based on pharmacokinetic data to approximate a total drug exposure or AUC similar to that achieved in adults that was associated with safety and efficacy.[3, 21] Table 3 displays the pharmacokinetic parameter estimates for pediatric patients based on data from the PI and the single pediatric study.[1, 3] The pharmacokinetic data presented in this study (Table 2) suggest that the pharmacokinetics of PRV differ considerably in PICU patients with confirmed influenza viral infections as compared with the pharmacokinetic estimates reported in the PI and a trial.[3] The pharmacokinetic data from these 11 PICU patients suggest that dosing modifications would be needed for PRV to better

Table 1. Patient Demographics and Peramivir Dosing Information for 11 Pediatric ICU Patients Treated for Influenza A and B Viral Infections

Patient	Gender	Age (yrs)	Weight (kg)	Dose (mg)	Dose (mg/kg)	Virus	Respiratory Support	PRISM III	LOS (days)	Alive	PRV duration (days)
1	F	6	25.6	250	9.8	Influenza A H1N1 2009 and Rhinovirus	CPAP/BiPAP/ Vapotherm	4	8	Y	5
2	M	0.83	9.76	120	12.3	Influenza A H1N1 2009 and B	Intubated	16	6	Y	3
3	M	1	11.6	130	11.2	Influenza A H1N1 2009	Intubated	2	8	Y	7
4	M	12	48	480	10.0	Influenza B	CPAP/BiPAP/ Vapotherm	0	9	Y	3
5	M	5	22.3	250	11.2	Influenza A H3	CPAP/BiPAP/ Vapotherm	6	5	Y	3
6	M	5	15.8	200	12.7	Influenza A H3 and Rhinovirus	CPAP/BiPAP/ Vapotherm	5	5	Y	3
7	M	2	16.4	200	12.2	Influenza B	CPAP/BiPAP/ Vapotherm	4	5	Y	3
8	F	7	18	180	10.0	Influenza A H3	Intubated	17	9	Y	6
9	M	0.75	12.2	140	11.5	Influenza B	CPAP/BiPAP/ Vapotherm	5	8	Y	3
10	M	4	19.5	235	12.1	Influenza A H3 and Coronavirus OC43	CPAP/BiPAP/ Vapotherm	10	16	Y	4
11	M	8	26.9	320	11.9	Influenza A H1N1 2009	CPAP/BiPAP/ Vapotherm	5	11	Y	8

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; LOS = length of stay; PRISM = pediatric risk of mortality score; PRV = peramivir.

Table 2. Individual Pharmacokinetic Parameter Estimates for Peramivir for 11 Pediatric ICU Patients Treated for Influenza A and B Viral Infections

Patient	k_e (1/hr)	Half-Life (hrs)	V_d (L/kg)	% Increase in V_d	CL (ml/min/kg)	% Increase in CL	Peak (μg/ml)	AUC_{24} (μg/hr/ml)
1	0.25	2.7	0.27	50	1.12	1020	36.6	145.6
2	0.29	2.3	0.64	255.6	3.09	2990	19.3	66.3
3	0.64	1	0.58	222.2	6.15	6050	19.4	30.4
4	0.32	2.1	0.39	116.7	2.06	1960	25.7	80.7
5	0.39	1.79	2.5	1288.9	16.09	15,990	14.3	11.6
6	0.44	1.5	0.7	288.9	5.1	5000	18.1	41.3
7	0.41	1.7	3.76	1988.9	25.44	25,340	3.24	7.99
8	0.58	1.2	0.57	216.7	5.44	5340	17.6	30.6
9	0.53	1.3	2.25	1150	19.75	19,650	5.1	9.65
10	0.56	1.2	0.31	72.2	2.94	2840	38.8	68.4
11	0.38	1.8	0.17	-	1.1	1000	69.8	181.6
Median	0.41	1.7	0.58	239	5.1	5000	19.3	41.3
IQR, 25	0.35	1.25	0.35	141.7	2.5	2400	15.95	21
IQR, 75	0.55	1.95	1.47	934.7	11.12	11,020	31.15	74.55

AUC_{24} = area under the curve; CL = clearance; IQR = interquartile range; k_e = elimination rate constant; kg = kilograms; L = liters; min = minutes; ml = milliliters; V_d = volume of distribution.

achieve drug exposures similar to those described earlier[3] and in the PI.[1, 3] The pharmacodynamic parameter suggested to affect morbidity and mortality is the AUC.[2] Since AUC is a marker of total drug exposure, there are several options for the clinician to increase total drug exposure. The two primary options are to either increase the dose (mg/kg or total mg dose) or adjust the dosing interval to allow for more frequent drug administration. Current recommendations state that upon dilution of PRV to a concentration suitable for administration it should be administered immediately or stored at 2°C to 8°C for up to 24 hours; unused diluted solution should be discarded after 24 hours.[1] Combining this pharmacokinetic data with the limited stability information, utilizing a more frequent dosing regimen (i.e., every 8 or every

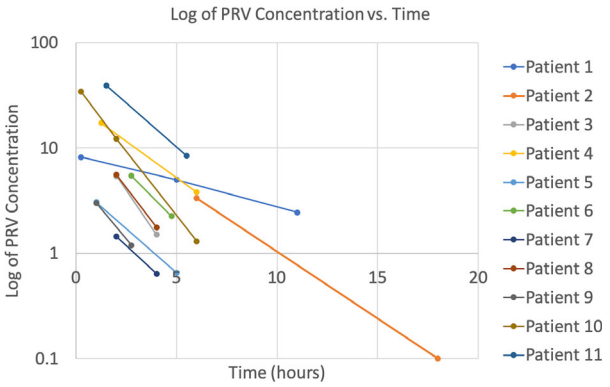

Figure 1. Graph of individual peramivir (PRV) concentrations for 11 pediatric ICU patients treated for suspected or confirmed influenza infections

12 hours) may allow for reduced PRV waste, which depicts our approach to dosing regimen modifications in our patient population.

These pharmacokinetic alterations are not unexpected as similar changes have previously been described in the PICU setting.[10–15, 22, 23] As TDM becomes more common to the practice of caring for critically ill children, recognition of pharmacokinetic variations similar to those described here will most likely become customary. The 1997 Society for Healthcare Epidemiology of America (SHEA) and The Infectious Diseases Society of America (IDSA) guidelines for the prevention of antimicrobial resistance in hospitals suggested "...appropriate antimicrobial stewardship, that includes optimal drug selection, dose, and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among microorganisms."[24] Often a "one dose fits all" mindset hinders clinicians in the treatment of infectious diseases; a paradigm that needs to end.[25] Reliance on an "approved dose" rather than achieving the target serum concentrations and exposures associated with safety and efficacy during the drug development and regulatory process is problematic. Underdosing and low exposures have been associated with anti-infective resistance and increased morbidity and mortality,[12] whereas active management of anti-infective concentrations and exposures has been associated with improved outcomes.[5, 12, 26–28] The concept of replacing "approved dose" with "approved concentrations and exposures" and tailoring dosing regimens to individual patients considering inter- and intra-patient variability across populations is profound.[25] With a growing body of literature demonstrating the benefit of anti-infective TDM, optimization of anti-infective pharmacokinetics and pharmacodynamics can dramatically change how infections are treated, allowing for customized and optimized anti-infective dosing, and allowing for a longer "life-span" of the currently approved antimicrobial agents and future anti-infective pipeline.

Table 3. Peramivir Pharmacokinetic Parameter Estimates for Pediatric Patients[a]

PK Parameter	PI[1]	Trial[3]
Half-life (hrs)	20	"Similar to PI"
Vd (L/kg)	0.18	"Similar to PI"
CL (ml/min/kg)	0.1	"Similar to PI"
Peak (μg/ml)	46.8	33.1
AUC (μg/hr/ml)	102.7	"Similar to PI"

"Similar to PI" = the authors of the trial[3] do not provide actual values yet explicitly state "similar to PI" in their manuscript.
AUC = area under the curve, CL = clearance; PI = package insert; PK = pharmacokinetic; V_d = volume of distribution.
[a]Package insert data, see Ref. [1]; Pediatric trial, see Ref. [3]

Similar to pharmacokinetic reports described previously,[11, 12] there are several limitations regarding this pharmacokinetic case series. First, this is a single center's experience utilizing PRV for suspected or confirmed influenza viral infections. Second, a single pharmacodynamic target was utilized and there is still debate regarding the optimal clinical pharmacodynamic target(s). Third, blood concentrations serve as a surrogate marker and do not necessarily reflect the PRV concentrations at other actual or potential sites of infection. However, blood samples are more readily available and analyzable and are likely to correlate with the concentrations at the site of infection. Fourth, drug concentration measurements were performed as total drug and not unbound drug concentrations with a static protein binding estimate. Fifth, we utilized an opportunistic sampling strategy which may not be ideal to fully characterize the pharmacokinetics of PRV in each individual child. Sixth, repeat PRV levels were not obtained to demonstrate whether the dosage adjustments resulted in expected observed concentrations based on the dosing calculation adjustments and whether concentrations might potentially be supra-therapeutic. However, individual parameter estimates are capable of providing a reasonable pharmacokinetic profile for individual patients and are commonly employed in clinical practice for aminoglycosides and vancomycin.

Conclusion

The pharmacokinetics of PRV demonstrated in this PICU cohort differs in comparison to

healthy pediatric and adult patients, and alterations to dosing regimens may be needed in PICU patients to achieve pharmacodynamic exposures. Additional investigations in the PICU population are needed to confirm these findings.

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