Outcomes and Adverse Effects With Peramivir for the Treatment of Influenza H1N1 in Critically Ill Pediatric Patients

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OBJECTIVES Influenza is an environmental pathogen and infection presents as a range from asymptomatic to fulminant illness. Though treatment is supportive, antiviral agents have a role in the management of infection. Pediatric use of peramivir is largely based on reports and extrapolations of pharmacokinetic data. We seek to describe efficacy and safety of peramivir in critically ill pediatric patients.

METHODS This is a retrospective, institutional review board–approved chart review of all patients under 21 years of age, admitted to the PICU, and treated with peramivir for influenza H1N1 infection between January 1, 2016, and March 31, 2016, at a single-center, 12-bed PICU. The primary outcome was time to sustained resolution of fever; secondary outcomes included dose, duration, and adverse effects of peramivir therapy.

RESULTS Seven patients were included with median age of 3.7 years. Median time to sustained resolution of fever was 49.3 hours, median duration of mechanical ventilation was 14.2 days, median ICU LOS was 18.7 days, and hospital LOS was 24.7 days. No patients suffered mortality. Three patients experienced leukopenia, one of which experienced a concurrent neutropenia. Three patients experienced hyperglycemia, 2 experienced hypertension, 1 experienced increased aspartate aminotransferase and increased alanine aminotransferase, and 1 experienced diarrhea. All adverse events assessed were classified as possible using published adverse event causality assessments.

CONCLUSIONS Peramivir has been shown to be an effective therapy for the treatment of influenza H1N1 in critically ill pediatric patients. In our experience with 7 pediatric patients, peramivir was well tolerated at typical durations of therapy; however, increased vigilance is warranted during prolonged courses or in patients with reasons for altered pharmacokinetics and pharmacodynamics.

ABBREVIATIONS ADR, adverse drug reaction; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; LOS, length of stay; MV, mechanical ventilation; NA, neuraminidase inhibitor; PICU, pediatric intensive care unit

KEYWORDS adverse drug events; critical care; influenza; pediatric; safety

J Pediatr Pharmacol Ther 2019;24(6):497–503

DOI: 10.5863/1551-6776-24.6.497

Introduction

Influenza is an environmental virus causing acute respiratory illness and is divided into type A, B, and C, with influenza A and B viruses causing seasonal epidemics, and influenza C viruses generally causing mild disease. Influenza A viruses are further classified into subtypes on the basis of the antigenic properties of their 2 surface glycoproteins, hemagglutinin and neuraminidase.¹ The pandemic 2009 H1N1 influenza A virus (H1N1pdm09) cocirculated with H3N2 and influenza B viruses during the 2015–2016 influenza season, and more than half of the infections reported to the CDC nationally were caused by H1N1.²

The presentation of seasonal influenza ranges from an asymptomatic infection to a fulminant illness, depending on the characteristics of both the host and

virus.^{3,4} Although most healthy patients experience illnesses that are self-limited and uncomplicated, some patients experience courses that are more severe and result in significant morbidity and mortality. In particular, there is an increased risk of hospital admission in children younger than 2 years of age and in those with severe, chronic underlying disease. Symptoms are characterized by systemic features, including fever, chills, headache, myalgia, malaise, and anorexia, accompanied by respiratory symptoms, including non-productive cough, nasal discharge, and pharyngitis.^{3,4} Children have higher maximum temperatures compared with adults and can present with an undifferentiated fever or febrile seizures. They can also present with laryngotracheobronchitis or bronchiolitis, gastrointestinal symptoms, severe myalgia in the calf muscles, and complications of myositis. Patients may present with

Table 1. Patient Demographics (n = 7)

Characteristics	Result
Age, yr, median (IQR)	3.7 (2.4–9.8)
Male, n (%)	5 (71.4)
Past medical history, n (%)	
No past medical history	3 (42.9)
Seizure disorder	2 (28.6)
Hereditary sensory and autonomic neuropathy	1 (14.3)
Dextrocardia, lung aplasia, tracheal stenosis	1 (14.3)
Normal renal function (creatinine clearance > 90 mL/min/1.73 m ²) at time of antiviral administration, n (%) [*]	7 (100)
Suspected or confirmed concomitant bacterial pneumonia, n (%)	6 (85.7)
Requirement of non-invasive positive pressure ventilation, n (%)	7 (100)
Requirement of mechanical ventilation, n (%)	5 (71.4)

IQR, interquartile range

^{*} Calculated via modified Schwartz equation.

or develop a secondary bacterial pneumonia with *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and group A β -hemolytic streptococci as well, worsening acuity or contributing to mobility and mortality.^{3,4}

Although annual vaccination is the mainstay for influenza prevention and control and treatment is largely supportive, the use of antiviral agents must be considered for prophylaxis and treatment against influenza.¹ Currently available antiviral drugs include neuraminidase inhibitors (NAIs) and adamantanes.⁵ In December 2014, intravenous peramivir was approved by the US FDA for the treatment of acute, uncomplicated influenza in adults who have been symptomatic for up to 48 hours.⁶ NAIs such as oseltamivir, peramivir, and zanamivir have been shown to decrease the severity and duration of illness in a pediatric population.^{7,8}

Intravenous peramivir is FDA-approved for the treatment of influenza in patients 2 years and older and is used frequently in patients who are unable to tolerate oral therapy or have concerns for malabsorption of enterally administered medications. Current recommendations for pediatric dosing are based on clinical reports and with extrapolations of pharmacokinetic and pharmacodynamics data from the adult population.^{7–11} We aim to describe our experience with the use of peramivir for the treatment of influenza H1N1 in critically ill pediatric patients.

Materials and Methods

This was an institutional review board–approved, retrospective chart review of all patients younger than 21 years of age, admitted to the PICU, and treated with intravenous peramivir for influenza H1N1 infection confirmed by respiratory viral panel polymerase chain reaction assay between January 1, 2016, and March

31, 2016, at a large, urban, tertiary care children's hospital within an adult hospital. Patients were identified using pharmacy department medication dispensing records, and all patient information was collected from the electronic medical record. Admission to the PICU, antiviral agent selection, dose, and duration were at the discretion of the treating provider and were based on available data at the time. Peramivir was administered daily as a diluted intravenous infusion over 60 minutes. All other care, including but not limited to use of antipyretics and other supportive measures, were provided as standards of usual care.

The primary outcome was time to sustained resolution of fever, defined as time from initiating peramivir to defervescence (less than 38°C) for 24 hours; fever was considered a temperature reading over 38°C. Secondary outcomes included a description of dose, duration, and adverse effects of peramivir therapy. Adverse effects were assessed if included in package insert or standard medication references, and consisted of dermatologic reactions, hypertension, hyperglycemia, diarrhea, constipation, leukopenia, neutropenia, transaminitis, anaphylaxis, elevations in serum creatinine phosphokinase, behavioral abnormalities, hallucinations, and insomnia.^{10,11} Dermatologic reactions, hypertension, diarrhea, constipation, anaphylaxis, behavioral abnormalities, hallucinations, and insomnia were detected by reviewing daily progress notes and event notes in the electronic medical record. Hyperglycemia (blood glucose > 200 mg/dL), leukopenia (WBC count < 4000 cells/mcL), neutropenia (absolute neutrophil count [ANC] < 1000 cells/mcL), transaminitis (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 3× upper normal limit), and elevations in serum creatine phosphokinase ($\geq 6\times$ upper normal limit) were detected by reviewing all laboratory values during

Figure. Time to sustained resolution of fever.

treatment. Adverse events were assessed for causality using 3 published objective adverse drug reaction (ADR) detection instruments: Kramer modified ADR scoring system, Naranjo ADR probability scale, and the Jones algorithm.^{12–14} An event was considered an adverse drug event if 2 of the 3 tools' results agreed on possible, probable, or definite.^{15–17} A sensitivity analysis was conducted for the detection of an ADR by just 1 tool as well as detection and agreement by all 3 tools. The use of 3 ADR detection tools has been reported as a more rigorous approach to accurately detect ADRs and was applied in an attempt to overcome limitations of retrospective review.^{18,19} Duration of mechanical ventilation (MV), duration of hospital and ICU LOS, and mortality were reported, as well as discharge disposition. All statistics reported were descriptive in nature.

Results

Seven patients were included in this case series with baseline demographics described in Table 1. Median age was 3.7 years with majority of patients being male. Three patients were healthy at baseline; 2 had a past medical history of seizure disorder; 1 with hereditary sensory and autonomic neuropathy; and 1 with dextrocardia, lung aplasia, and tracheal stenosis. All patients had normal baseline renal function at time of antiviral administration. Five patients were treated for a suspected bacterial pneumonia, and 1 patient was treated for a confirmed concomitant polymicrobial bacterial pneumonia. All patients received positive pressure ventilation, and 5 patients required invasive MV.

The median time to sustained resolution of fever was

Table 2. Clinical Outcomes (n = 7)

Variables	Results
Peramivir dose, mg/kg, median (IQR)	11.4 (10.4–11.8)
Antiviral therapy duration, days, median (IQR)	11.0 (9.1–13.4)
Conversion to oral oseltamivir, n (%)	1 (14.3)
Duration of mechanical ventilation, days, median (IQR)*	14.2 (4.3–15.5)
ICU LOS, days, median (IQR)	18.7 (8.1–46.3)
Hospital LOS, days, median (IQR)	24.7 (12.8–50.3)
Mortality	0 (0)
Discharge disposition, n (%)	
Home with parents	3 (42.9)
Inpatient rehabilitation	2 (28.6)
Home with home care	1 (14.3)
Outside hospital transfer	1 (14.3)

IQR, interquartile range

* n = 5.

Table 3. Adverse Effects With Peramivir Therapy (n = 7)

Parameter	Result
Leukopenia, n (%)	3 (42.9)
Associated neutropenia, n (%)	1 (14.3)
Hyperglycemia, n (%)	3 (42.9)
Hypertension, n (%)	2 (28.6)
Increased AST, n (%)	1 (14.3)
Increased ALT, n (%)	1 (14.3)
Diarrhea, n (%)	1 (14.3)
Constipation, n (%)	0 (0)
Dermatology, n (%) (erythema multiforme, general exfoliative dermatitis, rash, Stevens-Johnson syndrome)	0 (0)
Elevated Creatine Phosphokinase, n (%)	0 (0)
Anaphylaxis, n (%)	0 (0)
Neurology, n (%) (abnormal behavior, hallucinations, insomnia)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase

49.3 hours with an interquartile range of 46.4 to 54.4 hours in the 6 patients who were febrile during their illness (Figure). One patient remained afebrile throughout the hospital course.

Patients received a median peramivir dose of 11.4 mg/kg daily for a median duration of 11 days (Table 2). One patient was converted to oral oseltamivir on day 2 of antiviral therapy during transfer from ICU to general medicine floor, receiving an additional 5 days of therapy. Of patients requiring invasive MV, the median duration of MV was 14.2 days. Median ICU LOS was 18.7 days and hospital LOS was 24.7 days; no patients suffered mortality as a result of their influenza H1N1 infection. Three patients were discharged home with parents, 2 patients required inpatient rehabilitation, 1 was discharged home with chronic home care, and 1 patient was transferred to an outside hospital.

Adverse effects can be seen in Tables 3 and 4. Twelve adverse events across 5 patients were detected in this analysis, all of which scored as “possible” for causality by peramivir as scored by the ADR detection instruments; 2 patients did not experience an adverse effect associated with peramivir. Three patients experienced leukopenia, one of which experienced a concurrent neutropenia. Leukopenia was experienced on days 3 and 4 of peramivir in 2 patients. One patient experienced leukopenia with concurrent neutropenia 2 days after discontinuation of a 12-day course of peramivir. Three patients experienced hyperglycemia, 2 experienced hypertension, 1 experienced increased AST and increased ALT, and 1 experienced diarrhea. All adverse effects noted were self-limiting with no

documentation of direct treatment of any ADRs. These adverse effects were not responsible for the discontinuation of therapy in any of the included patients. In the sensitivity analysis, 12 adverse events were detected as “possible” in the causality assessment to peramivir by a single ADR tool. Eleven adverse events were identified with a “possible” causality assigned when using combined 3 ADR tools.

Discussion

In this assessment, we evaluated the efficacy via surrogate markers for resolution of illness and rates of adverse events during intravenous peramivir therapy for the treatment of influenza H1N1 in critically ill pediatric patients compared with rates published in prior literature. In this heterogeneous population of both previously healthy children and those with prior complex medical disorders, we saw that all patients required respiratory support and many presented with concomitant infections and experienced a median time to sustained fever resolution of 2 days after peramivir was initiated. Patients remained in intensive care for 2.5 weeks and were hospitalized for 25 days, with most patients being discharged to home with varying levels of support. Over the median duration of therapy of 11 days, 71% of the patients experience an adverse effect that was possibly attributed to peramivir. Most commonly, leukopenia and hyperglycemia were experienced and resolved after completion of therapy.

The median time to resolution of fever in this cohort was 49.3 hours, which is consistent with other pediatric studies reporting time to defervescence of 24 to 72 hours.^{20–22} The relatively long ICU and hospital lengths of stay may suggest a baseline increased index of acuity, possibly explaining the slightly prolonged febrile period. The median duration of therapy in these patients was 11 days, longer than commonly described in other trials or indicated by the FDA.^{7,8,11,22,23} This may also be attributable to this population’s acuity and the slightly prolonged time to defervescence, justifying prolonged durations of therapy.

Komeda et al²² describe the adverse effects seen with peramivir when used in a pediatric population in a review of over 1200 patients in Japan from 2010 to 2012. The authors noted an ADR incidence of 7.67%, with diarrhea and abnormal behavior amongst the most common events. Serious ADRs were observed in 1% of patients, most commonly involving abnormal behavior and decreased neutrophil count; leukopenia was observed in 0.33% of the included patients. The vast majority of these events occurred within the first 3 days of therapy and resolved upon discontinuation. The authors found a much smaller incidence of leukopenia and neutropenia in their population compared with this study’s cohort, with a notable difference between groups being the duration of peramivir therapy. All patients in the Komeda et al²² study received no more

Table 4. Adverse Effects With Peramivir Therapy by Patient

Patients	Tool	Hypertension*	Hyperglycemia (Glucose > 200 mg/dL)	Leukopenia (WBC < 4000 cells/mcL)	Neutropenia (ANC < 1000 cells/ mcL)	Increased AST (>3 Times ULN)	Increased ALT (> 3 Times ULN)	Diarrhea*
2	Final Score	Possible	Possible	Possible		Possible	Possible	
	Kramer	Possible	Possible	Possible		Possible	Possible	
	Naranjo	Possible	Possible	Possible		Possible	Possible	
	Jones	Possible	Possible	Possible		Possible	Possible	
4	Final Score		Possible					Possible
	Kramer		Possible					Unlikely
	Naranjo		Possible					Possible
	Jones		Possible					Possible
5	Final Score	Possible						
	Kramer	Possible						
	Naranjo	Possible						
	Jones	Possible						
6	Final Score		Possible	Possible				
	Kramer		Unlikely	Possible				
	Naranjo		Possible	Possible				
	Jones		Possible	Possible				
7	Final Score			Possible	Possible			
	Kramer			Possible	Possible			
	Naranjo			Possible	Possible			
	Jones			Possible	Possible			

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase

* Noted in progress notes.

than 3 days of therapy, with 96.7% of patients receiving only a single dose. The prolonged therapy provided in the present study's patients could possibly explain the increased rate of adverse events experienced, most notably with leukopenia. Although 2 patients experienced leukopenia shortly after initiating treatment, the third patient experienced leukopenia with an associated neutropenia 2 days after discontinuing a 12-day course of peramivir during a period of otherwise normal recovery from critical illness, suggestive of a delayed reaction possibly related to the prolonged duration of therapy. Due to the difference in pharmacokinetics and pharmacodynamics of medications in critical illness, it is possible that serum and tissue concentrations exceed predicted values, thus increasing the risk of adverse effects as well though not assessed in this evaluation.^{24,25} Other adverse effects noted in this case series are consistent with known adverse effects and are mild in nature and rapidly resolve upon discontinuation of therapy.^{8,20–22,26,27}

Given the time to sustained resolution of fever was similar to prior studies and the possibility of increased adverse effects related to prolonged duration of therapy, it may be advisable to limit duration of therapy to the minimum effective duration. Future evaluations should

evaluate the role of prolonged therapy on both efficacy and adverse effects of peramivir and the relationship between pharmacokinetics and pharmacodynamics and adverse effects.

Limitations of this case series include the retrospective nature, the inclusion of a single center, and a small sample size. It may also be difficult to determine causality of adverse events retrospectively, and the tools included in these assessments have limitations in clinical practice. Nonetheless, 3 independent and validated scoring systems were used to strengthen the assessments made in this analysis, which is a suggested method reported in safety and adverse effect analyses.^{18,19,28} The use of 3 tools does not mitigate the possibility that they could erroneously agree on the evaluation of an ADR, but this more rigorous approach was applied to increase the robustness of these assessments. Assessment of other agents' causing or contributing to these adverse events was not conducted as the assessment tools account for the presence of other possible contributing factors. This study did not address other indicators of resolution of illness, which may diminish association of treatment and resolution of illness. The effect of a concurrent infection on resolution of illness was also not assessed. Antipyretic use

was not specifically assessed in this study, though use is considered standard of care. Dosing of peramivir was based on available evidence at the time of treatment, notably before the expansion of FDA approval to patients 2 years old and older, thus application of these results to current practice should consider this difference.

Peramivir has been shown to be an effective therapy in critically ill pediatric patients with influenza H1N1 based on previous studies. In our experience, peramivir was well tolerated at typical durations of therapy with self-limited possible ADEs; however, increased vigilance is warranted during prolonged courses or in patients with reasons for altered pharmacokinetics and pharmacodynamics.

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Disclosure 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. Dr. Witcher had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgment This work was presented in abstract form at the Annual Congress of the Society of Critical Care Medicine in Honolulu, Hawaii in January 2017.

Accepted March 29, 2019

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