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An Update on Oseltamivir Use in Infants and Children

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During the 2009 H1N1 pandemic, 274,000 patients were hospitalized and 12,470 deaths occurred in the United States alone.¹ There was a disproportionately higher incidence of severe disease in children, especially among those with an underlying illness. The use of neuraminidase inhibitors, oseltamivir and zanamivir, became wide-spread for both prophylaxis and treatment during the pandemic, after the virus was found to be resistant to amantadine and rimantadine.

Oseltamivir was approved by the Food and Drug Administration (FDA) in 1999 for the prophylaxis or treatment of uncomplicated acute illness resulting from influenza infection in adults and children 13 years of age and older. On December 14, 2000, approval for the treatment of influenza was extended to children 1 year of age and older; on December 21, 2005, oseltamivir was approved for prophylaxis in this age group. On April 26, 2009, the FDA issued a temporary emergency use authorization for oseltamivir in infants which remained in effect until June 23, 2010.^{2,3} As a result of the experience gained during the pandemic, several papers describing the pharmacokinetics, efficacy, and safety of oseltamivir in infants and children have recently been published.

Pharmacokinetics

Oseltamivir, the ethyl ester prodrug of the active moiety oseltamivir carboxylate, is well absorbed from the gastrointestinal tract following oral administration. It is rapidly converted by hepatic esterases to the active carboxylate metabolite. Administration with food produces no significant change in absorption. Oseltamivir carboxylate is widely distributed throughout the body, with minimal protein binding (3%). It is eliminated in the urine, with a half-life of 6-10 hours in adults.³

The pharmacokinetic profile of oral oseltamivir was assessed by the manufacturer in a single-dose study of 18 children (5-16 years of age) and in five children (3-12 years of age) taking part in a clinical trial, as well as a subsequent study in 24 children 1-5 years of age.^{4,5} While the

pharmacokinetic characteristics of oseltamivir in children over 12 years of age were similar to those of adults, younger children were found to have lower maximum oseltamivir carboxylate concentrations and total exposure. The authors concluded that these differences are due to a more rapid clearance, but others have suggested the results may represent a combination of reduced bioavailability, larger volume of distribution, and faster renal clearance.²

Oseltamivir carboxylate concentrations have also been evaluated after nasogastric administration in infants and children. During the 2009 H1N1 pandemic, Giraud and colleagues treated 11 patients with oseltamivir in their pediatric intensive care unit.⁶ The patients, ranging in age from 1 month to 16 years, were treated with a mean oseltamivir dose of 3.7 ± 1.5 mg/kg twice daily for 1 to 7 days. Mean concentrations were 27 ± 52 ng/mL (range 0.2-215 ng/mL) for oseltamivir and 678 ± 852 ng/mL (range 79-1,871 ng/mL) for oseltamivir carboxylate. Although the mean oseltamivir concentration was lower than concentrations reported in adults receiving the recommended dose (mean 65 ng/mL), oseltamivir carboxylate concentrations were higher than that reported in adults (mean 348 ng/mL).² The oseltamivir carboxylate concentrations also significantly exceeded the reported 50% inhibitory concentration (IC₅₀) for influenza A isolates, signifying no detrimental effects from administration via nasogastric tube.⁶

Similar results have also been reported in three children receiving oseltamivir during extracorporeal membrane oxygenation (ECMO), although there was considerable interpatient variability.⁷ The patients, 6, 14, and 15 years of age, received oseltamivir doses between 1.5 and 6.8 mg/kg twice daily via nasogastric or gastric tube. Plasma samples were obtained 24 hours after the start of ECMO. Maximum oseltamivir concentrations ranged from 3.4 to 92.4 ng/mL, with maximum oseltamivir carboxylate concentrations ranging from 77.2 to 736 ng/mL. The authors concluded that their results reflect variations due to impaired renal function in one

patient producing elevated plasma concentrations and gastric bleeding in another resulting in reduced absorption and lower concentrations.

Antiviral Activity and Resistance

Oseltamivir selectively inhibits neuraminidases, surface enzymes found on influenza A and B, interfering with the release of progeny viruses. While the efficacy of oseltamivir in reducing viral load has been well documented, the development of influenza A resistance limits its benefit. Resistance may result from amino acid substitutions in viral neuraminidase or hemagglutinin proteins. Oseltamivir resistance appears to occur more frequently in children than in adults, possibly the result of repeated courses for prophylaxis. In pediatric clinical trials, rates of resistance have ranged from 3% to 37%.³ Several recent case reports also demonstrate a tendency for rapid development of resistance in immunocompromised children.^{8,9} The presence of viral mutations, however, does not always predict treatment failure.^{8,10}

The effect of viral resistance on oseltamivir response in children was studied by Rath and colleagues at the Charité University and Worms City Hospitals in Berlin during the 2010-2011 influenza season.¹⁰ Of the 36 patients evaluated (27 with influenza A and 9 with influenza B), 32 (89%) responded to oseltamivir with a significant decrease in viral load. In the 21 patients with follow-up samples, all had an undetectable viral load at the completion of therapy. The authors noted that three of the four non-responders had severe diarrhea or vomiting that may have led to reduced oseltamivir absorption. Of the 27 children with influenza A, seven (26%) developed resistance. Time to achieve an undetectable viral load was significantly longer in the patients with oseltamivir-resistant influenza A than in those with drug-sensitive influenza A or influenza B (median 15.4 days compared to 7.7 or 5 days, respectively, $p = 0.003$). Based on their findings, the authors recommend serial assessments of viral load to optimize the duration of therapy in children.

Recent Experience in Infants and Children

While the clinical significance of the 1 to 2 day reduction in symptoms and shorter period of viral shedding produced by oseltamivir in otherwise healthy children continues to be debated, use during the 2009 pandemic brought to light the benefit of treatment in pediatric patients at risk for severe disease. Launes and colleagues described 127 children (median age 4 years) hospitalized during the pandemic at the Hospital

Universitari Sant Joan de Déu in Barcelona.¹¹ Twenty-four children required intensive care, primarily for acute respiratory failure. Oseltamivir was given to 110 children for 5 days, except for seven immunocompromised patients who were treated until polymerase-chain-reaction testing was negative (7-15 days). Logistic regression identified a delay in oseltamivir more than 72 hours after the onset of symptoms and the presence of a chronic illness as variables associated with ICU admission (OR, 95% CI 3.7, 1.1-11.7 and 4.1, 1.1-15, respectively, $p < 0.05$).

The potential for a significant benefit from oseltamivir in critically ill children has also been suggested in a recent retrospective study. In their 2011 paper, Coffin and colleagues evaluated 1,257 children (median age 1.7 years) admitted to a PICU in one of 41 children's hospitals throughout the United States from 2001 to 2007.¹² A total of 264 children received oseltamivir within 24 hours of admission. Multivariate analysis of 252 of the treated patients and a cohort of matched controls revealed an 18% reduction in total length of hospitalization ($p=0.02$). Length of PICU stay, mortality, and readmission rates did not differ.

The 2009 pandemic also resulted in the need for treatment of infants.¹³⁻¹⁷ Acosta and colleagues reported their experience with oseltamivir in 32 neonatal intensive care unit patients inadvertently exposed to the H1N1 virus by a health care provider.¹³ Following the exposure, 29 neonates were given prophylaxis with a dose of 1.5 mg/kg twice daily for 10 days. None of the patients developed influenza. The average oseltamivir carboxylate concentration in the 17 patients with evaluable data was 728 ng/mL. The higher concentrations seen in the premature neonates in this study, compared to those in older children and adults, led the authors to conclude that a lower dose of oseltamivir (1 mg/kg twice daily) is more appropriate for the neonatal population.

Standing and colleagues studied oseltamivir kinetics and outcomes in nine infants during the 2009 pandemic.¹⁴ Utilizing four plasma samples per patient and population pharmacokinetic modeling, they concluded that a dose of 1 mg/kg twice daily in premature neonates and 2 mg/kg twice daily in term infants (≥ 37 weeks postmenstrual age) would provide oseltamivir carboxylate concentrations similar to those in adults and more than 200-fold the IC_{50} for H1N1. These doses were also found to be effective in a retrospective survey of 44 Japanese infants and in two additional case series.¹⁵⁻¹⁷

Contraindications and Precautions

Oseltamivir should not be administered to patients with a history of hypersensitivity to any component of the product. Although rare, severe hypersensitivity and serious dermatologic reactions, including toxic epidermal necrolysis and Stevens Johnson syndrome, have been reported after oseltamivir use. Delirium and the onset of abnormal behavior following initiation of oseltamivir have been reported in children and adults. Reported symptoms include agitation, anxiety, altered levels of consciousness, confusion, delusions, hallucination, nightmares, and self-injurious behavior. There has not been a definitive determination of causation, in part because of the potential for influenza to produce the same symptoms.³

Adverse Effects

Adverse effect data for oseltamivir was compiled by the manufacturer from 1,032 pediatric patients (1-12 years of age) enrolled in clinical trials. A total of 515 children received oseltamivir in these trials while 517 served as controls.³ Oseltamivir was generally well-tolerated, with only eight children (2%) discontinuing treatment. The most frequently reported adverse effects were vomiting (in 15% of treated patients and 9% of controls), diarrhea (in 10% and 11%, respectively), abdominal pain (in 5% and 4%), and nausea or epistaxis (in 3% and 3-4%). Dermatitis and lymphadenopathy were reported in 1% of the treated patients and 2% of controls. Other events, including worsening of asthma symptoms and the development of other infections such as otitis media, were reported in 1-9% of treated patients and 1-11% of controls.

Pediatric oseltamivir adverse effect data is also available from a recent observational study of 191 children (median age 3 years) receiving treatment for presumed or confirmed H1N1 infection during the first three months of 2010.¹⁸ Sixty-nine children (36%) developed at least one adverse effect. As in the clinical studies, the most frequently reported reactions were vomiting (16%), diarrhea (12%), and neuropsychiatric symptoms (13%). Other common adverse effects were ear disorders (9%) and insomnia (7%). Seventy-seven percent of the adverse effects were classified as mild, with 23% considered moderate. The incidence of adverse effects did not differ by age group.

Adverse effect data in infants has included diarrhea, dehydration, mild rash, and conjunctivitis.¹⁵⁻¹⁷ Transient elevations in serum transaminases were reported in two papers. One

case of necrotizing enterocolitis occurring 3 days after completion of oseltamivir has been reported, but a causal relationship could not be established or disproven. No cases of neurotoxicity have been reported.

Drug Interactions

Use of oseltamivir is not recommended for patients who have received live attenuated influenza vaccine (LAIV) within the previous 2 weeks due to the potential for a reduction in vaccine efficacy. LAIV should not be administered until 48 hours after the last oseltamivir dose. Trivalent inactivated influenza vaccine can be given at any time during oseltamivir use. No other clinically significant pharmacokinetic drug interactions have been reported with oseltamivir.³

Availability and Dosing Recommendations

Oseltamivir is available in 30 mg, 45 mg, and 75 mg capsules, as well as a 6 mg/mL tutti-frutti flavored oral suspension (60 mL bottle). This new 6 mg/mL suspension replaces the earlier 12 mg/mL product. The change in concentration was made in 2011 to reduce frothing when the suspension was shaken.³

The recommended oseltamivir dose for treatment of influenza in adults and adolescents 13 years of age and older is 75 mg given twice daily for 5 days.³ Children should receive the appropriate weight-based dose (Table 1) twice daily for 5 days. Although the FDA has not approved its use in infants, oseltamivir has been given at doses of 1 mg/kg twice daily in premature neonates and 1.5-2 mg/kg twice daily in older infants with severe disease.

Table 1. Weight-based Oseltamivir Dosing³

<u>Weight</u>	<u>Dose</u>	<u>Volume of Suspension</u>
≤ 15 kg	30 mg	5 mL
16-23 kg	45 mg	7.5 mL
24-40 kg	60 mg	10 mL
≥ 41 kg	75 mg	12.5 mL

Treatment may be continued beyond 5 days. Guidelines from the World Health Organization published at the time of the 2009 pandemic suggest that in cases where the clinical course is severe or progressive, treatment may be continued until the infection is resolved or there is satisfactory clinical improvement.¹⁹

For prophylaxis, oseltamivir should be administered as 75 mg once daily for at least 10 days in adults and adolescents. Children should receive a weight-based dose as described in

Table 1 once daily for 10 days. Prophylaxis should be initiated within 48 hours of exposure. It has been continued for up to 6 weeks in healthy children during a community outbreak and up to 12 weeks in immunocompromised patients without an increase in adverse effects. Oseltamivir may be taken with food to decrease nausea. Oseltamivir oral suspension contains sorbitol (11 grams per 60 mL bottle). Patients with fructose intolerance may experience diarrhea when taking this formulation.³

The treatment dose of oseltamivir should be reduced to 75 mg once daily for 5 days in patients with severe renal dysfunction (creatinine clearance 10-30 mL/min). Prophylaxis dosing should be reduced to 75 mg every other day or 30 mg once daily. Although no specific dosage adjustment recommendations are available for pediatric patients, a similar reduction to once daily dosing would be prudent. Oseltamivir should not be used in patients with severe renal dysfunction (creatinine clearance < 10 mL/min). Dosage adjustment is not necessary in patients with hepatic dysfunction.³

Summary

Recent papers resulting from the 2009 H1N1 pandemic have provided clinicians with useful new data on oseltamivir. While its clinical benefit and economic value in uncomplicated influenza remain controversial, there is now more substantial data on the efficacy and safety of oseltamivir in children and infants, including premature neonates, requiring hospitalization.

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Formulary Update

The Pharmacy and Therapeutics Committee did not meet in August.

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