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Oseltamivir: A New Option for the Management of Influenza in Children

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It is estimated that influenza causes 18-20 million cases of respiratory illness each year in the United States. The majority of these infections, approximately 13 to 16 million, occur in children and adolescents.[1] Infants and children with underlying respiratory and cardiovascular disease are at greatest risk from complications related to influenza infection.[2,3] Until recently, there were few therapies to offer patients with influenza. Amantadine and rimantidine were effective only against influenza A and frequently caused adverse effects. In 1999, the Food and Drug Administration (FDA) approved the use of zanamivir and oseltamivir, two drugs in a new therapeutic class called neuraminidase inhibitors, for influenza infection. In their first two seasons of use, these agents have had a substantial impact on the management of influenza in adults.

Oseltamivir was initially approved by the FDA for the prevention and treatment of influenza in adults and children greater than 13 years of age. In December 2000, oseltamivir gained additional FDA approval for treatment of influenza in children greater than 1 year of age.[4,5] Zanamivir is currently under investigation in children.[6] This issue of *Pediatric Pharmacotherapy* will review the efficacy of oseltamivir in adults and children, describe its pharmacokinetics and adverse effects, and provide pediatric dosing recommendations.

Mechanism of Action

Oseltamivir phosphate is an oral prodrug which undergoes hydrolysis by hepatic esterases to form active oseltamivir carboxylate, also referred to as GS4071. Oseltamivir carboxylate acts by selective inhibition of influenza A and B viral neuraminidase. A lipophilic side chain of the active drug binds to the virus enzyme, blocking its ability to cleave sialic acid residues on the surface of the infected cell and resulting in an inability to release progeny virions.[4,5,7,8]

Clinical Trials

Prophylaxis

Oseltamivir has been shown to be effective in the prevention of influenza infection in adolescents and adults if taken within 48 hours of exposure. As part of a combined prophylaxis/treatment trial published in the October 6, 1999 issue of *JAMA*, Hayden and colleagues evaluated the safety and efficacy of oseltamivir in adults (ages 18-40 years).[9] The prophylaxis arm involved 33 volunteers who were given 100 mg oseltamivir orally, either once or twice daily, or placebo for 5 days. Subjects began therapy 26 hours prior to being innoculated with influenza virus. Eight (67%) of the 12 subjects given placebo became infected after being exposed to the influenza virus, compared with eight (38%) of the 21 given oseltamivir. A third of the placebo recipients developed clinical symptoms of influenza; none of the oseltamivir-treated subjects became ill. Fifty percent of the subjects in the placebo group shed virus, while none of the group given oseltamivir had documented viral shedding.

A larger trial was published later that month in the *New England Journal of Medicine*. Hayden et al (as the Oseltamivir Study Group) enrolled 1,559 adults in a study of oseltamivir prophylaxis.[10] Subjects received oseltamivir 75 mg, either once or twice daily, or placebo for 6 weeks during peak influenza season. The primary end point of the study was laboratory- confirmed influenza illness (based on the presence of a fever, respiratory and systemic symptoms). The rate of influenza illness was significantly reduced in the oseltamivir group

(5.3% versus 10.6% for placebo). The protective efficacy of oseltamivir was found to be 74% overall. Neither the results of this study, nor the one described earlier, showed a significant difference between once and twice daily dosing. In both of these trials, the authors concluded that oseltamivir was safe and effective for the prevention of influenza infection in adults.

Treatment

In the treatment arm of the initial *JAMA* paper, Hayden and colleagues reported the results of oseltamivir versus placebo in 69 adult subjects innoculated with influenza virus in a controlled setting.[9] The authors reported that oseltamivir significantly reduced the viral titer area under the curve compared to placebo. Oseltamivir-treated subjects also had a reduction in the duration of viral shedding (58 hours for the combined treatment groups versus 107 hours for placebo). In addition, symptom scores and nasal proinflammatory cytokine levels were lower in the subjects receiving oseltamivir.

In the February 23, 2000 issue of *JAMA*, many of these same investigators, as the United States Oral Neuraminidase Study Group, published the results of a randomized, placebo-controlled, double-blind treatment study conducted in 60 healthcare centers.[11] A total of 629 adults were enrolled within 36 hours of onset of influenza-like symptoms. Subjects were given oseltamivir, 75 or 150 mg twice daily, or placebo. Three hundred and seventy-four patients became infected and were evaluated for response. Oseltamivir reduced the duration of illness by more than 30% compared to placebo in infected patients. Severity of illness scores were reduced by 38%. Oseltamivir use also significantly reduced the duration of fever (average 71.5 hours for the 75 mg group and 69.9 hours for the 150 mg group, versus 103.3 hours for the placebo group) and allowed subjects to return to usual activities 2-3 days sooner than placebo.

Three months later, Nicholson and colleagues reported the results of a multinational trial of oseltamivir for the treatment of influenza in *The Lancet*.[12] Seven hundred and twenty-six patients were enrolled throughout Europe, Canada, and China. As in the previous study, subjects were randomized to receive either 75 mg or 150 mg oseltamivir or placebo twice daily for 5 days. Duration of illness was significantly shorter in both treatment groups compared to placebo. The median duration was 87.4 hours for the 75 mg dose, 81.8 hours for the 150 mg dose, and 116.5 hours for placebo, similar to the results seen in the paper from the Oral Neuraminidase Study Group. Oseltamivir use was associated with improved symptom scores, less viral shedding, and subjective improvements in health, activity levels, and sleep quality.

While these studies have established the utility of oseltamivir in adults, data on its use in children have only recently become available. In a double-blind, placebo-controlled trial enrolling children between 1 and 12 years of age, oseltamivir, when started within 48 hours of symptoms, significantly reduced the length of illness. On average, resolution of symptoms occurred 1.5 days sooner in the oseltamivir-treated children than in the placebo group. The oseltamivir dose used in this study, 2 mg/kg given twice daily, became the foundation for the dosage recommendations now provided by the manufacturer.[5]

Pharmacokinetics

Oseltamivir phosphate is readily absorbed from the gastrointestinal tract, with approximately 80% bioavailability. The prodrug is extensively converted to active oseltamivir carboxylate by hepatic esterases; less than 5% of a dose is eliminated unchanged. Administration with food does not appear to affect overall absorption, but may slightly delay time to maximum serum concentration of the active compound.[4,5,7]

Oseltamivir is well distributed to the nasal mucosa, the tracheal lining, and the tissues of the middle ear. In adults, the volume of distribution for oseltamivir carboxylate has ranged from 23 to 27 L. There are currently no data available in children. Neither the prodrug or the active form are highly protein bound.

Oseltamivir carboxylate is eliminated by glomerular filtration and renal tubular excretion without further metabolism. The average half-life of elimination in adults is 6-10 hours. It is recommended that the dosing frequency be reduced from twice to once daily for treatment and from once daily to every other day for prophylaxis in patients with moderate renal dysfunction (creatinine clearance 10-30 ml/min). Dosing has not been established in patients with renal failure.[4,5,7]

Adverse Reactions

In clinical trials, oseltamivir has been generally well tolerated by both adults and children. Information on adverse effects in children has been gathered from the results of Phase III trials of oseltamivir involving 1,032 patients between 1 and 12 years of age. In the 515 children receiving oseltamivir in these trials, the most frequently reported adverse effects were vomiting (15.0%), diarrhea (9.5%), and abdominal pain (4.7%). These percentages were not significantly different in the children receiving placebo. They were also similar to values reported in adults receiving oseltamivir during earlier clinical trials.[7]

Otitis media was diagnosed in 8.7% of patients during oseltamivir treatment, and symptoms of asthma were reported in 3.5%; in both cases, similar responses occurred with placebo. Other adverse effects reported in 1-3% of pediatric trial participants included (in order of frequency): nausea, epistaxis, pneumonia, sinusitis, bronchitis, conjunctivitis, dermatitis, lymphadenopathy, and unspecified ear disorders. All of these occurred in higher or equivalent percentages of children given placebo.[7,8]

There is currently no information on oseltamivir overdosage in children. In adults, single doses of up to 1,000 mg produced only nausea and vomiting, without clinically significant changes in vital signs, electrocardiogram readings, or other routine laboratory tests.[5]

Dosing Recommendations

In adults and adolescents over 13 years of age, the recommended dose of oseltamivir for the treatment of influenza is 75 mg twice daily for 5 days. In younger children, dosing should be based on patient weight, according to the chart below:

Oseltamivir Dosing in Children

Body weight	Dose[a]
≤15 kg	30 mg
16-23 kg	45 mg
24-40 kg	60 mg
> 40 kg	75 mg

[a] given twice daily for 5 days

As mentioned previously, it is recommended that dosing frequency be reduced in adult patients with moderate renal dysfunction. No studies in pediatric patients with renal dysfunction have been published.[5]

For influenza prophylaxis in adults and children over 13 years of age, a dose of 75 mg taken once daily for at least 7 days is recommended. The duration of protection lasts as long as therapy is continued.[5] Patients and/or parents should be reminded that oseltamivir is not a substitute for the influenza vaccine.

Product Availability and Cost

Oseltamivir (Tamiflu®; Roche Pharmaceuticals) is available as 75 mg capsules and a powder for oral suspension. When reconstituted, the suspension contains 12 mg oseltamivir per ml and is tutti-frutti flavored. The suspension may be stored at room temperature or refrigerated, but it should not be frozen. An oral dosing dispenser is provided with the bottle for accurate dose measurement. Oseltamivir capsules come in blister packs of 10, for one treatment course.[5]

As anticipated for a new therapy, oseltamivir is considerably more expensive than other therapies for influenza. Average wholesale prices (AWP) for a standard adult treatment course are $3.51 for amantadine, $17.50 for rimantidine, and $53.00 for oseltamavir.[8]

Summary

Oseltamivir, one of the new neuraminidase inhibitors, appears to be a safe and effective

therapy for the prevention and treatment of influenza. The primary disadvantages to its use are the need to initiate treatment within 2 days of the onset of symptoms and cost. The recent FDA approval of this agent for use in children and the availability of an oral liquid dosage formulation will likely result in a significant change in the management of influenza in the pediatric population.

References

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Pharmacology Literature Review

Compliance Tools for Adolescents

In this study from Denver's Children's Hospital, two measures to improve compliance for adolescents with HIV were evaluated. Twenty-five patients, ages 9-21 years, who were taking at least three medications were enrolled. The program used both pagers and electronic dose-monitoring bottle caps. Patients were sent "reminder" pages by a contracted service prior to each dose. The bottle caps contained microchips which recorded the timing of any opening. At the end of the 3 month observation period, average percent change in viral load was -63.3%. Average change in CD4 percent was 2.5% and average change in T4 count was 126.6. Based on their results, the authors are currently expanding this program to a larger patient population. Todd TJ, Miller S. Increasing adherence to antiretroviral therapy in adolescent patients with HIV via novel compliance tools. **J Pediatr Pharm Pract 2000;5:229-34.**

Enoxaparin in a Preterm Infant

While the pharmacokinetics of enoxaparin have been established in older children and adults, little is known of its disposition in infants. The authors present a 29-week gestational age baby with radial artery thrombosis. The patient was treated with enoxaparin 1 mg/kg every 8 hours for 7 days, and experienced a return of blood flow. Serum anti-X_a concentrations on the third day of treatment were 0.78 units/ml 4 hours post-dose and 0.39 units/ml 8 hours post-dose. Pharmacokinetic analysis revealed an elimination half-life of 4 hours, similar to values reported in adults, and a volume of distribution of 0.13 L/kg, larger than that seen in adults. Dunaway KK, Gal P, Ransom JL. Use of

enoxaparin in a preterm infant. **Ann Pharmacother 2000;34:1410-3.**

Gentamicin Dosing in Neonates

The authors of this multicenter observational study compared the results of traditional weight and age-based gentamicin dosing to dosing by pharmacokinetic parameters. A total of 309 neonates from 3 hospitals were evaluated. Initial peak serum concentrations were greater than 6 mcg/ml in 40% of the traditionally-dosed patients versus 93% of the patients dosed by pharmacokinetics. However, 67% of the pharmacokinetic group had peaks greater than 8 mcg/ml. Average trough concentrations did not differ between methods, but the traditionally-dosed group had a higher number of troughs greater than 2 mcg/ml. The authors suggest that pharmacokinetic-based gentamicin dosing may be more efficacious in neonates. Glover ML, Shaffer CL, Rubino CM, et al. A multicenter evaluation of gentamicin therapy in the neonatal intensive care unit. **Pharmacotherapy 2001;21:7-10.**

Unintentional Metformin Ingestions

Metformin, an oral antihyperglycemic drug, has become one of the most frequently prescribed agents for type 2 diabetes mellitus. This paper reviews 55 cases of accidental ingestion of metformin by children reported to the American Association of Poison Control Centers. The average age of the children involved was 4.2±4.4 years, and the average dose ingested was 1,710±500 mg, with a range of 250 mg to 16.5 grams. Thirty-seven of the children were seen by a healthcare provider; 29 received gastric decontamination. Clinical symptoms were limited to nausea, diarrhea, and dizziness. None of the patients experienced significant hypoglycemia. The authors concluded from these cases that metformin ingestions less than 1,700 mg were unlikely to result in significant adverse events, but monitoring of blood glucose and serum electrolytes is still recommended. Spiller HA, Weber JA, Winter ML, et al. Multicenter case series of pediatric metformin ingestion. **Ann Pharmacother 2000;34:1385-8.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/26/01:

1. Rapacuronium (Raplon®; Organon) use has been extended to the Emergency Department. Rapacuronium was previous restricted to the OR, VASC, and intensive care units.
2. Doxacurium (Nuromax®; GlaxoWellcome) was removed from the Formulary.

If you have any comments or suggestions for future issues, please contact us at Box 800674, UVA Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.