Use of oseltamivir in children

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ABSTRACT

QUESTION Because of the recent outbreak of pandemic H1N1 2009, I am anticipating a large number of children with influenza-like symptoms or children diagnosed with influenza. Is oseltamivir effective and safe when used for children?

ANSWER Oseltamivir is effective for prevention of complications associated with influenza A (including H1N1) in children. Oseltamivir also reduces the duration of influenza by a median of 36 hours, with nausea and vomiting as the primary reported adverse effects. The World Health Organization recommends oseltamivir as first-line treatment for H1N1, with the use of zanamivir only for suspected or confirmed oseltamivir resistance. Recently, in preparation for the influenza A (H1N1) 2009 pandemic, Health Canada published an interim order permitting the expanded use of oseltamivir for treatment or prophylaxis for children younger than 1 year of age.

RÉSUMÉ

QUESTION En raison de la récente éclosion de la grippe pandémique H1N1 en 2009, je m'attends à voir un grand nombre d'enfants présentant des symptômes grippaux ou ayant eu un diagnostic de grippe. L'oseltamivir est-il efficace et sûr chez les enfants?

RÉPONSE L'oseltamivir est efficace pour la prévention des complications associées à la grippe A (y compris H1N1) chez les enfants. L'oseltamivir réduit aussi la durée de la grippe d'environ 36 heures en moyenne et ses principaux effets secondaires signalés sont la nausée et les vomissements. L'Organisation mondiale de la Santé recommande l'oseltamivir comme traitement de première intention pour le H1N1, et l'utilisation du zanamivir seulement dans les cas soupçonnés ou confirmés de résistance à l'oseltamivir. Récemment, en prévision de la pandémie de grippe A (H1N1) en 2009, Santé Canada a publié une ordonnance provisoire permettant une utilisation plus élargie de l'oseltamivir pour le traitement ou la prévention chez les enfants de moins de 1 ans.

Influenza virus is highly contagious, affecting people of all ages and all socioeconomic backgrounds, and has a particularly profound effect on children. Community studies indicate that school-aged children have had the highest rates of influenza infection, with annual rates as high as 42% in prospective surveillance studies.[1] Furthermore, children who do contract influenza are particularly susceptible to nonrespiratory complications. The most common of these complications is acute otitis media, which annually affects 3% to 5% of children. There has also been a report of a substantial increase (ie, 10% to 30%) in the number of antimicrobial courses prescribed to children during the influenza season, and influenza infection is sometimes associated with development of pneumococcal and staphylococcal pneumonia in children.[1]

There have been reports of febrile convulsions, sinusitis, myositis, myocarditis, pericarditis, and encephalopathy. Approximately 1% of all infected children require hospitalization as a result of these primary and secondary sequelae of influenza.[2]

Seasonal influenza, which arises each year, is due to small adaptive mutations (termed *antigenic drift*) that occur as a result of immunologic pressures on strains of influenza already circulating within the human population.[3] In the spring of 2009, an entirely new strain of influenza A (H1N1) arose owing to a chance recombination of swine, avian, and human influenza.[4] As a result of the genetic uniqueness of the 2009 H1N1 virus (ie, 27% and 18% change in the amino acid sequences of hemagglutinin and neuraminidase, respectively), there is a complete lack of herd immunity, allowing this strain to spread quickly and efficiently across the globe.[4] The emergence of any novel influenza strain, H1N1 included, poses the risk of pandemic levels of infection.

Mechanism of oseltamivir

Oseltamivir selectively inhibits neuraminidase enzymes, which are glycoproteins found on the surface of influenza A and B.[5] As neuraminidase is responsible for cleaving sialic and neuraminic acid, it is one of the key factors responsible for the influenza virion's entrance and exit from the host cell.[4] Inhibiting neuraminidase

enzymes effectively halts the influenza virion's ability to spread to new human cells.

Pharmacologic management of influenza

Two drug classes are used to treat influenza: M2 inhibitors (eg, amantadine, rimantadine) and neuraminidase inhibitors (eg, oseltamivir, zanamivir). Because H1N1 isolates show universal resistance to M2 inhibitors, neuraminidase inhibitors are the treatment of choice.[6]

Treatment is recommended for children who present with clinical or radiologic signs of pneumonia, or who present with severe dehydration, renal or multiorgan failure, rhabdomyolysis, myocarditis, septic shock, or central nervous system findings, such as encephalopathy. Complications of influenza are mostly seen among children younger than 2 years of age. Children with exacerbations of underlying chronic diseases requiring hospitalization should also be treated.[7]

On September 22, 2009, the Centers for Disease Control and Prevention (CDC) released updated guidelines on the treatment of novel influenza A (H1N1).[8] **Table 1**[8,9] lists treatment dosing guidelines for both oseltamivir and zanamivir for individuals older than 1 year of age. While oseltamivir has been approved by the US Food and Drug Administration for children older than 1 year of age, zanamivir is only approved for use in children older than 5 years of age (older than 7 years of age in Canada).

Infants

Owing to a lack of data on the safety and effectiveness of oseltamivir in patients younger than 1 year of age, oseltamivir is currently not recommended for use in these patients. When novel influenza A (H1N1) started to spread throughout the world earlier this year, the CDC requested an Emergency Use Authorization for oseltamivir in infants younger than 1 year of age, in anticipation that this population would need prophylaxis and treatment.[10] In preparation for pandemic influenza A (H1N1) 2009, Health Canada released an interim order permitting the expanded use of oseltamivir for treatment or prophylaxis of children younger than 1 year of age.[11] It appears Health Canada's approval is based on a short letter to the Editor of the *Pediatric Infectious Diseases Journal* from Japanese medical researchers.[12] Health Canada reports the following: "After a careful assessment, antivirals may be prescribed with clinical discretion providing the potential benefits to the health of the infant outweigh the risks. The parents or guardian should be informed that this is exceptional use. This may apply to suspect cases where [a] rapid test [result] is positive, febrile children without another clear cause and a positive contact history, and febrile infants with respiratory compromise." **Table 2**[11] presents the recommended doses for treatment.

Table 2. Oseltamivir dosing recommendations for treatment of infants younger than 1 year of age when weight measures* are unavailable

AGE, MO	DOSE
0 to < 3	12 mg twice daily for 5 days
3 to < 6	20 mg twice daily for 5 days
6 to < 12	25 mg twice daily for 5 days

*A weight-based calculation for dosing is 2 mg/kg twice daily for 5 days.[11]
Data from Public Health Agency of Canada.[11]

Some experts prefer weight-based dosing for infants. Data are limited however, about which method of dosing is most effective. The CDC website offers information on preparation of an oral oseltamivir suspension for children who are not able to swallow capsules.[13] Physicians might find that children are better able to swallow capsules with liquid drawn from a straw.

Table 1. Antiviral medication dosing recommendations for treatment and chemoprophylaxis of novel influenza A (H1N1) infection: *Age 1 year and older.*

AGENT	GROUP	TREATMENT (5 DAYS)	CHEMOPROPHYLAXIS (10 DAYS)
Oseltamivir	Adults	75-mg capsule twice daily*	75-mg capsule once daily
	Children, weight, kg		
	• ≤ 15 kg	60 mg per day, divided twice daily	30 mg once daily
	• 16-23 kg	90 mg per day, divided twice daily	45 mg once daily
	• 24-40 kg	120 mg per day, divided twice daily	60 mg once daily
	• > 40 kg	150 mg per day, divided twice daily	75 mg once daily
Zanamivir	Adults	Two 5-mg inhalations (10-mg total) twice daily	Two 5-mg inhalations (10-mg total) once daily
	Children	For children ≥ 7 y, two 5-mg inhalations (10-mg total) twice daily	For children ≥ 5 y, two 5-mg inhalations (10-mg total) once daily

*Can consider treating with a 150-mg dose twice daily and for longer durations, depending on clinical response.[9]
Data from Centers for Disease Control and Prevention.[8]

Effectiveness

Previously healthy children between the ages of 1 and 12 years with laboratory-confirmed influenza show a 36-hour (26%) reduction in the median duration of illness when treated with oseltamivir.[9] In children, oseltamivir treatment has also been shown to result in a 53% reduction in the adjusted risk of pneumonia; a 39% reduction in the adjusted risk of otitis media; and a 28% reduction in the adjusted risk of respiratory illness.[14] In a retrospective analysis, the Cochrane Collaboration also reported that the protective efficacy of oseltamivir was 80% in pediatric patients who were influenza-negative before beginning prophylaxis.[9]

Safety

Oseltamivir has been shown to cause vomiting in approximately 15% of children.[9] Other adverse effects included abdominal pain, epistaxis, ear disorders, and conjunctivitis. Children with severe renal failure (≤ 10 mL/min creatinine clearance) should not be given oseltamivir. At present, there are no known drug-drug interactions or adverse events from reported cases of overdose (single doses up to 1000 mg have been reported).[9]

Several reports from Japan provide some evidence for neuropsychiatric adverse effects, resulting in Japanese authorities strongly urging physicians not to prescribe oseltamivir to adolescents.[15] However, similar findings were not reported in later studies.[15]

In an industry-sponsored review, no plausible genetic explanations for neuropsychiatric adverse events were found.[16] One retrospective study reported no increase in the incidence of insurance claims for neuropsychiatric events in patients receiving oseltamivir compared with those with no antiviral prescribed.[17] It is possible that the neuropsychiatric events reported were actually a result of viral illness.

Oseltamivir resistance

The oseltamivir monograph published in the *Compendium of Pharmaceuticals and Specialties* reports that 5.4% of influenza cases in children between the ages of 1 and 12 years are resistant to oseltamivir.[18] Of the more than 10000 novel influenza A (H1N1) isolates identified thus far, 21 have been found to be resistant to oseltamivir while none is resistant to zanamivir.[19] Most of these resistant strains (76%) were identified in individuals receiving post-exposure prophylaxis or in patients with immunosuppression who were taking long-term oseltamivir treatment for H1N1.[13,19,20] As most H1N1 strains are still sensitive to oseltamivir, the World Health Organization recommends oseltamivir as first-line treatment for H1N1, with the use of zanamivir only in situations of suspected or confirmed oseltamivir resistance.[7]

Competing interests
None declared

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References

1. Committee on Infectious Diseases. Policy statement—recommendations for the prevention and treatment of influenza in children, 2009-2010. *Pediatrics* 2009;124(4):1216-26. Epub 2009 Sep 7.
2. Sugaya N, Nerome K, Ishida M, Nerome R, Nagae M, Takeuchi Y, et al. Impact of influenza virus infection as a cause of pediatric hospitalization. *J Infect Dis* 1992;165(2):373-5.
3. Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2004;(3):CD001269.
4. Gallaher WR. Towards a sane and rational approach to management of Influenza H1N1 2009. *Virol J* 2009;6:51.
5. Ismail I. Influenza A resistance to oseltamivir. *Thorax* 2009;64(9):828.
6. Centers for Disease Control and Prevention. Update: drug susceptibility of swine-origin influenza A (H1N1) viruses, April 2009. *MMRW Morb Mortal Wkly Rep* 2009;58(16):433-5.
7. World Health Organization. *WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses*. Geneva, Switz: World Health Organziation; 2009. Available from: **www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html**. Accessed 2009 Nov 12.
8. Centers for Disease Control and Prevention. *Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season*. Atlanta, GA: Centres for Disease Control and Prevention; 2009. Available from: **www.cdc.gov/h1n1flu/recommendations.htm**. Accessed 2009 Oct 1.
9. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev* 2007;(1):CD002744.
10. US Food and Drug Administration [website]. *Emergency Use Authorization (EUA) review: oseltamivir phosphate for swine influenza A*. Silver Spring, MD; US Food and Drug Administration; 2009. Available from: **www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM153547.pdf**. Accessed 2009 Nov 12.
11. Public Health Agency of Canada [website]. *Interim guidance for emergency use of oseltamivir (Tamiflu®) in children under one year of age in the context of 2009 (H1N1) pandemic*. Ottawa, ON: Public Health Agency of Canada; 2009. Available from: **www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-07-20-eng.php**. Accessed 2009 Oct 27.
12. Okamoto S, Kamiya I, Kishida K, Shimakawa T, Fukui T, Morimoto T. Experience with oseltamivir for infants younger than 1 year old in Japan. *Pediatr Infect Dis J* 2005;24(6):575-6.
13. Centers for Disease Control and Prevention. *Emergency use authorization of Tamiflu®: fact sheet for health care providers*. Atlanta, GA: Centres for Disease Control and Prevention; 2009. Available from: **www.cdc.gov/h1n1flu/eua/pdf/tamiflu-hcp.pdf**. Accessed 2009 Oct 1.
14. Peters PH, Moscona A, Schulman KL, Barr CE. Study of the impact of oseltamivir on the risk for pneumonia and other outcomes of influenza, 2000-2005. *Medscape J Med* 2008;10(6):131.
15. Maxwell SR. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007;334(7606):1232-3.
16. Toovey S, Rayner C, Prinssen E, Chu T, Donner B, Thakrar B, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Saf* 2008;31(12):1097-114. DOI: 10.2165/0002018-200831120-00006.
17. Smith JR, Sacks S. Incidence of neuropsychiatric adverse events in influenza patients treated with oseltamivir or no antiviral treatment. *Int J Clin Pract* 2009;63(4):596-605.
18. Roche. Tamiflu® [Product Monograph]. In: Repchinsky C, editor-in-chief. *Compendium of pharmaceuticals and specialties 2009*. Ottawa, ON: Canadian Pharmacists Association; 2009. p. 2236-8.
19. World Health Organization. *Pandemic (H1N1) 2009—update 65*. Geneva, Switz: World Health Organization; 2009. Available from: **www.who.int/csr/don/2009_09_11/en/print**.html. Accessed 2009 Oct 1.
20. Centers for Disease Control and Prevention. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis—North Carolina, 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(35):969-72.

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