Influenza and Oseltamivir Phosphate (Tamiflu®) in Infants:
What You Need to Know

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Influenza is a highly contagious virus that causes an average of 20,000 hospitalizations a year in children under five years of age. As of March 30, 2013, the 2012-2013 flu season had seen 111 pediatric deaths, with 21 deaths in the 0- to 23-month-old range. Rates of influenza-associated hospitalization are substantially higher among infants and young children than among older children, and those under six months old are at the highest risk. Research shows that influenza vaccine is not as effective in children two years of age relative to adults, and the vaccine is not approved in infants younger than six months. Thus, preventing influenza and proper treatment are important for keeping this high-risk group safe from complications. With infants being highest at risk for complications and the extrapolation of efficacy and safety from the older population, the U.S. Food and Drug Administration (FDA) recently approved the use of the antiviral oseltamivir phosphate (Tamiflu®) for treatment of uncomplicated influenza in patients two weeks and older. This young population is susceptible to the benefits as well as the risks of the drug. Health care providers must be aware of dosing, adverse reactions, and monitoring parameters to better treat and educate their patients.

Pathophysiology

Symptoms of influenza include fever, cough, sore throat, runny/stuffy nose, muscle/body aches, headaches, fatigue, and sometimes vomiting and diarrhea in children (CDC, 2011). The influenza virus infects humans by attaching its virions to the epithelial cells of the respiratory system and entering the cell by endocytosis (McCance & Huether, 2010). The virions enter by expressing two surface proteins, hemagglutinin (HA) and neuraminidase (NA) (McCance & Huether, 2010). HA is a glycoprotein necessary for the entrance of the virus into the cell, and NA is an enzyme that is necessary for the release of new virions from cells infected by the virus. When one receives the influenza vaccine, the body produces antibodies to respond to HA and NA antigens. A yearly flu vaccine is required because of the ability of the HA and/or NA to mutate (McCance & Huether, 2010). In the 2011-2012 flu season, influenza A (subtype H1N1), influenza A (subtype...
setting, clinic visits for influenza were estimated to be 50 to 95 per 1,000 children, and the rate of visits to emergency departments was estimated to be six to 27 per 1,000 children (Fiore et al., 2009). For children, the risk for severe complications from seasonal influenza is highest among those younger than two years of age (Fiore et al., 2011). Although influenza-associated deaths are uncommon among children, an estimated annual average of 92 influenza-related deaths (0.4 deaths per 100,000 persons) occurred among children younger than five years of age during the 1990s (Fiore et al., 2009). As of March 23, 2013, the 2012-2013 flu season had seen 110 pediatric deaths, with 20 deaths in the 0 to 23 months old range (CDC, 2013f).

**Diagnostic Testing**

Rapid influenza diagnostic tests (RIDTs) are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens, and display results as positive or negative in a short time frame (usually in 15 minutes) (CDC, 2012b). However, RIDTs have limited sensitivity to detect influenza virus infection, and negative test results should be interpreted with caution given the potential for false-negative results (CDC, 2012b). RIDTs should be used to confirm diagnosis rather than rule it out. Antiviral treatment should always be determined through a combination of clinical suspicion, knowledge of circulating influenza strains in the area, severity of risk, and the results of the RIDT (CDC, 2012b).

**Oseltamivir Phosphate (Tamiflu®)**

Oseltamivir phosphate is the prodrug converted by the liver to oseltamivir carboxylate, the active neuraminidase inhibitor (Roche Laboratories Inc., 2008). It works by preventing the viral neuraminidase required for infection and viral reproduction (Yaffe & Aranda, 2011). This inhibition also prevents viral spread to respiratory secretions, thereby reducing respiratory infections (Taketomo, Hoddng, & Kraus, 2012). It is eliminated via the kidneys, and dosage adjustment is required for patients with a serum creatinine clearance of 10 to 30 mL/min (Genentech, Inc., 2012).

**Indications**

Oseltamivir phosphate is approved for treatment of influenza A and B in infants two weeks of age and older for those with symptoms for no more than two days (FDA, 2012). It is the only antiviral approved for the treatment of influenza in this young population (FDA, 2012). For the population over one year of age, oseltamivir phosphate can be used prophylactically for those at high risk, including those in close contact with individuals with known or suspected influenza infection (FDA, 2012). A double-blind placebo-controlled treatment trial showed that when oseltamivir phosphate is given within 48 hours of symptoms of influenza, children one to 12 years of age are free from disease symptoms one and a half days sooner than those not treated (Roche Laboratories Inc., 2008).

According to the CDC (2013c), oseltamivir phosphate is not meant to replace the use of the influenza vaccine, which is the best way to protect against the flu. Oseltamivir phosphate should not be administered to patients two weeks prior or 48 hours after vaccination with live attenuated influenza vaccine (Genentech, Inc., 2012). Oseltamivir phosphate has not been shown to affect the use of the trivalent inactivated influenza vaccine (Genentech, Inc., 2012). There are no other clinically significant drug interactions with oseltamivir phosphate (Genentech, Inc., 2012).

**Approval**

In December 2012, the FDA expanded the use of oseltamivir phosphate to include infants under two weeks old (FDA/Center for Drug Evaluation and Research [CDER], 2012). Previously, the drug was only approved for use in children one year of age and older. In an application from the manufacturer of oseltamivir phosphate (Hoffman-LaRoche, Inc./Genentech) to the FDA, a proposal was made to approve its use (FDA/CDER, 2012). The document stated that previous testing in rats showing toxic levels of the drug in the neonatal brain tissue was proven to be erroneous, and subsequent animal studies done by the National Institutes of Health (NIH) showed no such effects (FDA/CDER, 2012). Further, a retrospective study was conducted by the National Institute of Allergy and Infectious Diseases (NIAID) and NIH to review charts of infants who were...
Table 1.
Treatment (twice daily dosing for 5 days) and Prophylaxis (once daily dosing for 10 days) Dosing of Oral TAMIFLU for Influenza in Pediatric Patients

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Treatment Dosing for 5 days</th>
<th>Prophylaxis Dosing for 10 days</th>
<th>Volume of Oral Suspension (6 mg/mL) for each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Weight</td>
<td>3 mg/kg twice daily</td>
<td>Not applicable*</td>
<td>0.5 mL/kg†</td>
</tr>
<tr>
<td>Patients 2 to Less Than 1 Year of Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 kg or less</td>
<td>30 mg twice daily</td>
<td>30 mg once daily</td>
<td>5 mL</td>
</tr>
<tr>
<td>15.1 kg thru 23 kg</td>
<td>45 mg twice daily</td>
<td>45 mg once daily</td>
<td>7.5 mL</td>
</tr>
<tr>
<td>23.1 kg thru 40 kg</td>
<td>60 mg twice daily</td>
<td>60 mg once daily</td>
<td>10 mL</td>
</tr>
<tr>
<td>40.1 kg or more</td>
<td>75 mg twice daily</td>
<td>75 mg once daily</td>
<td>12.5 mL‡‡</td>
</tr>
<tr>
<td>Patients 1 to 12 Years of Age Based on Body Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 kg or less</td>
<td>30 mg twice daily</td>
<td>30 mg once daily</td>
<td>5 mL</td>
</tr>
<tr>
<td>15.1 kg thru 23 kg</td>
<td>45 mg twice daily</td>
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<td>12.5 mL‡‡</td>
</tr>
</tbody>
</table>

§Tamiflu® is not approved for prophylaxis of patients less than one year of age.
**A 10 mL oral dosing dispenser is provided with the oral suspension. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volumes.
†For patients less than one year of age, remove the provided 10 mL oral dosing dispenser from the packaging, and provide an appropriate dosing device that can accurately measure and administer small volumes.
‡‡Delivery of this Tamiflu for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.
§§Oral Suspension is the preferred formulation for patients who cannot swallow capsules.


administered oseltamivir phosphate “off label” by their health care providers (FDA/CDER, 2012). It was concluded that there were no safety concerns with use of this drug in children under one year of age (FDA/CDER, 2012). This led to the subsequent studies done by the manufacturer and NIAID/NIH, which provided data on the pharmacokinetics and safety of the drug (FDA/CDER, 2012). The FDA’s approval was based on these studies as well as extrapolated data from the older population (FDA/CDER, 2012). Legislation allows extrapolated data to be used in children when adult safety and efficacy are established (FDA, 2012).

Dosing
For the infant population two weeks to one year of age, dosing is dependent on weight; in older children, the dose is standardized (see Table 1) (FDA, 2012). The dosing in infants is three milligrams per kilogram per dose twice daily for five days (FDA, 2012). This dose was extrapolated based on data of safety and efficacy of the adult and pediatric dosing. In the pediatric population under 12 years of age, it has been shown that clearance of the prodrug and its active form slows as the child gets older (Roche Laboratories Inc., 2008). This accounts for the higher mg/kg dose required for the younger population (Roche Laboratories Inc., 2008). The dosing syringe currently packaged with oseltamivir phosphate is not calibrated for these infant doses, and the pharmacist should include a dispenser to ensure accurate dosing and prevent overdosing (FDA, 2012).

Adverse Reactions
Oseltamivir phosphate’s manufacturer disclosed study findings that report the most common adverse reactions in infants two weeks to less than one year are vomiting, diarrhea, and diaper rash (Genentech, Inc., 2012). Health care providers should be cognizant of how common adverse reactions in older children can be manifested in infants. Children one to 12 years of age may experience nausea and vomiting as the most common side effect, but epistaxis, conjunctivitis, ear disorder, and abdominal pain may also occur (Genentech, Inc., 2012). Although noted in the older population, infants are not able to report certain side effects, such as nausea (FDA/CDER, 2012). Administering with food has not shown to have an effect on absorption, and food might lessen gastrointestinal irritability in some patients (Roche Laboratories Inc., 2008).

Other more serious side effects have been reported, mostly from Japan, where use of oseltamivir phosphate is more common than the United States (Mechcatie, 2006). These reports discuss neuropsychiatric disturbances after use of oseltamivir phosphate, including delirium, hallucinations, and even fatal injuries (Mechcatie, 2006). Post-marketing reports prompted Hoffman-LaRoche Inc./Genentech to disclose certain manifestations seen in current studies that could be indicative of neuropsychiatric episodes in the infant population (FDA/CDER, 2012). The studies reported few cases of irritability, lethargy, and staring in the young, non-verbal age group (FDA/CDER, 2012). Although these reports led to warnings on the oseltamivir phosphate package insert, there was no proof that the neuropsychiatric disturbances were caused by oseltamivir phosphate and could be due to influenza-related encephalitis.
to educate parents and caregivers about methods to decrease the risk of spreading influenza. Emphasis should be placed on vaccination, thorough hand washing, and hygiene techniques. However, when these methods fail, influenza can be burdensome and can lead to serious illness. Oseltamivir phosphate is a valuable treatment option for those at highest risk for influenza complications. It has been shown to shorten the duration of illness in influenza patients. Guidelines for proper administration of the drug in the infant population have been established and offer health care providers a safe and effective course of action in influenza treatment. Tamiflu®, like many other medications, was approved for use in children with a limited number of studies related to its safety and efficacy. Due to reports of significant adverse reactions in older children, close monitoring is warranted for this non-oral population.

Monitoring Parameters

Health care providers should consider oseltamivir phosphate therapy in high-risk populations with signs and symptoms of suspected influenza infection (Taketomo et al., 2012). Treatment should not be delayed due to diagnostic testing or a negative rapid influenza test (CDC, 2012b; Taketomo et al., 2012). In oseltamivir phosphate, there are two grams of sorbitol for each 75 mg of the oral suspension, which can cause diarrhea and dyspepsia in patients with hereditary fructose intolerance (Taketomo et al., 2012). Further, health care providers must monitor renal function and serum glucose in patients with diabetes mellitus (Taketomo et al., 2012). Families should be taught to refrigerate suspension at 2 to 8 degrees Celsius (36 to 46 °F) after constituted by the pharmacist and to shake well before use (Taketomo et al., 2012). Oseltamivir phosphate solution should be discarded after 10 days of constitution (Taketomo et al., 2012).

Conclusion

During flu season, influenza is ubiquitous in the pediatric population due to its transmission ability. Pediatric nurses have the opportunity to educate parents and caregivers about methods to decrease the risk of spreading influenza. Emphasis should be placed on vaccination, thorough hand washing, and hygiene techniques. However, when these methods fail, influenza can be burdensome and can lead to serious illness. Oseltamivir phosphate is a valuable treatment option for those at highest risk for influenza complications. It has been shown to shorten the duration of illness in influenza patients. Guidelines for proper administration of the drug in the infant population have been established and offer health care providers a safe and effective course of action in influenza treatment. Tamiflu®, like many other medications, was approved for use in children with a limited number of studies related to its safety and efficacy. Due to reports of significant adverse reactions in older children, close monitoring is warranted for this non-oral population.

References


Centers for Disease Control and Prevention (CDC). (2013c). Early estimates of seasonal influenza vaccine effectiveness – United States, January 2013. MMWR: Morbidity & Mortality Weekly Report, (Mechcatie, 2006). Further, a fatal toxicity known as “gaping syndrome” can occur from the high exposure to benzyl alcohol in neonates (Taketomo et al., 2012). Oseltamivir phosphate oral suspension contains the metabolite of benzyl alcohol sodium benzoate and should be used with caution in neonates (Taketomo et al., 2012). In post-marketing with oseltamivir phosphate, serious cases of anaphylaxis and serious skin conditions were reported (Genentech, Inc., 2012). Oseltamivir phosphate is contraindicated in patients with known hypersensitivity to it or its components (Roche Laboratories Inc., 2008). Patients and families need to be made aware to contact their health care provider immediately upon any signs and symptoms of an allergic-type reaction (Roche Laboratories Inc., 2008). Parents should be instructed to call 911 for immediate help for any difficulty in breathing, bluish color, changes to lips or skin, and/or signs of severe allergic reaction (swelling to face, mouth, lips). Health care providers should report any serious adverse reactions to MedWatch.
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Centers for Disease Control and Prevention (CDC). (2013g). Vaccine effectiveness – How well does the flu vaccine work?