

PHARMACOTHERAPY NEWSLETTER

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Question: How can the antiviral, oseltamivir (Tamiflu®) work to prevent or treat swine-origin influenza A strain (H1N1) viral infection?

Answer: The initial concern surrounding severe disease following the spread of the “swine flu” influenza A strain (H1N1) virus has caused many to wonder how the world will contain the spread of the virus, and treat those that come to need medical attention. Although severe disease caused by swine-origin influenza A H1N1 virus seems to be less frequent than initially feared, the virus has already spread to several countries. Even if the current wave of H1N1 infections wanes, the virus could return during a future influenza season.

One medication that has received significant attention and press of late is the oral antiviral medication, oseltamivir (Tamiflu®). Oseltamivir, along with inhaled zanamivir, are the only two antivirals with activity against the current H1N1 virus as it is resistant to the antivirals, amantadine and rimantadine.¹ Before explaining how oseltamivir works to prevent and treat the H1N1 virus it is important to understand the similarities and differences between this virus and the typical influenza virus encountered during flu season.

The influenza virus is an enveloped RNA virus that has a genome with either eight (influenza A and B) or seven (influenza C) segments. In humans, influenza A & B are the types most responsible for the yearly flu seasons. They are also further named based on the 2 major types of antigenic proteins present on the viral capsid (coating). Those two antigenic proteins are hemagglutinin (HA) and neuraminidase (NA) of which the NA is a primary target of oseltamivir and zanamivir. Unfortunately, each of these antigenic proteins is further broken down into subtypes that help to more specifically identify the virus. Hemagglutinin has 16 different subtypes (H1-H16) and NA has 9 different subtypes (N1-N9). The swine flu has a designation of H1N1, which tells the clinician what subtype of HA and NA are present on the capsid of the virus and at times may help to determine what species the virus possibly evolved from. The reason the swine flu (H1N1) has been given this particular designation is due to the fact that this virus is a combination of genes from influenza viruses normally found in pigs but also has genes from influenza viruses normally seen in birds and humans.¹ As such, when genes from multiple species of influenza virus' come together they can form a new virus that has the potential to infect humans. This process contributes to what is called “antigenic shift” that is known to result in the emergence of a new influenza virus. If this new recombinant can be easily transmitted from person to person, then a flu pandemic can emerge.

Why does this new H1N1 virus concern so many medical professionals? In short, the 20th century witnessed three flu pandemics that spread rapidly and killed over 20 million people, the majority being younger people. Of the three pandemics, the one from 1918 to 1920 was not only the worst of the three, but the virus was an H1N1 strain.² The other two pandemics from 1957-1958 and 1968 were caused by H2N2 and H3N2 strains, respectively.^{3,4}

How does oseltamivir work against the swine-origin influenza A (H1N1) viral infection? Upon exposure to the H1N1 virus, the virus' HA will be used to attach itself to receptors containing sialic (neuraminic) acid on the cell surface of the cell targeted for infection (typically respiratory mucosal epithelium). This H1 interaction with the sialic acid containing cell surface receptors facilitates the fusion between the viral envelope and the cell membrane.⁵ In addition to H1's influence on viral fusion, NA may also contribute to

the ability of the virus to invade the respiratory tract (lungs) by removing the sialic acid present in mucin, thereby enhancing the virus's pathogenicity.⁶

A second protein, M2, also contributes to the fusion of the viral envelop with the cell membrane. The M2 protein is an ion channel that aids in the regulation of pH in the endosome created from the fusion thereby permitting the release of the RNA into the cell cytoplasm where it directs synthesis of new viral proteins using the host's protein synthesis machinery. The M2 protein is the target of amantadine and rimantadine.

As the newly synthesized viral proteins assemble to form new virions (H1N1 virus), they will move to the surface of the cell membrane. However, these viral progeny are initially trapped on the cell surface by the same HA-sialic acid interactions that were used for infection. Neuraminidase is therefore required for spreading infection, as it cleaves sialic acid residues, allowing the virus to spread to uninfected cells.⁶ After oral administration and absorption of oseltamivir (a prodrug), it is rapidly converted to oseltamivir carboxylate which is a potent inhibitor of all influenza A NA subtypes (N1-9).⁷ Normally, in order for the newly formed virions to leave and infect another cell, the virus's NA must cleave the sialic acid residues on the cell surface receptors so they can be released. Oseltamivir carboxylate blocks the cleavage of these sialic acid residues because its lipophilic side chain is able to get into the membrane and block the viral NA from working.

Therefore, oseltamivir has the ability to block H1N1 virus from invading the respiratory epithelium as well as prevent the release of new H1N1 virions from infected cells, thus decreasing the infectivity of neighboring cells. Fortunately, oseltamivir has demonstrated some benefit in children one year and older, including a reduction in lower respiratory tract infections, bronchitis and hospitalizations.^{8,9} It has also been urgently approved by the FDA and recommended by the Centers for Disease Control and Prevention (CDC) for the treatment of swine-origin influenza A (H1N1) infection in all patients as young as 3 months of age. When compared to placebo, oseltamivir reduced the symptoms related to the regular influenza virus by about 36 hours when compared to placebo. The above benefits are best achieved with early initiation in relation to the onset of symptoms (generally within the first 48 hours). In adults and adolescents (greater than or equal to 13 years of age) oseltamivir should be given as 75 mg by mouth daily for 10 days for prophylaxis and 75 mg by mouth twice a day for 5 days for treatment. More information about dosing in children less than 13 years of age and the use of inhaled zanamivir can be found at the [CDC website](#). It remains to be determined how well oseltamivir will work against this H1N1 strain, but early analysis shows it to be effective against the virus.

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Take Home Points:

- The swine-origin influenza A (H1N1) virus is made up of a combination of influenza genes from several species (swine, avian, and human). The H stands for hemagglutinin (needed for viral binding to cell surface receptors) and N stands for neuraminidase (needed for new H1N1 virions to be released from the cell membrane of the infected cell).
- The current H1N1 strain is susceptible to both neuraminidase inhibitors, oseltamivir (Tamiflu®) and zanamivir (Relenza®), but resistant to amantadine and rimantadine.
- Oseltamivir works by blocking the H1N1 virus from invading respiratory epithelium as well as preventing the release of newly formed H1N1 virions from the cell membranes of infected cells.
- Oseltamivir works best when given early and should be initiated within 48 hours of the onset of symptoms. Recommendations are in place for the treatment and prevention of influenza virus in children 3 months of age or older. See the [CDC website](#) for more information.

Considerations for Clinicians Based on Setting:

Outpatient Setting:

Since many patients will initially present to the clinic, emergency department, and/or physician's office with complaints of the flu, clinicians in the outpatient setting will likely be initially triaging patients and making the determination for the need for prophylaxis, treatment and/or admission. Due to potential issues related to the availability of oseltamivir, clinicians should try to accurately determine who is likely to have the flu and require treatment and/or prophylaxis. The symptoms of the flu include: fever (generally greater than 100°F), chills, headache, dry cough, achy joints, and GI distress (including nausea /vomiting and even diarrhea). If patient has a high likelihood of having the flu, it is advisable to start oseltamivir within 48 hours of onset of

symptoms and prophylaxis for family members or close contacts. See the [CDC website](#) for more information.

Inpatient Setting:

The same information from the outpatient should apply to the inpatient as well. If oseltamivir treatment was initiated prior to admission, it should be continued in the hospital for at least 5 days (total treatment regimen) per the current CDC recommendations. Prophylaxis of family members or other close contacts should also be given consideration. See the [CDC website](#) for more information.

Important Counseling Bullet Point(s):

- It would be critical for clinicians to counsel their patients to start the medication without delay upon being given a valid prescription and to complete the entire course whether it is being used for prophylaxis or treatment. In addition, it would be advisable to counsel them on mechanisms to prevent further exposure to the public or close contacts should they have the current strain of H1N1 virus. These include: covering their mouths appropriately when coughing and sneezing, washing their hands routinely and using an alcohol based hand sanitizer, staying at home for at least 7 days, getting plenty of rest, and drinking appropriate fluids to prevent dehydration to name a few.

Medical/Legal Consideration(s):

- There were no cases identified in the 2008 edition of LexisNexis' Drugs in Litigation regarding oseltamivir, Tamiflu® or products liability claims against the drug manufacturer, and Pharmacology Weekly's legal counsel has not identified any such cases to date.¹⁰ Nevertheless, because of the risk which has now been clearly identified by the CDC and World Health Organization, it would be prudent to document in the medical chart that the patient has been appropriately screened for the current H1N1 strain and precautions to prevent its spreading and/or contraction. In addition, if prophylaxis and/or treatment are offered to the patient, documentation of the need to start the medication without delay and to complete the entire course would be important to also include in the medical chart.

Test Questions for CE:

Which of the following antivirals is not currently recommended in the prophylaxis or treatment of the swine-origin influenza A (H1N1) virus?

- Oseltamivir
- Zanamivir
- Amantadine
- B and C only

Which of the following best reflects the mechanism of action of oseltamivir for the treatment of swine-origin influenza A (H1N1) virus?

- Inhibition of hemagglutinin
- Inhibition of neuraminidase
- Inhibition of protease
- Inhibition of viral integrase

When should oseltamivir be initiated in relation to the onset of symptoms related to influenza?

- Within the first 48 hours
- Within the first 72 hours
- Within 7 days
- Within 10 days

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