FACT SHEET

Antiviral Agents for Influenza: Background Information for Clinicians

Introduction

Four prescription medications with antiviral activity against influenza viruses are commercially available in the United States (amantadine, rimantadine, oseltamivir, zanamivir). The four drugs are classified into two categories, the adamantane derivatives and the neuraminidase inhibitors, on the basis of their chemical properties and activities against influenza viruses.

Controlled clinical trials have demonstrated the efficacy of all four antiviral medications in reducing symptom duration when used for treatment of influenza infections. Three of the antiviral drugs have been approved for use as chemoprophylaxis. Table 1 summarizes information about the use of antiviral medications in the United States for influenza.

Neuraminidase Inhibitors (Zanamivir, Oseltamivir)

The neuraminidase inhibitors, zanamivir and oseltamivir, are chemically related drugs that have activity against both influenza A and B viruses.

- Zanamivir is an orally inhaled powdered drug that is approved for treatment of influenza in persons aged 7 years and older. Zanamivir is not approved for chemoprophylaxis of influenza.
- Oseltamivir is an orally administered capsule or oral suspension that is approved for treatment of influenza in persons aged 1 year and older. Oseltamivir is also approved for chemoprophylaxis of influenza in persons aged 13 years and older.

How do the neuraminidase inhibitor drugs work?

Zanamivir and oseltamivir block the active site of the influenza viral enzyme neuraminidase, which is common to both influenza A and influenza B viruses. This effect results in viral aggregation at the host cell surface and reduces the number of viruses released from the infected cell.

How effective are the neuraminidase inhibitor drugs?

Treatment

When used within 48 hours of illness onset, both drugs decrease shedding and reduce the duration of influenza symptoms by approximately 1 day compared with placebo. Summary results from randomized, placebo-controlled double-blinded studies of oseltamivir showed a significant reduction in influenza related lower respiratory tract complications (pneumonia and bronchitis) associated with antibiotic use and a significant reduction in hospitalizations. These impacts occurred in both healthy and high-risk adolescents and adults. No studies have assessed the impact of antiviral drug therapy on mortality. For both drugs, the recommended duration of treatment is 5 days. One study of healthy and high-risk adolescents and adults treated with oseltamivir compared with placebo showed a reduction in influenza-related lower respiratory tract complications associated with antibiotic therapy.

Chemoprophylaxis

Oseltamivir, but not zanamivir, is approved for chemoprophylaxis of influenza.

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Side effects of the neuraminidase inhibitor drugs:

Zanamivir and oseltamivir were approved in 1999, and therefore clinical experience to assess adverse effects is limited.

- Oseltamivir has been associated with nausea and vomiting during controlled treatment studies compared with placebo.
- Nausea, diarrhea, dizziness, headache, and cough have been reported during zanamivir treatment, but the frequencies of adverse events were similar to inhaled powdered placebo drug.
- Few serious CNS adverse effects have been reported for the neuraminidase inhibitor drugs.
- Zanamivir generally is not recommended for use in persons with underlying respiratory disease because of the risk of precipitating bronchospasm. Serious adverse respiratory events resulting from zanamivir use have been reported in persons with chronic pulmonary disease and in healthy adults.
- There are limited data about the use of neuraminidase inhibitors during pregnancy.

Antiviral resistance to the neuraminidase inhibitor drugs:

Data are limited on antiviral resistance to the neuraminidase inhibitor drugs.

- Studies have identified some evidence for the development of neuraminidase inhibitor-resistant influenza virus strains, but the studies have been limited by the short time that the neuraminidase inhibitors have been available for clinical use and by the lack of optimal methodology to detect viral resistance to these drugs.
- One pediatric study of oseltamivir treatment reported that 5.5% of influenza isolates had evidence of neuraminidase resistance.
- In vitro studies have found that cross-resistance occurs between the neuraminidase inhibitor drugs, but does not affect susceptibility to adamantane drugs.

Adamantane Derivatives (Amantadine, Rimantadine)

The adamantane derivatives, amantadine and rimantadine, are chemically related, orally administered drugs that are approved for treatment and chemoprophylaxis of influenza A. Amantadine and rimantadine specifically inhibit replication of influenza A viruses, but not influenza B viruses.

- Amantadine is approved for the treatment of influenza A in children aged 1 year and older and in adults.
- Rimantadine is approved for treatment of influenza A in adults.
- Both drugs are approved for chemoprophylaxis to prevent influenza A in people aged 1 year and older.

Antiviral activity: How do the adamantane drugs work?

Amantadine and rimantadine are thought to interfere with influenza A virus M2 protein, a membrane ion channel protein, and inhibit virus uncoating, which inhibits virus replication, resulting in decreased viral shedding.

How effective are the adamantane drugs?

Treatment

When administered within 48 hours of illness onset, controlled studies have found that both drugs decrease viral shedding and reduce influenza A illness by approximately 1 day compared with placebo. The usual recommended duration of treatment is 5 days.

Chemoprophylaxis

When used for chemoprophylaxis, amantadine and rimantadine are approximately 70% - 90% effective in preventing symptoms of influenza A illness. The efficacy and effectiveness of amantadine and rimantadine

to prevent complications of influenza A are unknown. Both drugs are effective when used for chemoprophylaxis during outbreaks of influenza A in institutions, such as nursing homes.

Side effects of the adamantane drugs:

Chemoprophylactic use of both drugs has been associated with

- Gastrointestinal and central nervous system (CNS) adverse effects in healthy adults and elderly nursing home residents.
- CNS toxicity, such as lightheadedness, difficulty concentrating, nervousness, insomnia, and seizures in patients with pre-existing seizure disorders. Rimantadine use has been associated with fewer CNS side effects than amantadine.

Amantadine is teratogenic and embryo toxic in animals. Rimantadine has not been found to be mutagenic. The safety of amantadine and rimantadine when used during pregnancy has not been established.

Antiviral resistance:

When used for treatment, amantadine and rimantadine have been associated with the rapid development of resistant viruses.

- Drug-resistant viruses can be spread to contacts of treated individuals, including persons receiving chemoprophylaxis.
- The mechanism of resistance is the same for both adamantane derivatives, and influenza A viruses resistant to one drug are also resistant to the other.
- No evidence indicates that adamantane-resistant viruses are more transmissible or more virulent than adamantane-sensitive viruses.
- Resistance to adamantanes does not affect susceptibility to neuraminidase inhibitors.
- Most influenza viruses isolated from the general population are not resistant to amantadine or rimantadine.

Adamantanes Compared with Neuraminidase Inhibitors

- No controlled studies have directly compared the adamantanes (amantadine, rimantadine) with the neuraminidase inhibitors (zanamivir, oseltamivir) for treatment or chemoprophylaxis of influenza A. A meta-analysis and a systematic review of published studies concluded that both the adamantanes and the neuraminidase inhibitor drugs reduce the duration of symptoms of influenza A by approximately 1 day compared with placebo.
- Data are very limited on the efficacy or effectiveness of any of the antiviral drugs in preventing complications from influenza in high-risk populations.
- The costs, routes of administration, adverse effects, contraindications, and potential for antiviral resistance differ among the four drugs.
- There are insufficient data on the use of any of the four antiviral agents during pregnancy.
- In general, clinical studies have reported that the neuraminidase inhibitors have resulted in fewer serious side effects compared to placebo than have been reported for amantadine and rimantadine. However, the relative frequency or severity of adverse effects of the adamantanes compared with the neuraminidase inhibitors has not been directly compared in controlled trials when used for treatment or chemoprophylaxis.

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Table 1: Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis

	Age Groups (yrs)				
Antiviral Agent	**1-6**	**7-9**	**10-12**	**13-64**	**≥65**
Amantadine*					
Treatment, influenza A	5mg/kg/day up to 150 mg in 2 divided doses†	5mg/kg/day up to 150 mg in 2 divided doses†	100mg twice daily§	100mg twice daily§	≤100 mg/day
Prophylaxis, influenza A	5mg/kg/day up to 150 mg in two divided doses†	5mg/kg/day up to 150 mg in two divided doses†	100mg twice daily§	100mg twice daily§	≤100 mg/day
Rimantadine¶					
Treatment,** influenza A	NA††	NA	NA	100mg twice daily§ §§	100 mg/day
Prophylaxis, influenza A	5mg/kg/day up to 150 mg in two divided doses†	5mg/kg/day up to 150 mg in two divided doses†	100mg twice daily§	100mg twice daily§	100 mg/day¶¶
Zanamivir* †††					
Treatment, influenza A and B	NA	10mg twice daily	10mg twice daily	10mg twice daily	10mg twice daily
Oseltamivir					
Treatment, §§§ influenza A and B	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	Dose varies by child's weight¶¶¶	75mg twice daily	75mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75mg/day	75mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel ®--tablet and syrup) and Geneva Pharms Tech (Amantadine HCL--capsule); USL Pharma (Amantadine HCL – capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL--syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine (R)--tablet and syrup); Corepharma , Impax Labs (Rimantadine HCL – tablet), and Amide Pharmaceuticals (Rimantadine HCL – tablet). Zanamivir is manufactured by Glaxo Smithkline (Relenza (R) -- inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu (R) — tablet). Information based on data published by the US Food and Drug Administration at www.fda.gov.

* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 ml/min/1.73m^2 .

† 5 mg/kg of amantadine or rimantadine syrup = 1 tsp/22 lbs.

§ Children ≥10 years who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg/day.

¶ A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

** Only approved by FDA for treatment among adults.

†† Not applicable.

§§ Rimantadine is approved by FDA for treatment among adults. However, certain experts in the management of influenza consider it appropriate also for treatment among children. (See American Academy of Pediatrics, 2000 Red Book.)

¶ ¶ Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years if they experience possible side effects when taking 200 mg/day.

***Zanamivir administered via inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.

††† Zanamivir is not approved for prophylaxis.

§§§ A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.

¶¶¶ The dose recommendation for children who weigh ≤15 kg is 30 mg twice a day, for >15 to 23 kg children the dose is 45 mg twice a day, for >23 to 40 kg children the dose is 60 mg twice a day, and for children >40 kg, the dose is 75 mg twice a day.

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