

Continuing Education for Pharmacists

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Antiviral Drug Therapy for Treatment of Influenza

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Goals. The goal of this lesson is to discuss the use of four antiviral drugs for prevention and control of influenza.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. identify etiologic and pathophysiologic characteristics of influenza;
2. recognize the pharmacologic, pharmacokinetic, and toxicologic principles relative to amantadine, rimantadine, oseltamivir, and zanamivir in prevention and control of influenza; and
3. recommend appropriate dosages of influenza antiviral medications for treatment and prophylaxis of influenza, based on the patient's age, weight, and renal function.

Influenza viruses are the most important pathogens that cause acute respiratory disease. Influenza epidemics cause approximately



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36,000 deaths each year in the United States; no age group is spared. The World Health Organization estimates that seasonal influenza epidemics result in three to five million cases of severe illness and one-quarter to one-half million deaths annually in the industrialized world alone. Infection rates are highest among children; rates of serious illness and death are greatest among persons aged 65 years or older, children under two years, and individuals of any age who suffer from medical conditions that place them at increased risk for complications from influenza.

Antiviral Drugs

Antiviral drugs are not a substitute for immunization with the influenza vaccine, but an adjunct to it. They offer a rational approach to influenza management that complements vaccination, particularly in high-risk individuals. There are four antiviral agents available in the United States for treating influenza: amantadine (Symmetrel and others), rimantadine (Flumadine and others), oseltamivir (Tamiflu), and zanamivir (Relenza) (Table 1). The drugs differ in approved age groups for use, pharmacokinetics, dosages, adverse effects, routes of administration, and costs.

Amantadine and Rimantadine

Amantadine and rimantadine are chemically related drugs known as adamantanes. They are active against influenza A viruses but not influenza B viruses. The drugs inhibit an early step in viral replication. For some strains, they act at a late step in viral assembly probably through alteration of hemagglutinin processing. The drugs inhibit dissociation of the ribonucleoprotein complex early in replication and incite changes in the structure of the hemagglutinin content within the virus during its intracellular transport later in replication. Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa.

Oseltamivir and Zanamivir

Oseltamivir (Tamiflu) and zanamivir (Relenza) are chemically related drugs known as neuraminidase inhibitors. They are active against influenza A and B viruses. With neuraminidase inhibition, alteration of virus particle aggregation and release is possible.

Treatment

Taken within two days of illness onset by otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A, and oseltamivir and zanamivir can reduce the duration of uncomplicated influenza A and B, by approximately one day.

Current data are limited regarding effectiveness in preventing serious influenza-related complications such as bacterial or viral pneumonia or exacerbation of chronic diseases. Evidence for effectiveness is based largely on studies of patients with uncompli-

Table 1
Antiviral Drug Products

Drug	Trade Name(s)	Dosage Form(s)	Approval Dates & Use(s)
Amantadine	Symmetrel and others	tablet, syrup tablet, capsule, syrup	1966 chemoprophylaxis of influenza A (H2N2), 1976 for treatment & prophylaxis of influenza A in adults & children ≥ 1 year
Rimantadine	Flumadine and others	tablet, syrup tablet	1993 for treatment & chemoprophylaxis of influenza in adults & children
Oseltamivir	Tamiflu	capsule, powder for oral suspension	1999 for treatment of persons ≥ 1 year; 2000 for chemoprophylaxis of influenza in persons ≥ 13 years
Zanamivir	Relenza	inhaled powder	1999 for treatment of persons ≥ 7 years

cated influenza. Data are also limited and inconclusive regarding effectiveness for treatment of influenza in persons at high risk for serious complications. The data are also inadequate regarding the safety and efficacy of the influenza antiviral drugs for use in children younger than one year of age.

Chemoprophylaxis

Amantadine and rimantadine are indicated for chemoprophylaxis of influenza A infection. Both drugs are approximately 60 to 90 percent effective in preventing illness from influenza A. Neither drug interferes with the antibody response to influenza vaccine. Used for prophylaxis, they can prevent illness while permitting subclinical infection with development of antibodies against circulating influenza viruses.

Tamiflu is the only neuraminidase inhibitor approved for prophylaxis, although studies show that both Tamiflu and Relenza are similarly effective in preventing febrile influenza illness (82 percent and 84 percent, respectively). Both antivirals have also been shown to prevent influenza illness in persons administered chemoprophylaxis after a household member developed influenza. Studies with Tamiflu and Relenza for prophylaxis among residents in institutional settings and patients with chronic medical conditions are limited in comparison with the adamantanes. One study of Tamiflu prophylaxis in nursing

home residents revealed a 92 percent reduction in influenza illness. There are no definitive data regarding the efficacy of any of the antiviral agents in preventing influenza in severely immunocompromised persons.

When assessing the timing and duration for administering influenza antiviral medications for prophylaxis, factors related to cost, compliance, and potential adverse effects need to be considered. To be maximally effective as prophylaxis, the drug must be taken daily while influenza is active in the community. One study using amantadine or rimantadine for prophylaxis revealed that the drugs should be taken only during the period of peak influenza activity in a community.

Target Groups for Chemoprophylaxis

Persons at High Risk who are Vaccinated after Influenza Activity Has Begun. Persons at high risk for complications of influenza still can be vaccinated following an outbreak of influenza; however, antibody development in adults takes approximately two weeks after vaccination. Chemoprophylaxis may be considered for persons at high risk during the time from vaccination until immunity has developed. Children less than nine years of age who receive influenza vaccine for the first time

may require six weeks of prophylaxis dosing (i.e., prophylaxis for four weeks after the first dose of vaccine and an additional two weeks of dosing following the second dose).

Caregivers to Those at High Risk. Chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Individuals with frequent contact include employees and volunteer workers in health care institutions and chronic-care facilities, and household members. Chemoprophylaxis should be considered for all such persons, regardless of their vaccination status, if an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine.

Persons with Immune Deficiencies and Others. Chemoprophylaxis can be considered for individuals at high risk who have an inadequate antibody response to influenza vaccine. These persons may include those infected with HIV or those who have other medical conditions that impair the immune system.

Chemoprophylaxis throughout the influenza season or during peak influenza activity may be appropriate for persons at high risk of infection who should not or wish not to be vaccinated. Health care providers and patients should make the decision to use chemoprophylaxis on an individual basis.

Control of Influenza Outbreaks in Institutions

Antiviral drug use for treatment and prophylaxis of influenza is a component of controlling influenza outbreaks in institutions. The majority of published reports concerning use of antiviral agents for this purpose are based on studies of influenza A outbreaks among nursing home populations where amantadine or rimantadine were used. Less information is available concerning use of oseltamivir or zanamivir in influenza A or B institutional outbreaks. To reduce

Table 2
Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis

Antiviral Agent	Age Groups in Years				
	1 to 6	7 to 9	10 to 12	13-64	≥65
Amantadine*					
Treatment/Prophylaxis influenza A	5 mg/kg/day up to 150 mg in 2 divided doses [†]	5 mg/kg/day up to 150 mg in 2 divided doses [†]	100 mg twice daily [§]	100 mg twice daily [§]	≤100 mg/day
Rimantadine[¶]					
Treatment influenza A	NA	NA	NA	100 mg twice daily ^{§†}	100 mg/day
Prophylaxis influenza A	5 mg/kg/day up to 150 mg in 2 divided doses [†]	5 mg/kg/day up to 150 mg in 2 divided doses [†]	100 mg twice daily [§]	100 mg twice daily [§]	100mg/day [¶]
Zanamivir					
Treatment influenza A & B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment influenza A & B [‡]	dose varies by weight [#]	dose varies by weight [#]	dose varies by weight [#]	75 mg twice daily	75 mg twice daily
Prophylaxis influenza A & B	NA	NA	NA	75 mg/day	75 mg/day

NA = Not applicable
^{*}The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 mL/min/1.73m².
[†]5 mg/kg body weight of amantadine or rimantadine syrup = 1 tsp/2.2 lbs.
[§]Children aged ≥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.
[‡]Rimantadine is approved for treatment among adults. However, certain specialists in the management of influenza consider rimantadine appropriate for treatment among children. Studies evaluating the efficacy of amantadine and rimantadine in children are limited, but they indicate that treatment with either drug diminishes the severity of influenza A infection when administered within 48 hours of illness onset.
[#]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 children who weigh >15-23 kg, the dose is 45 mg twice a day. For children who weigh >23-40 kg, the dose is 60 mg twice a day. And, for children who weigh >40 kg, the dose is 75 mg twice a day.
 Data from *MMWR*. 2005;54:1-40

the spread of the virus, chemoprophylaxis should be started as early as possible when confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk. Ideally, it should be offered to all residents, regardless of whether they previously received influenza vaccinations that season. If new cases continue to occur, chemoprophylaxis should be continued until approximately one week after the end of the outbreak. It can be offered to all unvaccinated staff who provide care to persons at high risk. Chemoprophylaxis also can be considered for individuals in other closed or

semiclosed settings (e.g., dormitories, prisons, etc.).

Measures should be instituted to limit contact between individuals taking antiviral medications for treatment and other persons, including those taking chemoprophylaxis, to limit the potential transmission of drug-resistant viruses during outbreaks in institutions.

Usage Considerations

The patient's age, weight, and renal function should be considered when contemplating use of influenza antiviral medications (Table 2). The presence of other medical conditions,

indications for use (i.e., prophylaxis or treatment), and the potential for interaction with other medications must also be factored into decisions whether to initiate antiviral drug therapy.

Adverse Events

Amantadine and Rimantadine. Amantadine and rimantadine can cause CNS and gastrointestinal adverse effects when administered to healthy, young adults. The incidence of CNS side effects (e.g., anxiety, nervousness, insomnia, difficulty in concentrating, and lightheadedness) is higher in persons taking amantadine than

in those taking rimantadine. In a six-week study of prophylaxis in healthy adults, 6 percent of participants taking rimantadine at a dosage of 200 mg/day and approximately 13 percent of those taking the same dosage of amantadine experienced one or more CNS symptoms versus 4 percent of those taking placebo. Fewer CNS side effects are associated with rimantadine compared with amantadine in elderly persons. GI side effects (e.g., nausea and anorexia) occur in approximately 1 to 3 percent of persons taking either drug, compared with 1 percent of persons receiving placebo. Adverse effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drugs. Serious side effects (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures) have been noted. These more serious adverse events have been associated with high plasma drug concentrations and have been observed most often in persons with renal insufficiency, seizure disorders, or certain psychiatric disorders, as well as in older persons who have been taking amantadine for prophylaxis at a dosage of 200 mg/day. Lowering the dosage of amantadine reduces the incidence and severity of such effects (Table 2). With acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported. Rimantadine's safety among chronically ill and older persons has been evaluated less frequently. Because amantadine has anticholinergic effects, it should not be used in patients with untreated angle closure glaucoma.

Oseltamivir. Nausea and vomiting have been reported more frequently in adults receiving oseltamivir for treatment of influenza than in persons receiving placebo. Among children, oseltamivir caused vomiting in 14.3 percent compared with 8.5 percent of recipients given placebo. Similar types and rates of adverse events were reported in studies of

oseltamivir prophylaxis. Severity of nausea and vomiting can be modified by taking Tamiflu with food.

Zanamivir. In a study of patients with Influenza-like Illness (ILI) along with asthma or chronic obstructive pulmonary disease where zanamivir was administered after use of a beta₁-agonist, 13 percent of patients receiving Relenza versus 14 percent of patients who received placebo experienced greater than 20 percent decline in forced expiratory volume one second after treatment. In a study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir. During postmarketing surveillance, Relenza has been shown to cause respiratory function deterioration after its inhalation. Some patients had underlying airway disease (e.g., asthma or chronic obstructive pulmonary disease). Because of the risk for serious adverse events and because the efficacy has not been demonstrated in patients with asthma or chronic obstructive pulmonary disease, Relenza is not recommended for them. If Relenza is given to patients with underlying chronic respiratory disease, it should be used with caution under conditions of appropriate monitoring and supportive care, including the availability of short-acting bronchodilators. Patients with asthma or chronic obstructive pulmonary disease should be advised to have a rapid-acting inhaled bronchodilator available when inhaling Relenza, and to stop using Relenza and contact their physician if they experience difficulty breathing. Allergic reactions, including oropharyngeal or facial edema, have also been experienced during postmarketing surveillance.

In studies of persons with uncomplicated influenza, the frequency of adverse events was similar for persons receiving inhaled Relenza and for those receiving placebo. The most common adverse events reported by both groups at less than 5 percent incidence included diarrhea; nausea; sinusitis;

nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections.

Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS, including CNS stimulants. Concurrent administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions. No clinically significant interactions between rimantadine and other drugs have been identified.

No known drug interactions have been reported with zanamivir. Limited data are available regarding drug interactions with oseltamivir. Because oseltamivir is excreted in the urine by glomerular filtration and tubular secretion, there is potential for interaction with other drugs excreted by this pathway. Coadministration of oseltamivir and probenecid, for example, results in reduced clearance of oseltamivir by approximately 50 percent and a corresponding approximate two-fold increase in the plasma levels of oseltamivir.

There are no published data available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs.

Summary

The influenza antiviral drugs are not replacements for influenza vaccine, but adjuncts to vaccination. The drugs are clinically effective for treating and/or preventing influenza when taken as directed.