Antiviral Drugs in the Immunocompetent Host:
Part II. Treatment of Influenza and Respiratory Syncytial Virus Infections

RICHARD COLGAN, M.D., University of Maryland School of Medicine, Baltimore, Maryland
ROBERT MICHOCKI, Pharm.D., B.C.P.S., University of Maryland School of Pharmacy, Baltimore, Maryland
LISA GREISMAN, M.D., University of Maryland Medical Center, Baltimore, Maryland
TRACY A. WOLFF MOORE, M.D., University of Maryland School of Medicine, Baltimore, Maryland

Family physicians should be familiar with the various drugs available for treating and preventing viral infections. Part II of this two-part article focuses on agents used to manage influenza and respiratory syncytial virus. Rimantadine and amantadine traditionally have been used to prevent and treat influenza type A infections. The neuraminidase inhibitors zanamivir and oseltamivir have a broadened spectrum of activity in the treatment and prevention of influenza types A and B. Ribavirin has been used in some high-risk infants to treat respiratory syncytial virus infections, and palivizumab can be used for prophylaxis. (Am Fam Physician 2003;67:763-6. Copyright© 2003 American Academy of Family Physicians.)

Richard W. Sloan, M.D., R.PH., coordinator of this series, is chairman of the Department of Family Medicine at York (Pa.) Hospital and clinical associate professor in family and community medicine at the Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pa.

See page 675 for definitions of strength-of-evidence levels.

This is part II of a two-part article on antiviral drugs. Part I, "Treatment of Hepatitis, Cytomegalovirus, and Herpes Infections," appears in this issue on page 757.

RNA viruses generally are benign in the early stage of infection, but they have the potential to induce acute respiratory distress syndrome if they spread to the lower respiratory tract or progress to pneumonia. Antiviral drugs can be used to treat and prevent these infections, although they are not a substitute for vaccine. Part II of this article focuses on antiviral agents used in the management of influenza and respiratory syncytial virus (RSV).

Influenza Viruses

Antiviral drugs that prevent and treat influenza should be considered adjuncts to vaccine—not substitutes. Traditionally, amantadine (Symmetrel) and, to a lesser extent, rimantadine (Flumadine) have been used for preventing and treating influenza type A *(Table 1)*.[1-4] However, in 1999, two drugs that effectively treat and prevent influenza types A and B were introduced. These drugs, zanamivir (Relenza) and oseltamivir (Tamiflu), provide more complete coverage when the type of influenza is unknown *(Table 2)*.[1-4]

INFLUENZA TYPE A

Amantadine and Rimantadine. Amantadine was the first drug approved for prophylaxis of influenza type A (in 1966), and in 1976, it was approved for treatment and prophylaxis in adults and children older than one year. Rimantadine became available in 1993 for treatment and prophylaxis of influenza type A in adults and for prophylaxis in children. Neither of these drugs is effective against influenza type B.

Treatment usually is continued for three to five days or discontinued 24 to 48 hours following resolution of symptoms. The efficacy of both drugs is similar, and the average duration of illness is shortened by approximately one day.[5]

These drugs can be used for prophylaxis in high-risk patients *(Table 3)*[6] and for influenza-related complications if an outbreak of influenza occurs within two weeks following vaccination.[4] In a recent review, the average effectiveness of amantadine and rimantadine for the prevention of influenza was 61 and 72 percent, respectively.[7]

Although amantadine is considerably less expensive than rimantadine, it crosses the blood-brain barrier and appears to cause more central nervous system side effects, including dizziness, ataxia, hallucinations, agitation, and confusion. This is especially true in elderly patients and may be associated with higher serum concentrations. A split dosage may help minimize adverse events.

Amantadine is primarily eliminated in the

TABLE 1
Comparison of Amantadine and Rimantadine

Drug factors	*Amantadine (Symmetrel)*	*Rimantadine (Flumadine)*
Generic availability	Yes	Yes
Dosage forms	Liquid and tablet	Liquid and tablet
Treatment and prevention of influenza type A in adults	Yes	Yes
Treatment of influenza type A in children	Yes	Not approved
Prevention of influenza type A in children	Yes	Yes
Dosages for treatment of influenza type A	Adults* and children ≥12 years of age: 200 mg daily until 24 to 48 hours after symptoms have disappeared *or* 100 mg twice daily† until 24 to 48 hours after symptoms have disappeared Children one to nine years of age: 5 mg per kg daily (up to 150 mg daily) until 24 to 48 hours after symptoms have disappeared Children 10 to 11 years of age: 100 mg twice daily until 24 to 48 hours after symptoms have disappeared	Adults* and children ≥10 years of age: 100 mg twice daily for seven days Not approved for children <10 years of age
Dosages for prevention of influenza A‡	Adults* and children ≥12 years of age: 200 mg daily for at least seven days *or* 100 mg twice daily for at least seven days Children one to nine years of age: 5 mg per kg daily (up to 150 mg daily) for at least seven days Children 10 to 11 years of age: 100 mg twice daily for at least seven days	Adults* and children ≥10 years of age: 100 mg twice daily for at least seven days Children <10 years of age: 5 mg per kg daily (up to 150 mg daily) for at least seven days
Prevention and treatment of influenza B	No	No
Dosage reduction in renal impairment	Yes (creatinine clearance ≤50 mL per minute [0.83 mL per second])	Yes (creatinine clearance ≤10 mL per min [0.17 mL per second])
Side effects	CNS and GI	Primarily GI
Cost (generic)§		
Five-day treatment (adult dosage)	$18 ($4 to $5)	$29 ($26)
42-day treatment (adult dosage in community outbreaks)	$106 ($28 to $31)	$171 ($154)

CNS = central nervous system; GI = gastrointestinal.

**—Dosage for adults up to age 64. Dosage for adults age 65 and older is 100 mg daily.*
†—*If CNS effects develop with the once-a-day dosage, the split dosage might reduce side effects.*
‡—*All dosages may be used for up to 42 days during community outbreaks.*
§—*Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2002. Cost to the patient will be higher, depending on prescription filling fee.*

Information from references 1 through 4.

kidneys as unchanged drug; therefore, the dosage must be modified in elderly patients and patients with reduced renal function *(Table 4)*.[8]

Rimantadine's adverse drug-reaction profile is similar to that of amantadine with respect to gastrointestinal side effects such as nausea, vomiting, and dyspepsia, but rimantadine appears to cause fewer central nervous system side effects.[9]

Oseltamivir and Zanamivir. Oseltamivir, which is taken orally, was approved for prophylaxis of influenza in late 2000, and zanamivir's approval for prophylaxis is pending. They are equally effective in reducing symptoms and duration of illness when taken within 48 hours of the onset of symptoms.[10-14]

Zanamivir is inhaled and requires the use of an inhalation device, which may be difficult for elderly patients to use. Because of its potential to induce bronchospasm and reduce lung function, use of zanamivir gener-

TABLE 2
Comparison of Oseltamivir and Zanamivir

Drug factors	*Oseltamivir (Tamiflu)*	*Zanamivir (Relenza)*
Generic availability	No	No
Dosage forms	Liquid and capsule	Powder for oral inhalation
Treatment of influenza types A and B in adults	Yes	Yes
Treatment of influenza types A and B in children	Yes, in children >one year of age	Yes, in children ≥seven years of age
Prevention of influenza types A and B in adults	Yes	FDA approval pending
Prevention of influenza types A and B in children	Yes, in children ≥13 years of age	FDA approval pending
Dosage for treatment of influenza types A and B*	Adults and children ≥13 years: 75 mg twice daily for five days Children one to 12 years (following doses are given twice daily for five days): 15 kg (33 lb) or less: 30 mg 15 kg to 23 kg (51 lb): 45 mg 23 kg to 40 kg (88 lb): 60 mg >40 kg: 75 mg	Two inhalations (10 mg) twice daily for five days
Dosage for prevention of influenza types A and B	Adults and children ≥13 years: 75 mg once daily for at least seven days†	Approval pending. Two inhalations (10 mg) once daily for at least seven days†
Dosage reduction in renal impairment	Yes (creatinine clearance ≤30 mL per minute [0.5 mL per second])	No
Side effects	GI	Minimal
Cost‡		
Five-day treatment (adult dosage)	$63	$50
42-day treatment (adult dosage in community outbreaks)	$265	$212 (approval pending)
Precautions	Take with food to improve tolerance Suspension should be shaken before each use and is stable at room temperature for 10 days	Not recommended in patients with asthma or COPD May cause bronchospasm

FDA = U.S. Food and Drug Administration; GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.

**—Begin treatment within 48 hours of onset of symptoms. If using zanamivir, two doses should be taken on the first day of dosing, provided there are at least two hours between doses. Subsequent doses should be spaced approximately 12 hours apart.*

†—May be used for up to 42 days during community outbreaks.

‡—Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2002. Cost to the patient will be higher, depending on prescription filling fee.

Information from references 1 through 4.

ally should be avoided in patients with asthma and chronic obstructive pulmonary disease.

INFLUENZA TYPE B

Oseltamivir and zanamivir are first-line choices for prevention and treatment of infection during outbreaks of influenza type B.

Respiratory Syncytial Virus (RSV)

RSV is a frequent cause of bronchiolitis in children. Treatment consists primarily of supportive care with fluids, oxygen, and aerosolized bronchodilators.

Ribavirin. In a select group of high-risk infants (premature infants younger than 36 weeks and infants with bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency) with severe infections, aerosolized ribavirin (Virazole) has been used.[15] The use of this drug requires special equipment and expert respiratory monitoring. It is expensive, with a cost exceeding $1,000 per day.

RSV Immune Globulin and Palivizumab. In

TABLE 3
Using Antiviral Drugs for Influenza

Prophylaxis

Unvaccinated patients at high risk

Patients at high risk who were vaccinated at the onset of the epidemic (two weeks for patients age nine and older; six weeks for patients age eight or younger)

Vaccinated patients at high risk, when vaccine virus and epidemic virus are a poor antigenic match

Patients with immunodeficiency

Unvaccinated patients caring for persons at high risk and patients living in households with persons at high risk

All residents and staff members in long-term care institutions where there are patients at high risk during an institutional outbreak (for at least 14 days)

Consider for persons in the patient's household who are exposed

Treatment

All patients at high risk who develop influenza

Patients with severe influenza

Consider for use in patients with influenza who wish to shorten the duration of illness

Reprinted with permission from Couch RB. Prevention and treatment of influenza. N Engl J Med 2000;343:1784.

TABLE 4
Amantadine (Symmetrel) Dosing Guidelines in Patients with Renal Impairment

Creatinine clearance, mL per minute (mL per second)	*Suggested maintenance regimen*
30 to 50 (0.5 to 0.83)	100 mg daily*
15 to 29 (0.25 to 0.48)	100 mg every other day*
< 15 (0.25)	200 mg every seven days

**—Loading dose of 200 mg recommended on the first day in patients with creatinine clearance between 50 and 15 mL per minute.*

Information from Symmetrel [package insert]. Chadds Ford, Pa.: Endo Pharmaceuticals, 2002.

high-risk patients, prophylaxis against RSV should be considered. During the winter months, monthly administration of intravenous RSV immune globulin (RespiGam) or intramuscular palivizumab (Synagis) may decrease the number of RSV episodes. Because of increased morbidity, RSV immune globulin should not be given to patients with congenital heart disease.

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