

MMWR

*Recommendations
and
Reports*

MORBIDITY AND MORTALITY WEEKLY REPORT

Prevention and Control of Influenza: Part II, Antiviral Agents

**Recommendations of the Advisory
Committee on Immunization Practices (ACIP)**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Prevention and Control of Influenza: Part II, Antiviral Agents Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

These recommendations provide information about two antiviral agents: amantadine hydrochloride and rimantadine hydrochloride. These recommendations supersede MMWR 1992;41(No. RR-9). The primary changes include information about the recently licensed drug rimantadine, expanded information on the potential for adverse reactions to amantadine and rimantadine, and guidelines for the use of these drugs among certain persons.

INTRODUCTION

The two antiviral agents with specific activity against influenza A viruses are amantadine hydrochloride and rimantadine hydrochloride. These chemically related drugs interfere with the replication cycle of type A (but not type B) influenza viruses. When administered prophylactically to healthy adults or children before and throughout the epidemic period, both drugs are approximately 70%–90% effective in preventing illness caused by naturally occurring strains of type A influenza viruses. Because antiviral agents taken prophylactically may prevent illness but not subclinical infection, some persons who take these drugs may still develop immune responses that will protect them when they are exposed to antigenically related viruses in later years.

In otherwise healthy adults, amantadine and rimantadine can reduce the severity and duration of signs and symptoms of influenza A illness when administered within 48 hours of illness onset. Studies evaluating the efficacy of treatment for children with either amantadine or rimantadine are limited. Amantadine was approved for treatment and prophylaxis of all influenza type A virus infections in 1976. Although few placebo-controlled studies were conducted to determine the efficacy of amantadine treatment among children prior to approval, amantadine is indicated for treatment and prophylaxis of adults and children ≥ 1 year of age. Rimantadine was approved in 1993 for treatment and prophylaxis in adults but was approved only for prophylaxis in children. Further studies may provide the data needed to support future approval of rimantadine treatment in this age group.

As with all drugs, amantadine and rimantadine may cause adverse reactions in some persons. Such adverse reactions are rarely severe; however, for some categories of patients, severe adverse reactions are more likely to occur. Amantadine has been associated with a higher incidence of adverse central nervous system (CNS) reactions than rimantadine (see Considerations for Selecting Amantadine or Rimantadine for Chemoprophylaxis or Treatment).

RECOMMENDATIONS FOR THE USE OF AMANTADINE AND RIMANTADINE

Use as Prophylaxis

Chemoprophylaxis is not a substitute for vaccination. Recommendations for chemoprophylaxis are provided primarily to help health-care providers make decisions regarding persons who are at greatest risk of severe illness and complications if infected with influenza A virus (i.e., persons at high risk). Groups at high risk for influenza-related complications include:

- persons ≥ 65 years of age;
- residents of nursing homes and other chronic-care facilities that house persons of any age with chronic medical conditions;
- adults and children with chronic disorders of the pulmonary or cardiovascular systems, including children with asthma;
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications); and
- children and teenagers (6 months–18 years of age) who are receiving long-term aspirin therapy and therefore may be at risk for developing Reye syndrome after influenza.

When amantadine or rimantadine is administered as prophylaxis, factors such as cost, compliance, and potential side effects should be considered when determining the period of prophylaxis. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost effective, amantadine or rimantadine prophylaxis should be taken only during the period of peak influenza activity in a community.

Persons at High Risk Vaccinated After Influenza A Activity Has Begun

Persons at high risk can still be vaccinated after an outbreak of influenza A has begun in a community. However, the development of antibodies in adults after vaccination can take as long as 2 weeks, during which time chemoprophylaxis should be considered. Children who receive influenza vaccine for the first time may require as long as 6 weeks of prophylaxis (i.e., prophylaxis for 2 weeks after the second dose of vaccine has been received). Amantadine and rimantadine do not interfere with the antibody response to the vaccine.

Persons Providing Care to Those at High Risk

To reduce the spread of virus to persons at high risk, chemoprophylaxis may be considered during community outbreaks for a) unvaccinated persons who have frequent contact with persons at high risk (e.g., household members, visiting nurses, and volunteer workers) and b) unvaccinated employees of hospitals, clinics, and chronic-care facilities. For those persons who cannot be vaccinated, chemoprophylaxis during the period of peak influenza activity may be considered. For those persons who

receive vaccine at a time when influenza A is present in the community, chemoprophylaxis can be administered for 2 weeks after vaccination. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that may not be controlled by the vaccine.

Persons Who Have Immune Deficiency

Chemoprophylaxis may be indicated for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons with human immunodeficiency virus (HIV) infection, especially those with advanced HIV disease. No data are available on possible interactions with other drugs used in the management of patients with HIV infection. Such patients should be monitored closely if amantadine or rimantadine chemoprophylaxis is administered.

Persons for Whom Influenza Vaccine Is Contraindicated

Chemoprophylaxis throughout the influenza season or during peak influenza activity may be appropriate for persons at high risk who should not be vaccinated. Influenza vaccine may be contraindicated in persons with severe anaphylactic hypersensitivity to egg protein or other vaccine components.

Other Persons

Amantadine or rimantadine also can be administered prophylactically to anyone who wishes to avoid influenza A illness. The health-care provider and patient should make this decision on an individual basis.

Use of Antivirals as Therapy

Amantadine and rimantadine can reduce the severity and shorten the duration of influenza A illness among healthy adults when administered within 48 hours of illness onset. Whether antiviral therapy will prevent complications of influenza type A among high-risk persons is unknown. Insufficient data exist to determine the efficacy of rimantadine treatment in children. Thus, rimantadine is currently approved only for prophylaxis in children, but it is not approved for treatment in this age group.

Amantadine- and rimantadine-resistant influenza A viruses can emerge when either of these drugs is administered for treatment; amantadine-resistant strains are cross-resistant to rimantadine and vice versa. Both the frequency with which resistant viruses emerge and the extent of their transmission are unknown, but data indicate that amantadine- and rimantadine-resistant viruses are no more virulent or transmissible than amantadine- and rimantadine-sensitive viruses.

The screening of naturally occurring epidemic strains of influenza type A has rarely detected amantadine- and rimantadine-resistant viruses. Resistant viruses have most frequently been isolated from persons taking one of these drugs as therapy for influenza A infection. Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy. Persons who have influenza-like illness should avoid contact with uninfected persons as much as possible, regardless of whether they are being treated with amantadine or rimantadine. Persons who have influenza type A infection and who are treated with either drug may shed amantadine- or rimantadine-

sensitive viruses early in the course of treatment, but may later shed drug-resistant viruses, especially after 5–7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge; however, they also can transmit infection to other persons with whom they come in contact. Because of possible induction of amantadine or rimantadine resistance, treatment of persons who have influenza-like illness should be discontinued as soon as clinically warranted, generally after 3–5 days of treatment or within 24–48 hours after the disappearance of signs and symptoms. Laboratory isolation of influenza viruses obtained from persons who are receiving amantadine or rimantadine should be reported to CDC through state health departments, and the isolates should be saved for antiviral sensitivity testing.

Outbreak Control in Institutions

When confirmed or suspected outbreaks of influenza A occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. Contingency planning is needed to ensure rapid administration of amantadine or rimantadine to residents. This planning should include preapproved medication orders or plans to obtain physicians' orders on short notice. When amantadine or rimantadine is used for outbreak control, the drug should be administered to all residents of the institution—regardless of whether they received influenza vaccine the previous fall. The drug should be continued for at least 2 weeks or until approximately 1 week after the end of the outbreak. The dose for each resident should be determined after consulting the dosage recommendations and precautions (see Considerations for Selecting Amantadine or Rimantadine for Chemoprophylaxis or Treatment) and the manufacturer's package insert. To reduce the spread of virus and to minimize disruption of patient care, chemoprophylaxis also can be offered to unvaccinated staff who provide care to persons at high risk. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that is not controlled by the vaccine.

Chemoprophylaxis also may be considered for controlling influenza A outbreaks in other closed or semi-closed settings (e.g., dormitories or other settings where persons live in close proximity). To reduce the spread of infection and the chances of prophylaxis failure due to transmission of drug-resistant virus, measures should be taken to reduce contact as much as possible between persons on chemoprophylaxis and those taking drug for treatment.

CONSIDERATIONS FOR SELECTING AMANTADINE OR RIMANTADINE FOR CHEMOPROPHYLAXIS OR TREATMENT

Side Effects/Toxicity

Despite the similarities between the two drugs, amantadine and rimantadine differ in their pharmacokinetic properties. More than 90% of amantadine is excreted unchanged, whereas approximately 75% of rimantadine is metabolized by the liver. However, both drugs and their metabolites are excreted by the kidney.

The pharmacokinetic differences between amantadine and rimantadine may partially explain differences in side effects. Although both drugs can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day, the incidence of CNS side effects (e.g., nervousness, anxiety, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine compared with those taking rimantadine. In a 6-week study of prophylaxis in healthy adults, approximately 6% of participants taking rimantadine at a dose of 200 mg/day experienced at least one CNS symptom, compared with approximately 14% of those taking the same dose of amantadine and 4% of those taking placebo. The incidence of gastrointestinal side effects (e.g., nausea and anorexia) is approximately 3% in persons taking either drug, compared with 1%–2% of persons receiving the placebo. Side effects associated with both drugs are usually mild and cease soon after discontinuing the drug. Side effects may diminish or disappear after the first week despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among elderly persons who have been taking amantadine as prophylaxis at a dose of 200 mg/day. Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects, and recommendations for reduced dosages for these groups of patients have been made. Because rimantadine has only recently been approved for marketing, its safety in certain patient populations (e.g., chronically ill and elderly persons) has been evaluated less frequently. Clinical trials of rimantadine have more commonly involved young, healthy persons.

Providers should review the package insert before using amantadine or rimantadine for any patient. The patient's age, weight, renal function, other medications, presence of other medical conditions, and indications for use of amantadine or rimantadine (prophylaxis or therapy) must be considered, and the dosage and duration of treatment must be adjusted appropriately. Modifications in dosage may be required for persons who have impaired renal or hepatic function, the elderly, children, and persons with a history of seizures. The following are guidelines for the use of amantadine and rimantadine in certain patient populations. Dosage recommendations are also summarized (Table 1).

Persons Who Have Impaired Renal Function

Amantadine

Amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion. Thus, renal clearance of amantadine is reduced substantially in persons with renal insufficiency. A reduction in dosage is recommended for patients with creatinine clearance ≤ 50 mL/min. Guidelines for amantadine dosage based on creatinine clearance are found in the packet insert. However, because recommended dosages based on creatinine clearance may provide only an approximation of the optimal dose for a given patient, such persons should be observed carefully so that adverse reactions can be recognized promptly and either the dose can be further

reduced or the drug can be discontinued, if necessary. Hemodialysis contributes little to drug clearance.

Rimantadine

The safety and pharmacokinetics of rimantadine among patients with renal insufficiency have been evaluated only after single-dose administration. Further studies are needed to determine the multiple-dose pharmacokinetics and the most appropriate dosages for these patients.

In a single-dose study of patients with anuric renal failure, the apparent clearance of rimantadine was approximately 40% lower, and the elimination half-life was approximately 1.6-fold greater than that in healthy controls of the same age. Hemodialysis did not contribute to drug clearance. In studies among persons with less severe renal disease, drug clearance was also reduced, and plasma concentrations were

TABLE 1. Recommended dosage for amantadine and rimantadine treatment and prophylaxis

Antiviral	Age			
	1-9 yrs	10-13 yrs	14-64 yrs	≥65 years
Amantadine*				
Treatment	5 mg/kg/day up to 150 mg [†] in two divided doses	100 mg twice daily [§]	100 mg twice daily	≤100 mg/day
Prophylaxis	5 mg/kg/day up to 150 mg [†] in two divided doses	100 mg twice daily [§]	100 mg twice daily	≤100 mg/day
Rimantadine[¶]				
Treatment	NA	NA	100 mg twice daily	100 or 200** mg/day
Prophylaxis	5 mg/kg/day up to 150 mg [†] in two divided doses	100 mg twice daily [§]	100 mg twice daily	100 or 200** mg/day

NOTE: Amantadine manufacturers include: Dupont Pharma (Symmetrel[®]—syrup); Solvay Pharmaceuticals (Symadine[™]—capsule); Chase Pharmaceuticals and Invamed (Amantadine HCL—capsule). Rimantadine is manufactured by Forest Laboratories (Flumandine[®]—tablet and syrup).

* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 mL/min.

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

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

¶ A reduction in dose 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 should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

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

NA=Not applicable.

higher compared with control patients without renal disease who were the same weight, age, and sex.

A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance ≤ 10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including elderly persons, should be monitored for adverse effects, and either the dosage should be reduced or the drug should be discontinued, if necessary.

Persons ≥ 65 Years of Age

Amantadine

Because renal function declines with increasing age, the daily dose for persons ≥ 65 years of age should not exceed 100 mg for prophylaxis or treatment. For some elderly persons, the dose should be further reduced. Studies suggest that because of their smaller average body size, elderly women are more likely than elderly men to experience side effects at a daily dose of 100 mg.

Rimantadine

The incidence and severity of CNS side effects among elderly persons appear to be substantially lower among those taking rimantadine at a dose of 200 mg/day compared with elderly persons taking the same dose of amantadine. However, when rimantadine has been administered at a dosage of 200 mg/day to chronically ill elderly persons, they have had a higher incidence of CNS and gastrointestinal symptoms than healthy, younger persons taking rimantadine at the same dosage. After long-term administration of rimantadine at a dosage of 200 mg/day, serum rimantadine concentrations among elderly nursing-home residents have been two to four times greater than those reported in younger adults.

The dosage of rimantadine should be reduced to 100 mg/day for treatment or prophylaxis of elderly nursing-home residents. Although further studies are needed to determine the optimal dose for other elderly persons, a reduction in dosage to 100 mg/day should be considered for all persons ≥ 65 years of age if they experience signs and symptoms that may represent side effects when taking a dosage of 200 mg/day.

Persons Who Have Liver Disease

Amantadine

No increase in adverse reactions to amantadine has been observed among persons with liver disease.

Rimantadine

The safety and pharmacokinetics of rimantadine have only been evaluated after single-dose administration. In a study of persons with chronic liver disease (most with stabilized cirrhosis), no alterations were observed after a single dose. However, in persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease. A dose reduction to 100 mg/day is recommended for persons with severe hepatic dysfunction.

Persons Who Have Seizure Disorders

Amantadine

An increased incidence of seizures has been reported in patients with a history of seizure disorders who have received amantadine. Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine

In clinical trials, seizures (or seizure-like activity) have been observed in a few persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine. The extent to which rimantadine may increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated, because such persons have usually been excluded from participating in clinical trials of rimantadine.

Children

Amantadine

The use of amantadine in children <1 year of age has not been adequately evaluated. The FDA-approved dosage for children 1–9 years of age is 4.4–8.8 mg/kg/day, not to exceed 150 mg/day. Although further studies to determine the optimal dosage for children are needed, physicians should consider prescribing only 5 mg/kg/day (not to exceed 150 mg/day) to reduce the risk for toxicity. The approved dosage for children ≥10 years of age is 200 mg/day; however, for children weighing <40 kg, prescribing 5 mg/kg/day, regardless of age, is advisable.

Rimantadine

The use of rimantadine in children <1 year of age has not been adequately evaluated. In children 1–9 years of age, rimantadine should be administered in one or two divided doses at a dosage of 5 mg/kg/day, not to exceed 150 mg/day. The approved dosage for children ≥10 years of age is 200 mg/day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg/day, regardless of age, also is recommended.

Drug Interactions

Amantadine

Careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS, especially CNS stimulants.

Rimantadine

No clinically significant drug interactions have been identified. For more detailed information concerning potential drug interactions for either drug, the package insert should be consulted.

SOURCES OF INFORMATION ON INFLUENZA-CONTROL PROGRAMS

Information regarding influenza surveillance is available through the CDC Voice Information System (influenza update), telephone (404) 332-4551, or through the CDC Information Service on the Public Health Network electronic bulletin board. From October through May, the information is updated at least every other week. In addition, periodic updates about influenza are published in the weekly *MMWR*. State and local health departments should be consulted regarding availability of influenza vaccine, access to vaccination programs, and information about state or local influenza activity.

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