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*Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices**

Part Two, Antiviral Treatment

ANTIVIRAL AGENTS FOR INFLUENZA A

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 can prevent illness but not subclinical infection, some persons who take these drugs can 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 might provide the data needed to support future approval of rimantadine treatment in this age group.

As with all drugs, amantadine and rimantadine can 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 for severe illness and complications if infected with influenza A virus.

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 can require as long as 6 weeks of prophylaxis (i.e., prophylaxis for 2 weeks after the second dose of vaccine has been received). Aman-

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tadine 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 might not be controlled by the vaccine.

Persons Who Have Immune Deficiency

Chemoprophylaxis might be indicated for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons who have HIV infection, especially those who have advanced HIV disease. No data are available concerning possible interactions with other drugs used in the management of patients who have 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 might be appropriate for persons at high risk who should not be vaccinated. Influenza vaccine may be contraindicated in persons who have 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 persons at high risk 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 can shed amantadine- or rimantadine-sensitive viruses early in the course of treatment, but can 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.

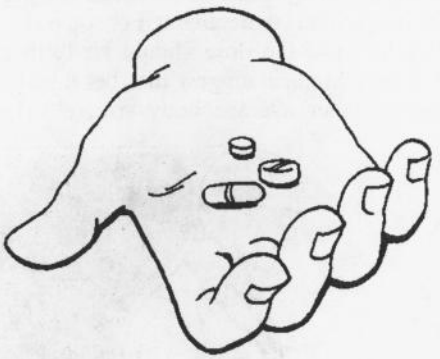
Chemoprophylaxis also may be considered for controlling influenza A outbreaks in other closed or semi-closed settings (e.g., dormitories or other settings where persons live in close proximity). To reduce the spread of infection and the chances of prophylaxis failure due to transmission of drug-resistant 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 might 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% among persons taking either drug, compared with 1%-2% among persons receiving the placebo. Side effects associated with both drugs are usually mild and cease soon after discontinuing the drug. Side effects can 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, and renal function; the presence of other medical conditions; the indications for use of amantadine or rimantadine (i.e., prophylaxis or therapy); and the potential for interaction with other medications must be considered, and the dosage and duration of treatment must be adjusted appropriately. Modifications in dosage might 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 2).

TABLE 2. Recommended dosage for amantadine and rimantadine treatment and prophylaxis

Antiviral Agent	Age			
	1-9 years	10-13 years	14-64 years	≥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); and Copley Pharmaceuticals, Barre National, and Mikart (Amantadine HCL - syrup). 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 of rimantadine 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.

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 might 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 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 might 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 might 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 interactions between rimantadine and other drugs 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.

MMWR 44(RR-3);1-22 April 21, 1995.

*Recommendations for Test Performance and Interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease**

The Association of State and Territorial Public Health Laboratory Directors, CDC, the Food and Drug Administration, the National Institutes of Health, the Council of State and Territorial Epidemiologists, and the National Committee for Clinical Laboratory Standards co-sponsored the Second National Conference on Serologic Diagnosis of Lyme Disease held October 27-29, 1994. Conference recommendations were grouped into four categories:

1. **Serologic test performance and interpretation,**
2. **Quality-assurance practices,**
3. **New test evaluation and clearance, and**
4. **Communication of developments in Lyme disease (LD) testing.**

This report presents recommendations for serologic test performance and interpretation, which include substantial changes in the recommended tests and their interpretation for the serodiagnosis of LD.

A two-test approach for active disease and for previous infection using a sensitive enzyme immunoassay (EIA) or immunofluorescent assay (IFA) followed by a Western immunoblot was the algorithm of choice. All specimens positive or equivocal by a sensitive EIA or IFA should be tested by a standardized Western immunoblot. Specimens negative by a sensitive EIA or IFA need not be tested further. When Western immunoblot is used during the first four weeks of disease onset (early LD), both immunoglobulin M (IgM) and immunoglobulin G (IgG) procedures should be performed. A positive IgM test result alone is not recommended for use in determining active disease in persons with illness >1 month's duration because the likelihood of a false-positive test result for a current infection is high for these persons. If a patient with suspected early LD has a negative serology, serologic evidence of infection is best obtained by testing of paired acute- and convalescent-phase serum samples. Serum samples from persons with disseminated or late-stage LD almost always have a strong IgG response to *Borrelia burgdorferi* antigens.

It was recommended that an IgM immunoblot be considered positive if two of the following three bands are present: 24 kDa (OspC)[†], 39 kDa (BmpA), and 41 kDa (Fla)[1]. It was further recommended that an IgG immunoblot be considered positive if five of the following ten bands are present: 18kDa, 21 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa[2].

The details of both plenary sessions and the work group deliberations are included in the publication of the proceedings, which are available from the Association of State and Territorial Public Health Laboratory Directors; telephone (202)822-5227.

References

1. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. J Clin Microbiol 1995;33:419-422.

2. Dressler F, Whelan JA, Reinhart BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis 1993;167:392-400.

[†]The apparent molecular mass of OspC is dependent on the strain of B. burgdorferi being tested. The 24 kDa and 21 kDa proteins referred to are the same.

**MMWR 44(31);590-91 Aug 11, 1995.*

Cases of Selected Notifiable Diseases, Virginia, August 1 through August 31, 1995.*

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
	State	Regions					This Yr	Last Yr	5 Yr Avg
		NW	N	SW	C	E			
AIDS	121	3	22	9	41	46	876	732	664
Campylobacteriosis	77	15	17	10	22	13	406	500	431
Giardiasis§	32	3	13	6	3	7	164	192	206
Gonorrhea	984	37	87	135	312	413	7253	8501	10008
Hepatitis A	25	0	14	7	3	1	133	108	116
Hepatitis B	16	4	2	3	1	6	75	84	124
Hepatitis NANB	0	0	0	0	0	0	9	18	24
HIV Infection§	137	0	8	8	15	106	767	683	876
Influenza	2	0	0	2	0	0	876	823	684
Legionellosis	5	3	2	0	0	0	13	5	8
Lyme Disease	7	2	3	0	0	2	37	105	81
Measles	0	0	0	0	0	0	0	2	24
Meningitis, Aseptic	172	14	35	8	14	101	356	152	174
Meningitis, Bacterial†	10	4	3	1	1	1	96	55	78
Meningococcal Infections	5	0	0	1	2	2	46	52	40
Mumps	1	0	0	0	0	1	16	32	47
Pertussis	0	0	0	0	0	0	10	27	22
Rabies in Animals	22	8	3	4	4	3	267	262	209
Rocky Mountain Spotted Fever	7	2	0	2	2	1	18	12	12
Rubella	0	0	0	0	0	0	0	0	0
Salmonellosis	141	12	45	15	47	22	671	689	714
Shigellosis	56	3	22	0	7	24	191	516	299
Syphilis, Early‡	121	2	6	5	20	88	844	918	994
Tuberculosis	16	0	5	3	4	4	167	210	250

Localities Reporting Animal Rabies: Accomack 1 raccoon; Augusta 1 skunk; Buckingham 1 cat; Carroll 1 cat; Chesterfield 1 raccoon; Culpeper 1 raccoon; Dinwiddie 1 raccoon; Fairfax 1 raccoon; Grayson 1 raccoon; King William 1 raccoon; Loudoun 1 raccoon; Page 1 skunk; Pittsylvania 1 raccoon; Prince William 1 groundhog; Shenandoah 1 raccoon, 1 skunk; Smyth 1 raccoon; Spotsylvania 1 fox; Stafford 1 raccoon; Sussex 1 raccoon; Virginia Beach 1 raccoon; Warren 1 raccoon.
Occupational Illnesses: Asbestosis 6; Carpal Tunnel Syndrome 48; Coal Workers' Pneumoconiosis 17; Lead Poisoning 3; Loss of Hearing 17.

*Data for 1995 are provisional.
†Other than meningococcal.
‡ Includes primary, secondary, and early latent.
§Giardiasis and HIV infection have replaced Kawasaki and Reye Syndromes in this table. This change was based on the current number of reports of these diseases and their public health significance.

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