disease prevention news

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Prevention and Control of Influenza, Part II
Antiviral Agents for Influenza A

This report is a summary of the Advisory Committee on Immunization Practices (ACIP), recommendations for the use of specific antiviral drugs for prophylaxis or treatment of influenza A infections during the 1996-97 Season. These recommendations supersede those published last year (MMWR 44/No. RR- 3:1-22)

Two chemically related drugs, amantadine hydrochloride and rimantadine hydrochloride, exert specific activity against influenza A viruses. These antiviral drugs interfere with the replication cycle of type A (but not type B) influenza viruses. When administered as prophylaxis to healthy adults or children before and during the influenza epidemic period, both drugs are approximately 70% to 90% effective in preventing illness due to influenza A viruses. These drugs, however, may not prevent subclinical infection, and some persons who become infected while receiving prophylaxis may develop an immune response to the type A virus in circulation. This immune response should provide these individuals some degree of protection when challenged with an antigenically similar virus in the future.

In previously healthy adults, amantadine and rimantadine can reduce the severity and duration of signs and symptoms of influenza illness when administered within 48 hours of onset. Amantadine was approved for treatment and prophylaxis of all influenza A virus infections in 1976. Adults and children 1 year of age and older may receive amantadine for either treatment or prophylaxis. In contrast, rimantadine, while approved for use in treatment or prophylaxis of adults, is approved only for prophylaxis in children. Rimantadine was approved in 1993.

Both amantadine and rimantadine can cause adverse reactions in some persons, although such adverse reactions are rarely severe. Amantadine has been associated with a higher incidence rate of central nervous system (CNS) reactions than has rimantadine.

Use of Antivirals as Prophylaxis

Chemoprophylaxis is not a substitute for vaccination. To be maximally effective as prophylaxis, either drug must be taken daily during the local influenza A season. Factors to consider in this decision are cost, compliance, and potential side effects. To be most cost-effective, either drug should be given only during the period of peak virus activity.

The following population groups are candidates for chemoprophylaxis during influenza A seasons:

- Medically high-risk persons who are vaccinated after influenza A activity has begun
- Persons who provide care to medically high-risk persons
- Persons who have immune deficiencies regardless of cause (Because there are no data regarding the potential for drug interactions with other drugs used in the management of HIV-infected persons, such patients should be monitored closely if amantadine or rimantadine chemoprophylaxis is given.)
- Persons for whom influenza vaccine is contraindicated
- Persons who wish to avoid influenza viral illness, but have not been vaccinated (following consultation with their health care providers.)

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Use of Antivirals as Therapy

Amantadine can be used for treatment of influenza A virus infections for both adults and children 1 year of age and older. Since there are insufficient data on which to determine the efficacy of rimantadine treatment in children, current use of rimantadine for pediatric patients is limited to prophylaxis only.

Amantadine- and rimantadine-resistant influenza A viruses can emerge when either drug is administered for treatment. Although the frequency of this emergence occurring and the extent of emergent virus transmission is not known, clinical studies indicate that the drug-resistant viruses are no more virulent or transmissible than are amantadine- and rimantadine-sensitive viruses. Persons who are household or institutional contacts of persons who are receiving or have received amantadine or rimantadine as therapy can be carriers of drug-resistant viruses even if they are not ill themselves. Persons who receive either drug for the treatment of influenza A infection can shed amantadine- or rimantadine-sensitive viruses early in the course of therapy, but can later shed drug-resistant viruses, especially after 5 to 7 days of treatment. Because of the possible induction of drug-resistance, treatment of persons who have influenza-like illness (ILI) should be discontinued as soon as clinically warranted, generally after 3 to 5 days of treatment, or within 24 to 48 hours of the cessation of signs and symptoms.

. . . the incidence of CNS side effects is higher among persons taking amantadine than among those taking rimantadine.

Use of Antivirals for Outbreak Control in Institutions

When confirmed or suspected outbreaks of influenza A occur in institutions that house high-risk populations, chemoprophylaxis should be started as early as possible to reduce the spread of virus. Health care facilities should have rapid implementation strategies in place to ensure adequate supplies of either drug and pre-approved medication orders or standing physicians' orders so that prophylaxis can be initiated on short notice.

When amantadine or rimantadine is given prophylactically, the drug should be given to all residents of the institution, regardless of whether they have received influenza vaccine that season. The drug should be continued for at least 2 weeks or until approximately 1 week after the end of the outbreak. Chemoprophylaxis may also be offered to unvaccinated staff who provide care to high-risk persons. Prophylaxis should also be considered for all employees of the institution, regardless of vaccination status, if the outbreak is caused by an influenza A virus strain that is not covered by the current vaccine. Chemoprophylaxis may also be considered for persons in other closed group settings, such as dormitories. To reduce the potential for the induction of drug-resistant viruses, persons who are receiving amantadine or rimantadine prophylactically should minimize contact with persons taking either drug for treatment of influenza A infection.

Guidelines for Choosing Between Amantadine and Rimantadine

Key considerations for selecting either drug include evaluating the impact of side effects and toxicity, and assessing specific concerns about drug action in specific populations.

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

Although both drugs can cause central nervous system (CNS) and gastrointestinal side effects when given to young,

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healthy adults at equivalent dosages of 200 milligrams per day (Table 1), the incidence of CNS side effects (eg, nervousness, anxiety, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine. The incidence of gastrointestinal side effects (eg, nausea and anorexia) is approximately 3% among persons taking either drug. Side effects of either drug are usually mild and generally cease soon after the drug is discontinued. Serious side effects (eg, marked behavioral changes, hallucinations, delirium, agitation, and seizures) have been associated with high plasma drug concentrations and are most likely to be observed among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among elderly persons who are taking amantadine at a dosage of 200 mg/day for prophylaxis. Clinical studies have shown that lowering the dosage for these populations reduces the incidence and severity of these side effects.

Table 1. Recommended Dosage for Amantadine and Rimantadine Treatment and Prophylaxis by Age Group

Antiviral Agent	1-9 Yrs.	10-13 Yrs.	14-64 Yrs.	65 Yrs.
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 given 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 reduced or the drug discontinued if necessary.

** Chronically ill elderly persons (eg, 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.

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Providers should review the package insert before using amantadine or rimantadine for their patients. The patient's age, weight, and renal function; the presence of other medical conditions; the indications for use of amantadine or rimantadine (ie, prophylaxis or therapy); and the potential for interaction with other medications must be considered, and the dosage and duration of treatment must be adjusted accordingly. Dosage modification might be required for persons with impaired renal function, the elderly, children, and persons with a history of seizures.

Persons with Impaired Renal Function

Amantadine. Renal clearance of amantadine is reduced substantially in persons with impaired renal function. A reduction in dosage is recommended for patients with creatinine clearance of 50 milliliters per minute or less. The package insert provides guidelines for determining the appropriate dosage for these patients. Such patients, however, should be observed carefully so that adverse reactions can be recognized promptly and the dose further reduced or the drug discontinued.

Rimantadine. The safety and pharmacokinetics of rimantadine among patients with renal insufficiency have been evaluated only after single dose regimens. Because of the potential for accumulation of rimantadine and its metabolites, however, patients with renal insufficiency should be monitored for side effects. A reduction in dosage to 100 milligrams per day is recommended for persons with creatinine clearance $\leq$10 mL/min. If adverse effects are observed in patients taking rimantadine, either the dosage should be reduced or the drug discontinued.

Persons 65 Years of Age and Older

Amantadine. Renal function tends to decline with age. Therefore, the daily dose for persons $\geq$65 years of age should not exceed 100 mg for either prophylaxis or treatment. The daily dosage may need to be reduced further for patients with smaller than average body size.

Rimantadine. Among elderly persons taking 200 mg/day of either rimantadine or amantadine, those taking rimantadine appear to experience fewer and less severe CNS side effects. However, chronically ill elderly persons taking 200 mg rimantadine daily still experience a higher incidence of CNS and gastrointestinal side effects than do healthy, young adults on the same dosage. Consequently, these elderly patients may need to have the dosage reduced to 100 mg/day.

Persons with Liver Disease

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

Rimantadine. Evaluation of the safety and kinetics of single-dose regimens of rimantadine suggests that clearance of the drug is reduced in persons with liver disease. Therefore, a dose reduction to 100 mg/day is recommended for these individuals.

Persons with Seizure Disorders

Amantadine. Since there is increased incidence of seizures reported among patients with a history of seizures who are taking amantadine, these patients need to be monitored closely for increased seizure activity while on an influenza antiviral regimen.

Rimantadine. Rimantadine has not been evaluated extensively in this patient group, although seizures have been observed in a few persons with a history of seizures who were not receiving anticonvulsant medication while on rimantadine.

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Children

Amantadine. The approved dosage for children ≥10 years of age is 200 mg/day; however, for children weighing less than 40 kilograms, a dosage of 5 mg/kg/day is advisable. The use of amantadine in children younger than 1 year of age has not been evaluated adequately. The approved dosage for children 1 to 9 years of age is 4.4-8.8 mg/kg/day, not to exceed 150 mg/day. Physicians may consider dosages of 5 mg/kg/day (not to exceed 150 mg/day) to reduce toxicity.

Rimantadine. The use of rimantadine in children <1 year of age has not been adequately evaluated. In children 1 to 9 years of age, rimantadine should be given in 1 or 2 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 100 mg twice a day; however, for children weighing <40 kg, a dosage of 5 mg/kg/day is advisable.

Drug Interactions

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

Rimantadine. No clinically significant interactions between rimantadine and other drugs have been described.

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Adapted from: CDC. Recommendations and Reports. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR 1996; 45(RR-5).

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FluLine

Wondering what strains of influenza are circulating in your county? Coming soon to the TDH homepage is an influenza site with vaccine information and state maps showing counties with positive isolates. Check out "What's New" at **http://tdh.texas.gov**.

Texas Health Steps

The Texas Department of Health endorses an approach to health care that emphasizes preventive and primary care as the most efficient and cost-effective ways to improve Texans' health. Texas Health Steps (THSteps) is the Texas version of the Medicaid program known as Early and Periodic Screening, Diagnosis and Treatment (EPSDT) Program. The mission of the THSteps is to provide preventive and primary health and dental care to Medicaid-eligible youth from birth through 20 years of age. Through THSteps, clients receive regularly scheduled medical and dental checkups at no charge, as well as treatment for problems discovered during the checkups. In case of illness or emergency, a client may see a doctor through the Medicaid Program. The following services are provided by THSteps:

◆ Medical Checkups

- medical history
- complete physical examination
- assessment of nutritional, developmental, and mental health needs
- laboratory tests (including lead screening)
- routine immunizations
- health education
- vision screening
- hearing screening
- referrals to other health care providers as needed

◆ Dental Services

THSteps clients are eligible for routine dental checkups every 6 months starting at 1 year of age and for a full range of dental services at any age.

◆ Vision Services

Each THSteps health checkup includes a vision screen. THSteps provides one eye examination per state fiscal year (September through August) and eyeglasses every 2 years. The clients may receive additional services if those services are medically necessary due to a change in vision.

◆ Hearing Services

Each THSteps health checkup includes a hearing screen. THSteps also provides testing and treatment of hearing problems. Hearing aids are available through the Program for Amplification for Children of Texas (PACT) administered by TDH. All services must approved in advance.

◆ Comprehensive Care Program (CCP)

Children and adults younger than 21 years of age are eligible for any medically necessary and appropriate health care service that is covered by Medicaid, regardless of the limitations of the current Texas Medical Program.

For additional information contact Rosemary G. Morris, MSW, LMSW-AP, at (512) 458-7745.

New HIV Treatment Promising, but Presents Challenges for Effective Treatment of Tuberculosis

In 1995 and 1996, the Food and Drug Administration (FDA) approved three products in the new protease inhibitor class of drugs: saquinavir, indinavir, and ritonavir. Another drug in this class of agents, nelfinavir, is expected to be available soon. Because these new drugs have been shown to interrupt the production of new infectious viruses in cells infected with human immunodeficiency virus (HIV), they are the most potent antiretroviral agents available to treat patients with HIV disease.

However, this new HIV therapy can cause problems for patients also being treated for tuberculosis. Rifamycin derivatives such as rifampin and rifabutin, are used to treat and prevent the mycobacterial infections commonly observed in HIV-infected patients. Rifamycins accelerate the metabolism of protease inhibitors, resulting in subtherapeutic levels of the protease inhibitors. In addition, protease inhibitors retard the metabolism of rifamycins, resulting in increased serum levels of rifamycins and the likelihood of increased drug toxicity.

In HIV infected individuals, TB disease can be fulminant if not effectively treated, sometimes leading to death in a matter of weeks. Rifampin is one of the most effective drugs available to treat tuberculosis. Without the use of rifampin, or with a reduced dosage, the treatment time may be lengthened and its effectiveness decreased. Because of the common association of TB and HIV infection, an increasing number of patients probably will be considered candidates for rifamycins used in conjunction with protease inhibitors. Case management for these patients is complex; an individualized approach, which includes consultation with an expert, is essential.

The Centers for Disease Control and Prevention (CDC) has developed preliminary guidelines for medical care providers to help them choose the best protocol for treating TB disease in HIV-infected patients. The October 25 issue of MMWR (Vol.45/No.42) contains a report that describes management options for these patients and presents interim recommendations for treatment until additional data are available and formal guidelines are issued. This issue is available on the World Wide Web of the Internet at **http://www.cdc.gov/**. The TDH TB Elimination Division will provide copies of this CDC report upon request; call (512) 458-7447.

Physicians who need advice regarding treatment of TB disease in patients with HIV infection can call the Texas Center for Infectious Diseases at (800) 839-5864 or the Center for Pulmonary Infectious Disease Control at (800) 428-7432.

Errata/Addendum Re: Influenza

In the October 14, 1996 issue of DPN (Vol. 56 No. 21), on page 6, the code number for Medicare reimbursement for administrative costs of influenza vaccination is incorrect. **The correct number is G0008**. TDH would also like to remind providers of its recommendation to administer pneumococcal vaccine to high-risk persons simultaneously with their influenza vaccination. The Medicare reimbursement billing code for pneumococcal vaccine is **90732** and for administering the vaccine is **G0009**. *For further information regarding pneumococcal vaccination contact Kate Hendricks, MD, at (512) 458-7676.*

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Registration Form DPN

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