

Amantadine Hydrochloride

Adamantanes 8:18.04 (AHFS primary); am800 (VA primary)

■ Amantadine hydrochloride, an adamantane derivative, is a synthetic antiviral agent that is active against influenza A virus.

Uses

Amantadine hydrochloride is used for symptomatic *treatment* and for *prophylaxis* of signs and symptoms of infection caused by susceptible influenza A viruses.

For information on the use of amantadine in the treatment of parkinsonian syndrome and drug-induced extrapyramidal reactions, see Amantadine Hydrochloride 28:36.04.

■ Treatment of Seasonal Influenza A Virus Infections

Amantadine is used for the treatment of uncomplicated respiratory tract illness caused by influenza A virus infection.

Emergence of amantadine-resistant influenza virus may decrease effectiveness of the drug.

The US Centers for Disease Control and Prevention (CDC) issued interim recommendations concerning the use of antiviral agents for the treatment of influenza during the 2009–2010 influenza season. As of October 2009, more than 99% of influenza viruses circulating in the US were the 2009 influenza A (H1N1) virus susceptible to oseltamivir and zanamivir. (See Uses: 2009 Influenza A (H1N1) Virus Infections.) When treatment of influenza illness is indicated and seasonal influenza is suspected, oseltamivir or zanamivir should be used. If viral surveillance indicates that seasonal influenza A (H1N1) resistant to oseltamivir is circulating and treatment is indicated, CDC states zanamivir should be used; oseltamivir in conjunction with rimantadine or amantadine is an alternative.

The most appropriate antiviral for the treatment of influenza is selected based on information regarding the likelihood that the influenza strain is susceptible and the known adverse effects of the drug. The fact that strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolves should be considered.

CDC recommends that adamantanes (amantadine, rimantadine) *not* be used alone for the treatment of *seasonal* influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses. During the 2005–2006 influenza season, most influenza A (H3N2) strains circulating in the US were resistant to adamantanes (amantadine, rimantadine). Resistance to amantadine and rimantadine among influenza A isolates remained high during the 2006–2007 and 2007–2008 influenza seasons, especially in influenza A (H3N2). (See Resistant Strains of Influenza A Virus under Uses: Treatment of Influenza A Virus Infections.)

Information regarding influenza surveillance and updated recommendations for treatment of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

When amantadine has been used in otherwise healthy adults and children for symptomatic treatment of uncomplicated *seasonal* influenza caused by susceptible influenza A virus and administered within 24–48 hours after the onset of symptoms, the drug has decreased viral shedding and reduced the degree and duration of fever, headache, and respiratory symptoms with a more rapid return to routine daily activities and improvement in airway function. It is not known whether amantadine is effective for the symptomatic treatment of these infections in patients whose symptoms have been present for more than 48 hours since most controlled studies evaluating efficacy of the drug only included patients whose symptoms had been present for 48 hours or less. Some clinicians state that they would still consider use of the drug during an influenza epidemic in patients whose symptoms have been present for longer than 48 hours.

While amantadine and rimantadine generally are comparably effective in the treatment of influenza A infection caused by susceptible strains, some evidence suggests that symptomatic improvement during the initial 24 hours of therapy with usual dosages of amantadine may be somewhat faster than that with rimantadine, probably because of pharmacokinetic differences between the drugs. In addition, although adverse effects of the drugs are similar, rimantadine may be associated with less frequent and/or severe nervous system effects. Therefore, decisions regarding use of amantadine versus rimantadine for the treatment of influenza A infection should consider the patient's age, weight, and renal function; presence of other medical conditions; the potential for drug interactions; and the adverse effect profile and cost of the drug.

There have been no well-controlled studies to date to determine the efficacy of amantadine treatment in preventing serious complications of influenza A virus infection (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Most studies evaluating efficacy of amantadine for the treatment of influenza A infections have been performed in otherwise healthy adults and children with uncomplicated influenza; data are limited and inconclusive concerning efficacy of amantadine for treatment of influenza in individuals at high risk for serious influenza-related complications.

Resistant Strains of Influenza A Virus

Influenza A viruses resistant to adamantanes (amantadine, rimantadine) can occur spontaneously or emerge rapidly during treatment with the drugs. The worldwide incidence of influenza A viruses resistant to adamantanes (amantadine, rimantadine) has increased over the last several years. Between October 2005 and January 2006, approximately 90% of influenza A (H3N2) strains isolated in the US were resistant to adamantanes. Data from the 2006–2007 and 2007–2008 influenza seasons indicate that

the incidence of resistance to the adamantanes among influenza A isolates remained high, especially in influenza A (H3N2). (See Resistance.)

Amantadine- and rimantadine-resistant strains of influenza A virus may emerge in up to approximately 33% of patients receiving the drugs for treatment of influenza A infection. Individuals with influenza A infection who are receiving amantadine or rimantadine antiviral treatment may shed strains of the virus that are susceptible to the drugs early in the course of treatment; however, they also can shed resistant strains after 2–7 days of therapy. Immunocompromised patients may shed resistant strains for prolonged periods.

To minimize emergence of resistant strains, amantadine treatment should be discontinued as soon as clinically warranted, usually after 3–5 days or within 24–48 hours after the disappearance of signs and symptoms. Although most patients recover uneventfully even after resistant strains emerge (because of host immune responses), resistant strains are pathogenic and transmissible and can result in failures of drug prophylaxis in close contacts (e.g., family members, nursing home contacts). Individuals with influenza-like illness should be separated from and avoid contact with uninfected individuals as much as possible, regardless of whether they are receiving antiviral therapy.

Differential Diagnosis of Influenza and Influenza-like Illnesses

Early diagnosis of influenza infection can provide the option of using antiviral therapy and reduce unnecessary use of other anti-infective agents. The appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. Some bacterial infections, including some that can lead to potentially severe or life-threatening complications, can produce symptoms similar to influenza infection. In addition, bacterial infection can occur as a complication of influenza. The possibility of primary bacterial infection should be considered when making treatment decisions for patients with influenza-like illness, and clinicians evaluating such patients should consider a combination of epidemiologic, clinical, and, if indicated, laboratory and radiographic tests.

Influenza-like illness is a nonspecific respiratory illness characterized by fever, fatigue, cough, and other symptoms. Most cases are not caused by influenza, but by other viruses (e.g., rhinoviruses, respiratory syncytial virus [RSV], adenoviruses, parainfluenza viruses) or, less commonly, by bacteria (e.g., *Legionella*, *Chlamydia pneumoniae* [*Chlamydia pneumoniae*], *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*). In addition, several patients with inhalational anthrax that occurred in the US during September and October 2001 in the context of bioterrorism-related exposures to anthrax spores presented with symptoms of influenza-like illness. Therefore, the possibility of inhalational anthrax also should be considered when evaluating patients with influenza-like illness.

Adults or children can average 1–3 or 3–6 episodes of influenza-like illness, respectively, each year. Although influenza-like illness associated with influenza virus or RSV generally peaks during the winter; illness caused by rhinoviruses and parainfluenza viruses usually peaks during the fall and spring, and illness caused by adenoviruses occurs throughout the year. Respiratory illness caused by bacteria can occur throughout the year; however, illness caused by *S. pneumoniae* peaks during the winter and illness caused by *Mycoplasma* or *Legionella* is more common during the summer and fall.

Clinical Considerations.

The presence of certain signs or symptoms may help to distinguish the various causes of influenza-like illness. Nasal congestion and rhinorrhea are features of most cases of influenza-like illnesses, but are infrequent in patients with inhalational anthrax. Fever and/or chills, fatigue/malaise, cough (minimal or nonproductive), headache, myalgia, sore throat, and rhinorrhea are present in 64–94% of cases of laboratory-confirmed influenza. In patients with influenza-like illness from other viral or bacterial causes (except inhalational anthrax), these same symptoms are present in 62–94% of patients, although fever is present in only 40–73%. In these 2 groups of patients, nausea or vomiting occurs in 12%, abdominal pain in 22%, shortness of breath in 6%, and chest discomfort or pleuritic chest pain in 23–35%. In contrast, data from 10 patients with inhalational anthrax indicated that shortness of breath and chest discomfort or pleuritic chest pain occurred in 60–80%, nausea or vomiting in 80–90%, and abdominal pain in 30% of patients. In addition, 70% of these inhalational anthrax patients had profound, often drenching, sweats and all presented with fever or chills and fatigue/malaise, 90% with cough (minimal or nonproductive), 50% with headache, and 50–60% with myalgia, but only 20% presented with sore throat and only 10% had rhinorrhea.

Results of initial chest radiographs of 10 patients with inhalational anthrax indicated that 7 had mediastinal widening, 7 had infiltrates, and 8 had pleural effusion at the time of initial presentation; eventually pleural effusions were present in all of these patients. Although most cases of influenza-like illness are not associated with radiographic findings of pneumonia, this can occur among the very young and in geriatric patients and patients with chronic lung disease. Influenza-associated pneumonia occurs in approximately 1–5% of adults, and in greater than 20% of influenza-infected geriatric adults. Influenza-associated pneumonia might be caused by the primary virus infection or, more commonly, by bacterial infection occurring coincident with or following influenza illness.

Diagnostic Tests.

Several commercially available assays can be used for the rapid detection of influenza-like illnesses. Rapid tests for identification of influenza virus and RSV are available and, if used, should be done within the first 3–4 days of the illness when viral shedding is most likely. RSV antigen detection tests have a peak sensitivity of 75–95%

in infants but do not have enough sensitivity to warrant their routine use among adults. Several available influenza rapid detection assays (e.g., Quidel Quickvue Influenza, ZymeTx Zstatflu) have a reported sensitivity and specificity range of 45–90% and 60–95%, respectively, and can easily be done in the clinician’s office. However, the clinical usefulness of these tests for the diagnosis of influenza in individual patients is limited because the sensitivity of the tests is relatively low. In addition, none of the available tests provide information about the specific influenza A subtype. These rapid influenza tests should not be done on every individual presenting with influenza-like illness, but (if used with viral cultures) can help determine whether influenza viruses are circulating among specific populations (e.g., nursing home residents, patients attending a clinic). The use of viral culture, in addition to rapid diagnostic tests, remains important because only cultures can provide information on the circulating influenza subtypes and strains and are used to monitor for emergence of antiviral resistance and emergence of novel influenza A subtypes that might pose a pandemic threat.

Although there are no rapid screening tests to aid in diagnosis of inhalational anthrax in the early stages, blood cultures performed prior to initiation of anti-infective therapy can be diagnostic. However, blood cultures should not be obtained routinely in patients with influenza-like illness who have no probable exposure to anthrax, but should be obtained in individuals in situations in which bacteremia is suspected.

■ Prevention of Seasonal Influenza A Virus Infections

Amantadine is used for prophylaxis against signs and symptoms of influenza A virus infection.

Emergence of amantadine-resistant influenza virus may decrease effectiveness of the drug.

The most appropriate antiviral for prevention of influenza is selected based on information regarding the likelihood that the influenza strain is susceptible and the known adverse effects of the drug. The fact that strains of circulating influenza viruses and the antiviral susceptibility of these strains constantly evolves should be considered.

CDC recommends that adamantanes (amantadine, rimantadine) *not* be used for prevention of influenza in the US until susceptibility to these antiviral agents has been reestablished in circulating influenza A viruses. (See Resistant Strains of Influenza A Virus under Uses: Treatment of Influenza A Virus Infections.)

Information regarding influenza surveillance and updated recommendations for prevention of seasonal influenza are available from CDC at <http://www.cdc.gov/flu>.

Individuals who are candidates for antiviral prophylaxis should receive the agent most likely to be effective against the influenza virus that caused the outbreak (if known).

Annual vaccination with influenza virus vaccine inactivated or influenza virus vaccine live intranasal, as recommended by the US Public Health Service Advisory Committee on Immunization Practices (ACIP), is considered the primary means of preventing *seasonal* influenza and its severe complications. However, prophylaxis with an appropriate antiviral agent is an important adjunct for the control and prevention of influenza.

Studies using amantadine or rimantadine for the prophylaxis of *seasonal* influenza A infection indicate that these drugs are about 60–90% effective in preventing illness from influenza A infection when strains are susceptible to the drugs. While amantadine and rimantadine are only effective in preventing influenza A infections, oseltamivir and zanamivir can be effective in preventing both influenza A and influenza B infections when strains are susceptible to the drugs. Studies using oseltamivir or zanamivir for the prophylaxis of influenza infection indicate that these drugs are about 82–84% effective in preventing febrile, laboratory-confirmed influenza A or B illness caused by susceptible strains. Data are not available to date regarding the efficacy of any of these antiviral agents in preventing influenza in individuals who are severely immunocompromised.

Results of numerous studies indicate that amantadine is about 60–90% effective in preventing influenza caused by susceptible strains of influenza A. Clinical studies indicate that amantadine is as effective as rimantadine or influenza vaccination in preventing influenza A illness. The protective effect of amantadine or rimantadine and influenza vaccination may be additive. In contrast to results of studies evaluating efficacy when antiviral prophylaxis is given for a season or part of a season, results of studies evaluating antiviral prophylaxis with amantadine or rimantadine after a known exposure have not been consistent. While postexposure prophylaxis with amantadine or rimantadine provided protection in families when the index case did not receive antiviral therapy, the drugs did not provide protection from influenza A infection in household contacts when amantadine or rimantadine was used to treat the index case, presumably because of spread of resistant virus within the household.

Adjunctive Prophylaxis with Influenza Virus Vaccine

Individuals at high risk for influenza complications still can be vaccinated against influenza after an outbreak of influenza has begun in a community. However, the development of antibodies in adults can take as long as 2 weeks after vaccination. Therefore, if influenza virus vaccine inactivated is administered after a local outbreak of influenza has begun, short-term antiviral prophylaxis should be considered for high-risk individuals. To provide protection until antibody responses to the vaccine develop, the antiviral agent usually is given for 2–4 weeks after vaccination; children younger than 9 years of age in this situation who are receiving influenza virus vaccine inactivated for the first time may require antiviral prophylaxis for up to 6 weeks following vaccination or until 2 weeks after the second dose of the vaccine. Safety and efficacy of concomitant use of influenza virus vaccine live intranasal and influenza antiviral agents (e.g.,

amantadine, oseltamivir, rimantadine, zanamivir) have not been studied. (See Influenza Vaccines under Drug Interactions.)

Antiviral agents are used in the prevention and control of influenza outbreaks in hospitals or other institutions. When institutional outbreaks occur, antiviral prophylaxis should be administered to all residents, regardless of their vaccination status. If an outbreak is caused by a variant strain of virus that may not be controlled by the vaccine, the ACIP recommends that antiviral prophylaxis be considered for all employees, regardless of their vaccination status. (See Uses: Outbreak Control of Influenza in Institutions and Settings with Close-Proximity Living Conditions.)

Antiviral prophylaxis may be indicated as an adjunct to influenza virus vaccine in individuals at high risk who are expected to have an inadequate antibody response to influenza virus vaccine, including HIV-infected individuals.

HIV-infected Individuals.

The ACIP, American Academy of Pediatrics (AAP), National Institutes of Health (HIVMA/NIH), HIV Medicine Association of the Infectious Diseases Society of America (IDSA), and other experts recommend that HIV-infected adults, adolescents, and children 6 months of age or older receive annual vaccination against influenza with influenza virus vaccine inactivated. Annual vaccination is recommended since these individuals may be at high risk of influenza complications (e.g., secondary bacterial respiratory infections). (See HIV-infected Individuals under Management of Exposure: Target Groups for Special Vaccination Programs in Uses in Influenza Virus Vaccine Inactivated 80:12.) Antiviral prophylaxis may be used in conjunction with, or as an alternative to, influenza virus vaccine in HIV-infected individuals who may have a poor antibody response to the vaccine and/or high risk of exposure to influenza A, especially during influenza epidemics or institutional outbreaks.

Hematopoietic Stem Cell Transplant Recipients.

Individuals who undergo hematopoietic stem cell transplant (HSCT) are at risk for a variety of opportunistic infections, including community-acquired respiratory viral infections (e.g., influenza, respiratory syncytial virus, parainfluenza virus, adenovirus). The CDC, the Infectious Diseases Society of America (IDSA), and the American Society of Blood and Marrow Transplantation (ASBMT) have established guidelines for preventing opportunistic infections in HSCT recipients. These guidelines recommend lifelong annual vaccination with influenza virus vaccine in all HSCT recipients who are 6 months of age or older. However, because the vaccine is not likely to be beneficial and is not recommended during the first 6 months after HSCT, antiviral prophylaxis can be used if community or nosocomial influenza outbreaks occur during this time period. If influenza outbreaks occur and it has been 6–24 months after HSCT or it has been longer than 24 months after HSCT and the patient is still substantially immunocompromised (i.e., receiving immunosuppressive therapy, having a relapse of the underlying disease, graft-versus-host disease [GVHD]), the HSCT recipient should immediately receive influenza virus vaccine if they have not yet received their annual vaccination. In addition, during influenza A outbreaks, the HSCT recipient can receive antiviral chemoprophylaxis to provide protection until antibody responses to the vaccine develop. To help prevent transmission of influenza A to a susceptible HSCT recipient, if influenza outbreaks occur and health-care workers, family members, or other close contacts of HSCT recipients receive influenza virus vaccine inactivated, they also should receive a regimen of antiviral chemoprophylaxis to provide protection until a response to the vaccine is obtained. (See Hematopoietic Stem Cell Transplant Recipients under Management of Exposure: Target Groups for Special Vaccination Programs in Uses in Influenza Virus Vaccine 80:12.) If a nosocomial outbreak occurs with an influenza A strain that is not contained in the available influenza virus vaccine, all healthy family members, close and household contacts, and health-care workers of HSCT recipients and candidates should receive antiviral prophylaxis until the end of the outbreak.

Recommendations for prevention of influenza virus infection in HSCT recipients are the same for both allogeneic and autologous transplants. The guidelines for preventing opportunistic infections among HSCT recipients published by the CDC, IDSA, and ASBMT should be consulted for additional information on preventing opportunistic infections in these patients (including vaccinations) and for information on hospital infection control, strategies for safe living after transplantation, and hematopoietic stem cell safety.

■ Control of Influenza Outbreaks in Institutions and Settings with Close-Proximity Living Conditions

Antiviral agents are used for the treatment and prophylaxis of influenza in hospitals and other institutions and are an important component of institutional outbreak control. In addition to use of antivirals, other outbreak control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, reoffering influenza vaccination to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients.

The adamantanes and neuraminidase inhibitors antivirals have been successful in controlling influenza outbreaks when the outbreak is caused by an influenza strain susceptible to the antiviral agent and the drug is used in conjunction with other infection control measures.

When confirmed or suspected outbreaks of influenza occur in institutions that house individuals at high risk, antiviral prophylaxis should be initiated as early as possible to reduce the spread of the virus. Antiviral prophylaxis also can be considered for controlling influenza A outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings where individuals live in close proximity).

Contingency planning for influenza outbreaks in institutions is needed to establish specific steps for rapid administration of antiviral agents when necessary, including preapproved medication orders or plans to obtain clinicians' orders on short notice. When institutional outbreaks occur, antiviral prophylaxis should be administered to all residents in the affected institution whether or not they received influenza vaccine the previous fall. Prophylaxis for outbreak control should be continued for at least 2 weeks or until 7–10 days after the end of the outbreak. To reduce the spread of the virus and to minimize disruption of patient care, antiviral prophylaxis can be offered to unvaccinated staff who provide care to high-risk patients. If the outbreak is caused by a variant strain of influenza A that may not be controlled by the vaccine, antiviral prophylaxis should be considered for all employees, regardless of their vaccination status.

To limit the potential transmission of drug-resistant influenza virus during institutional outbreaks, measures should be taken to prevent contact as much as possible between individuals receiving antiviral agents for *prophylaxis* and those receiving the drugs for *treatment*.

■ 2009 Influenza A (H1N1) Virus Infections

Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus, were reported in Mexico and other countries, including the US. The 2009 influenza A (H1N1) virus appears to be a triple-reassortant swine influenza virus containing genes from human, swine, and avian influenza A viruses. The virus contains a unique combination of gene segments not previously reported among human or swine influenza A in the US or elsewhere.

CDC issued interim recommendations concerning the use of antiviral agents for treatment and prophylaxis of infections caused by the 2009 influenza A (H1N1) virus (<http://www.cdc.gov/h1n1flu/recommendations.htm>). To date, isolates of 2009 influenza A (H1N1) have been resistant to amantadine and rimantadine. These drugs are not recommended for treatment or prophylaxis of these infections.

Recommendations for use of antiviral agents for treatment or prevention of infections caused by the 2009 influenza A (H1N1) virus may change as additional data become available (e.g., additional antiviral susceptibility data, efficacy data). The CDC website should be consulted for the most recent information regarding case definitions of confirmed, probable, and suspected 2009 influenza A (H1N1) infections and recommendations regarding diagnosis, treatment, and prophylaxis (including outbreak control) of these infections (<http://www.cdc.gov/h1n1flu/>).

■ Avian Influenza A Virus Infections

Adamantane derivatives (amantadine, rimantadine) can be used for the treatment or prophylaxis of avian influenza A virus infections† in certain situations.

The World Health Organization (WHO) recommends use of a neuraminidase inhibitor (i.e., oseltamivir) for the treatment of avian influenza A infections. Although many avian influenza A virus strains tested (including the H5N1 strains isolated from patients in Asia during 2004 and 2005) are resistant to adamantanes (amantadine, rimantadine), most strains have been susceptible to neuraminidase inhibitors (oseltamivir, zanamivir). Some strains from China may be susceptible to adamantanes.

When neuraminidase inhibitors are available, amantadine and rimantadine should *not* be used alone for the treatment of avian influenza A virus infections. However, clinicians can consider treatment with a neuraminidase inhibitor (i.e., oseltamivir) and an adamantane (amantadine, rimantadine) in a patient with pneumonic disease or clinical progression if local surveillance data indicate that the H5N1 virus is known or likely to be susceptible to an adamantane.

For additional information on treatment or prevention of avian influenza A virus infection, see Uses: Avian Influenza A Virus Infections in Oseltamivir 8:18.28.

■ Pandemic Influenza

Influenza viruses can cause pandemics, during which rates of illness and death from influenza-related complications can increase dramatically worldwide. Influenza antiviral agents may be important for prophylaxis and treatment if an influenza pandemic occurs. If novel influenza subtypes are involved, the drugs may provide some coverage until a new influenza vaccine active against these strains can be formulated, manufactured, and distributed.

On June 11, 2009, the WHO declared that the first global influenza pandemic in 41 years was occurring and issued a phase 6 pandemic alert regarding 2009 influenza A (H1N1). A phase 6 pandemic is characterized by human-to-human spread of an animal or human-animal reassortant virus and sustained community level outbreaks of the virus in at least 2 countries in a single WHO region and sustained community level outbreaks in at least one other country in a different WHO region.

For additional information on pandemic influenza, see Uses: Pandemic Influenza, in Oseltamivir 8:18.28.

Dosage and Administration

■ Administration

Amantadine hydrochloride is administered orally as a single daily dose or, preferably, in 2 equally divided doses to minimize transitory adverse effects. It has been suggested that if insomnia occurs, the last daily dose should be taken several hours before retiring.

■ Dosage

Adult Dosage

For symptomatic *treatment* or *prophylaxis* of uncomplicated seasonal influenza A virus illness, the usual dosage of amantadine hydrochloride for adolescents and adults younger than 65 years of age with normal renal function is 200 mg daily. This dosage can be given as a single daily dose or as 100 mg twice daily; use of 2 equally divided daily doses may minimize adverse CNS effects and therefore is preferred by some experts.

The usual dosage of amantadine may need to be reduced in patients with congestive heart failure, peripheral edema, orthostatic hypotension, or impaired renal function. Some clinicians currently recommend a maximum dosage of 100 mg daily for the *prophylaxis* of influenza A infection because limited evidence suggests that a 100-mg daily dosage may be effective for *prophylaxis* in healthy adults who are not at risk for influenza-related complications and is associated with fewer adverse effects. The relative efficacy of 100- versus 200-mg daily dosages for the *treatment* or *prophylaxis* of influenza virus A infection has not been elucidated. The 100-mg daily dosage is recommended for individuals who have CNS or other toxicities while receiving the 200-mg daily dosage.

Geriatric Dosage

Since renal function normally declines with age and amantadine-induced adverse effects have been reported more frequently in geriatric patients, the usual dosage of amantadine hydrochloride for patients 65 years of age or older without recognized renal disease is 100 mg once daily for the *treatment* or *prophylaxis* of seasonal influenza A virus infection to minimize the risk of toxicity. Some clinicians state that 100 mg daily should be the maximum dosage of amantadine hydrochloride for adults 65 years of age or older, and that dosage may need to be further reduced in some geriatric patients.

Pediatric Dosage

The dosage of amantadine hydrochloride recommended by the manufacturer for the symptomatic *treatment* or *prophylaxis* of uncomplicated seasonal influenza A virus illness in children 9–12 years of age is 100 mg twice daily. The American Academy of Pediatrics (AAP) states that children 10 years of age or older who weigh 40 kg or more may receive the drug in a dosage of 200 mg daily given in 2 divided doses, but that it may be advisable to administer the drug in a dosage of 5 mg/kg daily given in 2 divided doses to those who weigh less than 40 kg, regardless of age. While the manufacturer states that a dosage of 100 mg once daily has not been evaluated in children and there are no data demonstrating whether this dosage is as effective or safer than the 200 mg daily dosage in this age group, the AAP suggests that a dosage of 100 mg daily given in 2 divided doses is an acceptable alternative dosage for the *prophylaxis* of influenza A illness in children who weigh more than 20 kg.

For children 1–9 years of age, the manufacturer recommends that amantadine hydrochloride be given in a dosage of 4.4–8.8 mg/kg daily (up to a maximum dosage of 150 mg daily). AAP and other experts suggest that children 1–9 years of age receive 5 mg/kg daily given in 2 divided doses (up to a maximum dosage of 150 mg daily).

Duration of Therapy

Treatment.

In the symptomatic treatment of respiratory tract illness caused by influenza A virus, amantadine hydrochloride should be administered as soon as possible, preferably within 24–48 hours after the onset of symptoms. Treatment may be continued for up to 5 days or for 24–48 hours after symptoms disappear.

Prophylaxis.

When a presumed influenza A outbreak occurs in a hospital, nursing home, or other institution housing high-risk patients, amantadine prophylaxis should be started as soon as possible after recognition of the outbreak and continued at least 2 weeks or until 7–10 days after the end of the outbreak. When amantadine hydrochloride is used as an adjunct to influenza virus vaccine, the drug usually is administered for 2–4 weeks after the vaccine is given in order to provide chemoprophylaxis until protective antibody response develops. Children younger than 9 years of age receiving influenza virus vaccine for the first time may require prophylaxis for up to 6 weeks following vaccination or until 2 weeks after the second dose of vaccine.

Duration of antiviral prophylaxis should be individualized. For maximum effectiveness, the antiviral agent must be taken every day during influenza activity in the community.

■ Dosage in Renal Impairment

In patients with renal impairment, amantadine hydrochloride dosage should be carefully adjusted and some clinicians recommend that blood concentrations of the drug be monitored frequently. One manufacturer recommends that patients with creatinine clearances of 15–50 mL/minute per 1.73 m² receive 200 mg of amantadine on the first day, followed by 100-mg maintenance doses given once daily in patients with creatinine clearances of 30–50 mL/minute per 1.73 m² or once every other day in those with creatinine clearances of 15–29 mL/minute per 1.73 m². This manufacturer recommends that patients with creatinine clearances less than 15 mL/minute per 1.73 m² and hemodialysis patients receive 200 mg of amantadine every 7 days.

Because dosage adjustment based on creatinine clearance may provide only an approximation of the optimal dosage for a given patient, such patients should be observed carefully so that adverse reactions can be recognized promptly and either the dose can be reduced further or the drug can be discontinued as necessary. Hemodialysis contributes minimally to clearance of amantadine.

Cautions

Amantadine generally is well tolerated, although serious adverse effects have been reported rarely. The incidence of adverse effects associated with amantadine therapy appears to be dose related. The most frequently reported adverse effects with amantadine are similar to those observed with rimantadine and include adverse CNS and GI effects; however, amantadine is associated with more frequent and/or severe nervous system effects than rimantadine, including in geriatric adults.

Adverse effects associated with amantadine usually are mild and are reversible upon discontinuance of the drug. In some patients, adverse effects subside after the first week of therapy with the drug.

■ Nervous System Effects

Dizziness (lightheadedness), insomnia, nervousness, anxiety, and impaired concentration are among the most frequent adverse effects of amantadine and have been reported in up to 5–10% of healthy, young adults receiving the usual dosage of the drug (200 mg daily). However, limited data suggest that the incidence of adverse CNS effects may be lower in adults receiving a lower dosage of the drug. These adverse effects are usually mild, but may be more disturbing for geriatric patients than for younger patients.

Adverse CNS effects are more common with usual dosages of amantadine than of rimantadine, probably in part because of differences in pharmacokinetics of the drugs. In a 6-week study of daily 200-mg prophylactic doses of amantadine or rimantadine in healthy adults, about 13 or 6% of patients receiving the respective drug discontinued therapy because of adverse CNS effects versus about 4% of those receiving placebo.

Irritability, depression, ataxia, confusion, somnolence, abnormal dreams, agitation, fatigue, headache, and hallucinations have been reported in 1–5% and psychosis, abnormal thinking, amnesia, hyperkinesia, euphoria, weakness, and slurred speech have been reported in 1% or less of patients receiving amantadine. In addition, forgetfulness, a sense of drunkenness or detachment, drowsiness, coma, stupor, delirium, hypokinesia, hypertonia, delusions, aggressive behavior, paranoid reaction, manic reaction, involuntary muscle contractions, gait abnormalities, paresthesia, EEG changes, tremor, and, rarely, lingual facial dyskinesia or seizures have been reported.

Patients at Risk for CNS Effects

Patients with active seizure disorders appear to be at risk of an increased frequency of seizures during amantadine therapy; seizures also have been reported in patients with renal impairment and in geriatric individuals. Patients with a history of mental or behavioral disorders and those receiving concomitant anticholinergic drug therapy also may be at increased risk of adverse CNS effects of the drug. The more serious CNS effects (e.g., marked behavioral changes, delirium, agitation, hallucinations, seizures) of amantadine or rimantadine have been associated with high plasma concentrations of the drugs and have been observed most often among patients with renal impairment, seizure disorders, or certain psychiatric disorders and among geriatric patients who received prophylactic 200-mg doses daily. Clinical studies and experience indicate that lower dosages of amantadine in at-risk patients reduces the incidence and severity of these serious adverse effects.

Suicide Risk

Suicide attempts (resulting in death in some patients) have been reported rarely in patients receiving amantadine, many of whom received short courses of the drug for influenza prophylaxis or treatment. The manufacturer states that the incidence and pathophysiology of these suicide attempts are not known. Suicide ideation or attempts have been reported in patients with or without a prior history of psychiatric disorders. Amantadine can exacerbate mental status in patients with a history of psychiatric disorders or substance abuse. Patients with suicidal tendencies may exhibit abnormal mental states including disorientation, confusion, depression, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, somnolence, or insomnia.

Because of the possibility of serious adverse effects, amantadine should be administered with caution to patients receiving drugs with CNS activity and in those in whom potential risks outweigh benefits of therapy with the drug. Since intentional overdose with amantadine has been reported in some patients, the least amount of drug feasible should be prescribed.

Neuroleptic Malignant Syndrome

Possible neuroleptic malignant syndrome (NMS) has been reported in patients receiving amantadine and was associated with dosage reduction or withdrawal of the drug. NMS is potentially fatal and requires immediate initiation of intensive symptomatic and supportive care. Patients should be observed closely when the dosage of amantadine is reduced or the drug is discontinued; this precaution is especially important in patients receiving concomitant therapy with an antipsychotic agent. For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects in the Phenothiazines General Statement 28:16.08.24.

■ Livedo Reticularis

Livedo reticularis is a frequent adverse effect in patients receiving amantadine for the treatment of parkinsonian syndrome, and the possibility should be considered in patients receiving the drug for prolonged periods in the prevention of influenza A. Livedo reticularis occurs mainly in the legs and diminishes when the legs are elevated.

Livedo reticularis has been reported in 1–5% of patients, generally appears within 1 month to 1 year following initiation of amantadine therapy, and subsides within a few weeks to several months after discontinuance of the drug. In one study, livedo reticularis tended to fade or change into brown spots with prolonged amantadine therapy. It has

been suggested that, in many instances, this adverse effect is actually an accentuation of a preexisting, minor livedo reticularis and may result from abnormal capillary permeability associated with peripheral vasoconstriction accompanied by lowered skin temperature and decreased peripheral blood flow, and/or amantadine's depletion of catecholamines in peripheral nerve endings.

Peripheral edema may precede or accompany livedo reticularis and may require dosage reduction or discontinuance of amantadine. The edema does not appear to be associated with an increase in total body water or sodium retention; it may result from increased vascular permeability in cutaneous tissues.

■ GI Effects

Nausea is one of the most frequent adverse effects of amantadine and has been reported in 5–10% of patients receiving the usual dosage of the drug. Anorexia, constipation, diarrhea, and dry mouth have been reported in 1–5% and vomiting has been reported in up to 1% of patients receiving amantadine. Abdominal discomfort or dysphagia also has been reported. The incidence of adverse GI effects is comparable for amantadine and rimantadine.

■ Cardiovascular Effects

Orthostatic hypotension and peripheral edema have been reported in 1–5% and congestive heart failure and hypertension in up to 1% of patients receiving amantadine. Cardiac arrest, arrhythmias including malignant arrhythmias, and tachycardia have occurred in patients receiving amantadine.

■ Ocular Effects

Visual disturbance (e.g., punctate subepithelial or other corneal opacity), corneal edema, decreased visual acuity, ocular photosensitivity, or optic nerve palsy have been reported in up to 1% of patients receiving amantadine. Keratitis or mydriasis has occurred in patients receiving the drug. One patient experienced a sudden loss of visual acuity in both eyes, which gradually returned to normal several weeks after amantadine was discontinued.

■ Melanoma

Epidemiologic studies indicate that patients with parkinsonian syndrome have a twofold to sixfold higher risk of developing melanoma than the general population. It is unclear whether this increased risk is due to parkinsonian syndrome or other factors (e.g., drugs used to treat Parkinson's disease).

Patients receiving amantadine for any indication should be monitored for melanomas frequently and on a regular basis. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

■ Intense Urges

Intense urges (e.g., urge to gamble, increased sexual urges, other intense urges) and inability to control these urges have been reported in some patients receiving drugs that increase central dopaminergic tone and generally are used for the treatment of parkinsonian syndrome, including amantadine. Although a causal relationship has not been established, these urges stopped in some cases when dosage was reduced or the drug discontinued.

Clinicians should ask patients whether they have developed new or increased gambling urges, sexual urges, or other urges while receiving amantadine and should advise them of the importance of reporting such urges. If a patient develops such urges while receiving amantadine, consideration should be given to reducing the dosage or discontinuing the drug.

■ Sensitivity and Dermatologic Effects

Allergic reactions, including anaphylactic reaction, rash, eczematoid dermatitis, photosensitization, pruritus, and diaphoresis, have occurred rarely in amantadine-treated patients.

■ Hematologic Effects

Hematologic effects reported in less than 0.1% of patients receiving amantadine include leukopenia, neutropenia, and leukocytosis.

■ Genitourinary Effects

Urinary retention and decreased libido have occurred in up to 1% of patients receiving amantadine.

■ Respiratory Effects

Dyspnea has been reported in up to 1% of amantadine-treated patients. Adverse respiratory effects reported rarely in amantadine-treated patients include acute respiratory failure, pulmonary edema, and tachypnea.

■ Other Adverse Effects

Fever or dry nose has occurred in patients receiving amantadine. Increased concentrations of creatine kinase (CK, creatine phosphokinase, CPK), BUN, serum creatinine, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, γ -glutamyltransferase (GGT, γ -glutamyltranspeptidase, GGTP), ALT (SGPT), and AST (SGOT) have occurred in patients receiving amantadine.

■ Precautions and Contraindications

Amantadine should be administered with caution in patients with liver disease or a history of recurrent eczematoid dermatitis, uncontrolled psychosis or severe psychoneurosis, or seizure disorders, and in those receiving drugs with CNS activity. Patients with a history of seizure disorders should be observed closely for possible increased seizure activity. Because of possible CNS effects or visual disturbances, patients receiving amantadine should be warned that the drug may impair their ability to

perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a motor vehicle.

Because amantadine may cause mydriasis, the drug should not be used in patients with untreated angle-closure glaucoma. Because possible neuroleptic malignant syndrome was reported in patients receiving amantadine and was associated with a dosage reduction or withdrawal of the drug, patients, especially those receiving antipsychotic agents, should be observed closely when the dosage of amantadine is reduced or the drug is discontinued.

Amantadine should be used with caution and dosage of the drug may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Dosage of the drug should be reduced in patients with active seizure disorders and in geriatric patients 65 years of age or older.

Amantadine- and rimantadine-resistant strains of influenza A virus have been observed in some patients receiving the drug for the treatment of influenza A infection. Although most patients recover uneventfully even after resistant strains emerge, resistant strains are pathogenic and transmissible and can result in failures in drug prophylaxis in close contacts. The possibility of transmitting resistant strains should be considered when treating patients in close contact with other individuals at high risk for influenza A infection. Individuals with influenza-like illness should be separated from and avoid contact with uninfected individuals as much as possible, regardless of whether they are receiving antiviral treatment.

Clinicians should consider the possibility of primary or concomitant bacterial infection when making treatment decisions for patients with suspected influenza.

Amantadine is contraindicated in patients with known hypersensitivity to adamantane derivatives (i.e., amantadine, rimantadine).

■ Pediatric Precautions

Safety and efficacy of amantadine in children younger than 1 year of age have not been established. When used in children, amantadine has caused CNS symptoms which resolved when the drug was discontinued. The incidence of adverse CNS-related effects appears to be higher in individuals receiving amantadine than in those receiving rimantadine. An increased incidence of seizures has been reported in children with an underlying seizure disorder receiving amantadine.

■ Geriatric Precautions

While safety and efficacy of amantadine in geriatric patients have not been established specifically, the drug has been used in many geriatric patients. The frequency and severity of adverse CNS effects reported in individuals older than 65 years of age receiving amantadine are higher than those reported in geriatric individuals receiving rimantadine.

Geriatric adults may have decreased renal function and because individuals with renal impairment may be at increased risk of amantadine-induced toxicity, the dosage of amantadine hydrochloride for adults in this age group should not exceed 100 mg daily. This dosage may need to be reduced further in some geriatric patients. (See Adult Dosage in Dosage and Administration: Dosage.)

■ Mutagenicity and Carcinogenicity

Amantadine was not mutagenic in the Ames microbial test using *Salmonella typhimurium* or a mammalian mutagen assay using Chinese hamster ovary cells when the tests were performed with or without metabolic activation. In addition, there was no evidence of chromosome damage in an in vitro test using freshly derived and stimulated human peripheral blood lymphocytes (with or without metabolic activation) or an in vivo mouse bone marrow micronucleus test (140–550 mg/kg; estimated human equivalent dosage of 11.7–45.8 mg/kg based on body surface area conversion).

Long-term animal studies have not been performed to evaluate the carcinogenic potential of amantadine.

■ Pregnancy, Fertility, and Lactation

Pregnancy

Amantadine hydrochloride has been reported to be embryotoxic/teratogenic in rats when administered in dosages of 50 and 100 mg/kg daily (1.5 and 3 times, respectively, the maximum recommended human dosage on a mg/m² basis), but not when administered in a dosage of 37 mg/kg daily (the maximum recommended human dosage on a mg/m² basis). One woman with a movement disorder similar to parkinsonian syndrome who may have been treated with amantadine hydrochloride (100 mg daily) during the first trimester of pregnancy delivered a child with a complex cardiovascular lesion (single ventricle and pulmonary atresia) which may have been caused by the drug. Fallot and tibial hemimelia (normal karyotype) were reported in an infant exposed to oral amantadine hydrochloride during the first trimester of pregnancy (100 mg daily for 7 days during week 6 and 7 of gestation). There are no adequate and well-controlled studies using amantadine in pregnant women, and the drug should be used during pregnancy only when the potential benefits outweigh the possible risks to the fetus.

Fertility

In a rat reproduction study involving 3 litters, fertility was slightly impaired when amantadine hydrochloride was administered to both males and females in a dosage of 32 mg/kg daily (the maximum recommended human dosage on a mg/m² basis). Fertility was not affected when the drug was given in a dosage of 10 mg/kg daily (0.3 times the maximum recommended human dosage on a mg/m² basis); intermediate doses were not tested.

In one instance, failure was reported during human in vitro fertilization (IVF) when the sperm donor ingested amantadine 2 weeks before and during the IVF cycle.

Lactation

Amantadine is distributed into human milk. The manufacturer recommends that the drug not be used in nursing women.

Drug Interactions

Careful observation of the patient is advised if amantadine is administered concurrently with drugs that affect the CNS, including CNS stimulants, antihistamines, or anticholinergic agents.

■ Drugs with Anticholinergic Activity

Administration of amantadine in patients receiving drugs with anticholinergic activity may result in increased adverse anticholinergic and CNS effects. When amantadine is administered to patients already near the limit of tolerance for anticholinergic agents, atropinism with nocturnal confusion and hallucinations may gradually develop. It has been suggested that the dosage of the anticholinergic agent be reduced prior to the initiation of amantadine therapy or that the dose of either drug be reduced if atropine-like adverse effects appear.

While concomitant administration of amantadine and thioridazine has been reported to worsen tremor in geriatric patients with parkinsonian syndrome, it is not known whether a similar effect would occur with other phenothiazines.

■ Influenza Virus Vaccines

Amantadine hydrochloride does not interfere with the antibody response to influenza virus vaccine inactivated and the drug may be given concomitantly with this vaccine.

Safety and efficacy of concomitant use of influenza virus vaccine live intranasal and influenza antiviral agents (e.g., amantadine, oseltamivir, rimantadine, zanamivir) have not been studied. Because influenza antiviral agents reduce replication of influenza viruses, do not administer influenza virus vaccine live intranasal until at least 48 hours after amantadine is discontinued and do not administer amantadine until at least 2 weeks after administration of influenza virus vaccine live intranasal.

■ CNS Stimulants

To avoid the possibility of additive CNS stimulant effects, amantadine should be administered with caution to patients receiving CNS stimulants.

■ Co-trimoxazole

Toxic delirium has occurred following initiation of co-trimoxazole in at least one patient who had been stabilized on amantadine; rapid resolution occurred following discontinuance of the drugs.

■ Other Drugs

Concomitant administration of amantadine hydrochloride (100 mg 3 times daily) and a combination preparation containing triamterene and hydrochlorothiazide (co-triamterezide) in a 61-year-old man with parkinsonian syndrome resulted in increased plasma concentrations of amantadine; however, it is not known which component of the combination preparation may have been responsible for the interaction or whether related drugs would produce a similar effect.

Concomitant administration of quinidine or quinine with amantadine may reduce the renal clearance of amantadine.

Concomitant use of amantadine and antihistamines that affect that CNS (e.g., those exhibiting anticholinergic activity) may increase the incidence of adverse CNS reactions.

Acute Toxicity

■ Manifestations

Fatalities have been reported following overdosage of amantadine. The lowest reported acute lethal dose of the drug has been 1 g.

Acute overdosage of amantadine has resulted in cardiac dysfunction (e.g., arrhythmia, tachycardia, hypertension); pulmonary edema and respiratory distress (including adult respiratory distress syndrome [ARDS]); renal dysfunction (e.g., increased BUN, decreased creatinine clearance, renal insufficiency); or CNS toxicity (e.g., insomnia, anxiety, aggressive behavior, hypertonia, hyperkinesia, tremor, confusion, disorientation, depersonalization, fear, delirium, hallucinations, psychotic reactions, lethargy, somnolence, coma). Hyperthermia also has occurred with amantadine overdosage. In addition, seizures may be exacerbated in patients with a history of a seizure disorder.

In a patient who ingested 2.8 g of amantadine hydrochloride, manifestations of amantadine overdosage included slightly dilated pupils that contracted minimally to light; urinary retention; mild, mixed acid-base disturbances; and an acute toxic psychosis manifested as disorientation, visual hallucinations, and aggressive behavior. A patient who ingested 2.5 g became comatose and developed cardiopulmonary arrest several hours after the ingestion. Although the arrest was treated successfully, during the arrest and subsequent 48 hours, ventricular tachyarrhythmias manifested as atypical ventricular tachycardia (torsades de pointes) and ventricular fibrillation occurred; therapy with adrenergic agents, particularly dopamine, appeared to exacerbate the ventricular tachyarrhythmias. The patient subsequently died of aspiration pneumonia and respiratory distress.

■ Treatment

There is no specific antidote for amantadine overdose. If overdose of amantadine is recent, prompt gastric lavage or induction of emesis is indicated. General supportive measures (including establishment of adequate respiratory exchange by maintenance of an airway, control of respiration and oxygen administration) should be instituted and cardiovascular status, blood pressure, pulse, respiration, temperature, serum electrolytes, urinary output, and urine pH should be monitored. Electrocardiographic monitoring may be necessary since malignant tachyarrhythmias can occur following amantadine overdose. Fluids should be forced and, if necessary, given IV. Acidifying agents may be administered to increase the rate of amantadine excretion; only minimal amounts of amantadine are removed by hemodialysis. If there is no record of recent voiding, catheterization should be done.

The patient should be observed for hyperactivity and seizures; if required, sedatives and anticonvulsant therapy should be administered. Slow IV administration of physostigmine 1- and 2-mg doses at 1- to 2-hour intervals in one adult and 0.5-mg doses at 5- to 10-minute intervals (to a maximum of 2 mg/hour) in a child has been effective in the management of CNS toxicity caused by amantadine. However, the risk of physostigmine in the management of overdose should be considered. (See Physostigmine Salicylate 12:04.) Chlorpromazine was useful for the treatment of toxic psychosis in one patient. The patient also should be observed for the possible development of arrhythmias and hypotension; if required, appropriate antiarrhythmic and antihypertensive therapy should be administered. Caution should be employed when using adrenergic agents to maintain blood pressure and heart rate, since these agents may further predispose the patient to the development of serious ventricular tachyarrhythmias.

Mechanism of Action

The exact mechanism of the antiviral activity of amantadine has not been fully elucidated

Amantadine, like rimantadine, inhibits viral replication by interfering with the influenza A virus M2 protein, an integral membrane protein. The M2 protein of influenza A functions as a ion channel and is important in at least 2 aspects of virus replication, disassembly of the infecting virus particle and regulation of the ionic environment of the transport pathway. By interfering with the ion channel function of the M2 protein, amantadine inhibits 2 stages in the replicative cycle of influenza A. Early in the virus replicative cycle, amantadine inhibits uncoating of the virus particle, presumably by inhibiting the acid-mediated dissociation of the virion nucleic acid and proteins, which prevents nuclear transport of viral genome material. Amantadine also prevents viral maturation in some strains of influenza A (e.g., H7 strains) by promoting pH-induced conformational changes in influenza A hemagglutinin during its intracellular transport late in the replicative cycle. Adsorption of the virus to and penetration into cells do not appear to be affected by amantadine. In addition, amantadine does not interfere with the synthesis of viral components (e.g., RNA-directed RNA polymerase activity).

Amantadine treatment of established influenza A infection does not appear to interfere with antibody response to the infection; however, some reduction in local immune responses has been observed in some patients. Because prophylactic use of amantadine can prevent influenza illness and to a lesser extent subclinical infection, some individuals who take amantadine can still develop immune responses that may protect them when they are exposed to the same or antigenically related viruses following discontinuance of amantadine prophylaxis. Amantadine does not interfere with the immunogenicity of influenza virus vaccine inactivated.

Amantadine-mediated increases in lysosomal pH may inhibit virus-induced membrane fusion in enveloped RNA viruses that are susceptible to higher concentrations of amantadine than those required to inhibit influenza A.

Spectrum

Amantadine shares the antiviral spectrum of activity of rimantadine. Cell culture studies have shown that low concentrations of amantadine (i.e., less than 1 mcg/mL) produce an inhibitory action against many strains of influenza A that occur widely in humans, including H1N1, H2N2, and H3N2.

Almost all seasonal influenza A (H1N1) viruses circulating in the US in late 2008 and early 2009 were susceptible to amantadine and rimantadine; however, strains of seasonal influenza A (H3N2) circulating during the 2008-2009 influenza season have been resistant to these drugs. (See Resistance.)

Although some strains of avian influenza A (H5N1) may be susceptible to amantadine in vitro, most avian influenza A virus strains tested (including the H5N1 strains isolated from patients in Asia during 2004 and 2005) are resistant to adamantanes (amantadine, rimantadine).

Beginning in March and April 2009, cases of human infection with 2009 influenza A (H1N1) virus, previously referred to as the novel 2009 influenza A (H1N1) virus or swine-origin influenza A (H1N1) virus, were reported in Mexico and other countries, including the US. To date, isolates of 2009 influenza A (H1N1) virus have been resistant to amantadine and rimantadine.

In tissue culture systems, the 50% inhibitory concentration of amantadine for susceptible influenza A viruses ranges from 100 ng/mL to 25 mcg/mL depending on the assay protocol, size of the virus inoculum, influenza A strain, and the cell type used. By plaque inhibition, the 50% inhibitory concentration of rimantadine or amantadine for susceptible influenza A viruses ranges from 0.01 to less than 1 mcg/mL. The precise

relationship between in vitro susceptibility of influenza A virus to amantadine and clinical response to therapy with the drug has not been determined. Results of several in vitro studies indicate that amantadine is less active on a weight basis than rimantadine.

Genetic studies indicate that the amino acid sequence in the transmembrane portion of the M2 protein of influenza A virus influences susceptibility of the virus to amantadine and rimantadine. Single amino acid changes in a critical transmembrane region of the M2 protein are associated with antiviral resistance to the drugs, providing further evidence of the importance of this domain in the protein as a target site for antiviral activity. There is some evidence that susceptibility of certain strains (e.g., H7) may be influenced by gene coding for the viral hemagglutinin.

Amantadine has little or no activity against influenza B at concentrations that inhibit influenza A. At very high concentrations (10–50 mcg/mL), the drug exhibits some in vitro activity against influenza B and other enveloped viruses (e.g., influenza C, parainfluenzae, respiratory syncytial virus), but this activity is considered clinically irrelevant because of the relatively high, potentially toxic doses that would be required.

Resistance

In vitro, resistance to amantadine can be produced at a relatively high frequency in strains of influenza A virus exposed to low concentrations of the drug. Influenza A virus strains with an in vitro EC₅₀ (concentration of the drug required to produce a 50% reduction of antigenic material) exceeding 1 mcg/mL generally are considered resistant to amantadine. Naturally occurring amantadine-resistant strains of influenza A virus reportedly occur in vitro with a frequency of 1 in 10⁴ to 1 in 10³; however, such strains have been isolated in up to about 33% of individuals who have received amantadine or rimantadine therapy for influenza A infection, and resistant strains also have been isolated from individuals living at home or in an institution where other residents are taking or recently have taken one of these antivirals. Amantadine-resistant strains of influenza A can emerge within 2–3 days of initiating treatment with the drug.

The mechanism(s) of resistance to amantadine has not been fully elucidated, but resistance to the drug appears to result from point mutations in the viral RNA segment 7 encoding the M2 protein that leads to amino acid alterations at residue 31 or nearby positions in the transmembrane portion of the M2 protein of the virus.

Although the frequency with which resistant strains emerge and the extent of their transmission have not been elucidated fully, limited evidence suggests that following treatment with amantadine in immunocompetent patients infected with initially susceptible strains of influenza A, 10–30% will shed amantadine-resistant virus. Limited information is available on the emergence of drug-resistant influenza A virus in immunocompromised patients receiving amantadine or rimantadine; isolates recovered from immunocompromised patients (adult bone marrow transplant recipients, adults with leukemia) who shed virus for longer than 3 days have been screened for antiviral susceptibility. While initial viral isolates were susceptible to amantadine or rimantadine, subsequent isolates from almost all of the patients were resistant.

The worldwide incidence of influenza A viruses resistant to adamantanes (amantadine, rimantadine) has increased. Results of a study that screened circulating influenza A viruses obtained from various countries between 1994 and 2005 indicated a substantial increase in the percentage of amantadine- and rimantadine-resistant influenza A (H3N2) isolates in the US and Asia (China, Hong Kong, Taiwan, South Korea). In Asia, the incidence of such resistance was 1.1% in both 1995 and 2000 and increased to 24.3% in 2003 and 27% in 2004. In the US, the incidence of such resistance was 0.3% in 1995, 1.6% in 2000, and 1.9% in 2004; however, about 15% of influenza A (H3N2) strains obtained in the US from October 2004 to March 2005 were resistant to amantadine and rimantadine. Most strains of seasonal influenza A (H3N2) circulating in the US during the 2005-2006 influenza season contained the amino acid alteration associated with resistance to amantadine and rimantadine. Data from the 2006-2007 and 2007-2008 influenza seasons indicated that the incidence of resistance to adamantanes among influenza A isolates remained high, especially among influenza A (H3N2). All circulating strains of seasonal influenza A (H3N2) tested from the 2008-2009 influenza season have been resistant to amantadine and rimantadine.

While amantadine-resistant strains appear to be pathogenic and transmissible, there is no evidence that amantadine-resistant strains are more virulent or more transmissible than strains that are susceptible to the drug. Resistance has rarely been detected during screening of naturally occurring epidemic strains of influenza A, and most clinical or population-based strains isolated to date are susceptible to amantadine and rimantadine.

Amantadine-resistant strains of influenza A are completely cross-resistant to rimantadine. Influenza A virus strains resistant to amantadine and rimantadine may be susceptible to oseltamivir or zanamivir.

Pharmacokinetics

■ Absorption

Amantadine hydrochloride is well absorbed from the GI tract. Mean peak blood amantadine concentrations of 0.3 mcg/mL have been reported to occur 1–4 hours after an oral dose of amantadine hydrochloride 2.5 mg/kg. Following oral administration of a single 100-mg capsule of amantadine hydrochloride, mean peak plasma concentrations of 0.22 mcg/mL occurred within 3.3 hours. Following oral administration of a single 100-mg dose of amantadine hydrochloride as the oral solution, peak plasma concentrations averaged 0.24 mcg/mL and were achieved within 2–4 hours. Peak plasma concentrations averaged 0.47 mcg/mL in individuals

receiving amantadine hydrochloride oral solution 100 mg twice daily for 15 days. Following oral administration of amantadine hydrochloride 200 mg as a tablet in fasting adults 19–27 years of age or fasting geriatric individuals 60–70 years of age, peak plasma concentrations averaged 0.51 or 0.8 mcg/mL, respectively. While peak plasma concentrations are directly related to amantadine hydrochloride dose up to a dosage of 200 mg daily, dosages exceeding 200 mg daily may result in a greater than proportional increase in peak plasma concentration. In a small number of patients who received 300 mg of amantadine hydrochloride daily (200 mg in the morning and 100 mg in the afternoon), steady-state blood concentrations of 0.68–1.01 mcg/mL were reached after 4–5 days of therapy. In healthy young adults receiving 25, 100, or 150 mg twice daily, steady-state trough plasma concentrations averaged 0.11, 0.3, or 0.59 mcg/mL, respectively.

Plasma amantadine concentrations in geriatric patients receiving the drug in a dosage of 100 mg daily reportedly approximate those attained in younger adults receiving the drug in a dosage of 200 mg daily; it is not known whether this occurs because of normal decline in renal function or other age-related factors. In one study, 3 patients with severe renal impairment showed symptoms of toxicity and elevated steady-state blood concentrations (2.5–4.4 mcg/mL) following 200 mg of amantadine hydrochloride daily. One metabolite, acetylamantadine, has been detected in plasma in less than 50% of individuals receiving a single amantadine hydrochloride 200-mg dose. In those individuals with detectable plasma acetylamantadine, concentration of the metabolite represented up to 80% of the concurrent amantadine concentration.

■ Distribution

Distribution of amantadine hydrochloride into body tissues and fluids has not been fully characterized.

In animals, amantadine is distributed into heart, lung, liver, kidney, and spleen. In a study in mice, lung tissue concentrations of amantadine were much higher than blood concentrations.

Following oral administration, amantadine is distributed into nasal secretions in concentrations that are lower than plasma concentrations. Following oral administration of a single 200-mg dose of amantadine hydrochloride in healthy young and geriatric adults, amantadine concentrations in nasal secretions or plasma averaged 0.15 mcg/g or 0.58 mcg/mL at 1 hour, 0.28 mcg/g or 51 mcg/mL at 4 hours, and 0.39 mcg/g or 0.45 mcg/mL at 8 hours. A substantial proportion of amantadine appears to distribute into erythrocytes, with an erythrocyte to plasma ratio of 2.7 reported in men with normal renal function and 1.4 in men with substantial renal impairment. In one patient, the CSF concentration of amantadine was approximately one-half the blood concentration. Amantadine distributes into human breast milk.

The volume of distribution following IV administration of amantadine reportedly is 3–8 L/kg in healthy individuals. Amantadine is about 67% bound to plasma proteins over a concentration range of 0.1–2 mcg/mL.

■ Elimination

The elimination half-life of amantadine has been variously reported as 9–37 hours, with an average of 24 hours or less. Clearance of amantadine is reduced, plasma concentrations of the drug are increased, and elimination half-life may be prolonged in healthy geriatric adults compared with healthy young adults. A half-life of 29 hours (range: 20–41 hours) has been reported in geriatric men 60–76 years of age. In addition, the half-life of amantadine is prolonged at least twofold to threefold in patients with impaired renal function (i.e., creatinine clearance less than 40 mL/minute per 1.73 m²). In one study, the half-life ranged from 18.5–81.3 hours in patients with creatinine clearances of 13.7–43.1 mL/minute per 1.73 m² and averaged 8.3 days (range: 7–10.3 days) in patients undergoing chronic hemodialysis.

While amantadine principally is excreted unchanged in urine by glomerular filtration and tubular secretion, at least 8 metabolites have been identified in urine. Amantadine undergoes *N*-acetylation, and about 5–15% of an absorbed dose is excreted in urine as acetylamantadine. Whether this metabolic pathway is affected by acetylator phenotype remains to be determined. The clinical importance of amantadine metabolites is unknown. Acidification of urine increases the rate of amantadine excretion, and administration of urine-acidifying drugs may increase amantadine elimination from the body. Amantadine is only minimally removed by hemodialysis. In patients with renal failure who received a single 300-mg oral dose of amantadine hydrochloride, only 5% or less of the dose was removed into the dialysate following a 4-hour period of hemodialysis.

Chemistry and Stability

■ Chemistry

Amantadine hydrochloride is a synthetic adamantane-derivative (a symmetric tricyclic amine) antiviral agent. Amantadine is structurally related to rimantadine, differing only in the side chain of the 10 carbon ring. While the structure-activity relationship of the adamantanes remains to be determined, the octanol/water coefficient for amantadine is substantially lower than that for rimantadine.

Amantadine hydrochloride occurs as a white or practically white, crystalline powder which has a bitter taste and has solubilities of approximately 400 mg/mL in water and 200 mg/mL in alcohol at 25°C. Amantadine hydrochloride has a pK_a of 9.

■ Stability

Commercially available amantadine hydrochloride tablets and oral solution should be stored in tight containers at a controlled room temperature of 25°C; limited exposure to temperatures of 15–30°C is permitted. The oral solution should not be frozen.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Amantadine Hydrochloride

Oral		
Capsules	100 mg*	Amantadine Hydrochloride Capsules
Solution	50 mg/5 mL*	Amantadine Hydrochloride Solution
Tablets	100 mg*	Amantadine Hydrochloride Tablets
		Symmetrel [®] , Endo

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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