VIRGINIA
EPIDEMIOLOGY BULLETIN

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Amantadine Treatment and Prophylaxis for Influenza A

*Recommendations of the Immunization Practices Advisory Committee (ACIP) of the U.S. Public Health Service**

Editor's Note: *Because viral surveillance indicates the predominance of influenza type A in Virginia as well as other states (see box on this page) the antiviral drugs amantadine and rimantadine, which are effective against influenza type A viruses, can be used for prevention and treatment.*

When vaccine is administered after influenza type A has begun to circulate in a community, amantadine or rimantadine can be administered for 2 weeks after vaccination to provide protection until vaccine-induced antibody has developed.

The two antiviral agents with specific activity against influenza A viruses are amantadine hydrochloride and rimantadine hydrochloride. These chemically related drugs interfere with the replication cycle of type A (but not type B) influenza viruses, although the specific mechanisms of their antiviral activity are not completely understood.

Rimantadine was recently approved for the treatment and prophylaxis of influenza in persons over 18 years of age and prophylaxis in children 18 years of age and under. Amantadine is approved for treatment and prophylaxis of persons one year of age and older.

Because U.S. Public Health Service recommendations for rimandadine use are not yet available, the following recommendations only pertain to amantadine hydrochloride use. Readers wishing to use rimantadine in accordance with recently approved indications (as noted above) are referred to the November 26, 1993 issue of the *Medical Letter* for further information (Anonymous. Rimantadine for prevention and treatment of influenza. *Med Lett Drugs Ther* 1993;35:109-10).

When administered prophylactically to healthy young adults or children in advance of and throughout the epidemic period, amantadine is approximately 70%-90% effective in preventing illnesses caused by naturally occurring strains of type A influenza viruses. When administered to otherwise healthy young adults and children for symptomatic treatment within 48 hours after the onset of influenza illness, amantadine has been shown to reduce the duration of fever and other systemic symptoms and may permit a more rapid return to routine daily activities. Since antiviral agents taken prophylactically may prevent illness but not subclinical infection, some persons who take these drugs may still develop immune responses that will protect them when exposed to antigenically related viruses in later years.

A/Beijing/32/92(H3N2)-like Strain Predominates

As of the end of December, U.S. World Health Organization collaborating laboratories reported that 9,136 specimens were tested for respiratory viruses. Of these specimens tested, 251 were positive for influenza type A and one for influenza type B. Of the 133 influenza type A viruses subtyped, 128 (96%) have been identified as influenza type A(H3N2), and 5 (4%) have been type A(H1N1). The 34 influenza type A(H3N2) strains that have been further characterized at CDC have all been antigenically similar to the A/Beijing/32/92(H3N2) strain included in the 1993-94 influenza vaccine.

So far this season, influenza type A has been reported from 42 states, including Virginia (see figure, page 2). New York state reported one influenza type B isolate and Washington state reported one serologic rise to influenza type B.

As with all drugs, symptoms may occur that are side effects of amantadine among a small proportion of persons. Such symptoms are rarely severe, but may be important for some categories of patients.

Recommendations for Use

Outbreak Control in Institutions

When outbreaks of influenza A occur in institutions that house high-risk persons, chemoprophylaxis should begin as early as

Reports through December 30, 1993 of flu-like illness from sentinel physicians in Virginia (33 offices reporting). Isolates of influenza type A have been reported from northern and northwest Virginia and activity is characterized as "widespread."

possible to reduce the spread of the infection. Contingency planning is needed to ensure rapid administration of amantadine to residents and employees. This should include preapproved medication orders or plans to obtain physicians' orders on short notice. When amantadine is used for outbreak control, it should be administered to all residents of the affected institution regardless of whether they received influenza vaccine the previous fall. The dose for each resident should be determined after consulting the dosage recommendations and precautions that follow in this document and those listed in the manufacturer's package insert. To reduce spread of virus and to minimize disruption of patient care, chemoprophylaxis should also be offered to unvaccinated staff who provide care to high-risk persons. To be fully effective as prophylaxis, the antiviral drug must be taken each day for the duration of influenza activity in the community.

Prophylaxis for High-risk Persons Vaccinated After Influenza A Activity Has Begun

High-risk persons can still be vaccinated after an outbreak of influenza A has begun in a community. However, the development of antibodies in adults after vaccination usually takes 2 weeks, during which time amantadine should be administered. Children who receive influenza vaccine for the first time may require up to 6 weeks of prophylaxis, or until 2 weeks after the second dose of vaccine has been received. Amantadine does not interfere with the antibody response to the vaccine.

Prophylaxis for Persons Providing Care to High-risk Persons

To reduce the spread of virus and to maintain care for high-risk persons in the home, hospital, or institutional setting, chemoprophylaxis should be considered for unvaccinated persons who have frequent contact with high-risk persons in the home setting (e.g., household members, visiting nurses, volunteer workers) and unvaccinated employees of hospitals, clinics, and chronic-care facilities. For employees who cannot be vaccinated, chemoprophylaxis should be continued for the entire period influenza A virus is circulating in the community; for those who are vaccinated at a time when influenza A is present in the community, chemoprophylaxis should be administered for 2 weeks after vaccination. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza A that is not covered by the vaccine.

Prophylaxis for Immunodeficient Persons

Chemoprophylaxis may be indicated for high-risk persons who are expected to have a poor antibody response to influenza vaccine. This includes many persons with HIV infection, especially those with advanced disease. No data are available on possible interactions with other drugs used in the management of patients with HIV infection. Such patients must be monitored closely if amantadine is administered.

Prophylaxis for Persons for Whom Influenza Vaccine Is Contraindicated

Chemoprophylaxis throughout the influenza season may be appropriate for high-risk persons for whom influenza vaccine is contraindicated because of anaphylactic hypersensitivity to egg protein or other vaccine components.

Prophylaxis of Other Persons

Amantadine can also be administered prophylactically by anyone who wishes to avoid influenza A illness. This decision should be made by the physician and patient on an individual basis.

Use as Therapy

Amantadine can reduce the severity and shorten the duration of influenza A illness among healthy adults. However, there are no data on the efficacy of amantadine therapy in preventing complications of influenza A among high-risk persons. Therefore, no specific recommendations can be made regarding the therapeutic use of amantadine for these patients. This does not preclude physicians' using amantadine for high-risk patients who develop illness compatible with influenza during a period of known or suspected influenza A activity in the community. Whether amantadine is effective when treatment begins beyond the first 48 hours of illness is not known.

Other Considerations

Side Effects/Toxicity

When amantadine is administered to healthy young adults at a dose of 200 mg/day, minor central-nervous-system (CNS) side effects (nervousness, anxiety, insomnia, difficulty concentrating, and lightheadedness) or gastrointestinal side effects (anorexia and nausea) occur among approximately 5%-10% of patients. Side effects diminish or cease soon after discontinuing use of the drug. With prolonged use, side effects may also diminish or disappear after the first week of use. More serious but less frequent CNS-related side effects (seizures, confusion) associated with use of amantadine have usually affected only elderly persons, those with renal disease, and those with seizure disorders or other altered mental or behavioral conditions. Reducing the dosage to ≤100 mg/day appears to reduce the frequency of these side effects among such persons

without compromising the prophylactic effectiveness of amantadine.

The package insert should be reviewed before use of amantadine for any patient. The patient's age, weight, renal function, presence of other medical conditions, and indications for use of amantadine (prophylaxis or therapy) must be considered, and the dosage and duration of treatment adjusted appropriately. Modifications in dosage may be required for persons with impaired renal function, the elderly, children, persons who have neuropsychiatric disorders or who take psychotropic drugs, and persons with a history of seizures.

Development of Drug-resistant Viruses

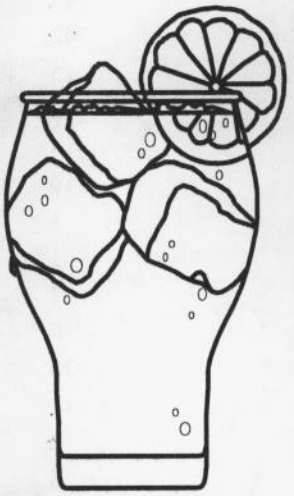
Amantadine-resistant influenza viruses can emerge when amantadine is administered for treatment. The frequency with which resistant isolates emerge and the extent of their transmission are unknown, but there is no evidence that amantadine-resistant viruses are more virulent or more transmissible than amantadine-sensitive viruses. Thus the use of amantadine remains an appropriate outbreak control measure. In closed populations such as nursing homes, persons with influenza who are treated with amantadine should be separated, if possible, from asymptomatic persons who are administered amantadine as prophylaxis. Because of possible induction of amantadine resistance, it is advisable to discontinue amantadine treatment of persons who have influenza-like illness as soon as clinically warranted, generally within 3-5 days. Isolation of influenza viruses from persons who are receiving amantadine should be reported through state health departments to CDC and the isolates saved for antiviral sensitivity testing.

**Adapted from: CDC. Prevention and control of influenza: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1992;41(No. RR-9):1-17.*

Outbreaks of Viral Gastroenteritis

Since the end of October 1993, six outbreaks of gastroenteritis, all with characteristics consistent with outbreaks of Norwalk or Norwalk-like viruses, have been reported to the Virginia Department of Health. During the same time period in 1992, no such outbreaks were reported.

Outbreaks caused by Norwalk and Norwalk-like viruses are characterized by sudden onset of vomiting, diarrhea, nausea, abdominal cramps, headache with little or no fever and an incubation period of 24 to 48 hours. According to the literature, illness is described as mild, but in at least one of the recent outbreaks in Virginia, about 20% of the ill persons required outpatient rehydration treatment. Illness is self-limiting and most patients recover within 12-60 hours. However, the likelihood of more severe disease may be increased for persons who are immunocompromised, elderly or have other chronic conditions (e.g., alcoholism; hepatic, gastrointestinal, or hematologic disorders; cancer; diabetes; or kidney disease).[1]



Norwalk virus or a Norwalk-like virus has been the most commonly confirmed viral agent associated with foodborne or waterborne outbreaks. It has been identified, however, in only about one third of outbreaks where a viral agent was sought; in the remaining two thirds no viral agent was identified.

The Centers for Disease Control and Prevention (CDC) has developed some new, sensitive techniques for the identification of Norwalk-like agents in stool and for the assessment of antibody titers in serum. With the advent of these new techniques, the Office of Epidemiology is interested in better characterizing foodborne or waterborne outbreaks believed due to viral agents.

Suspected foodborne or waterborne outbreaks should be reported promptly to the appropriate local health department or the Office of Epidemiology. An investigation will focus on confirming the vehicle of transmission and the etiologic agent.

In situations where they could be collected from at least 10 patients involved in an outbreak, we would be particularly interested in the prompt collection of specimens in order to maximize the possibility that a viral agent might be identified by CDC. For assistance and advice regarding specimen collection please contact Dr. Elizabeth Barrett or Dr. Elizabeth Turf at (804) 786-6261. Virus identification requires that specimens be handled as follows:

- Collect stool specimens in a clean, dry container (containers do not have to be sterile) during the first 48 hours of illness and keep stools refrigerated, *not frozen*;
- Collect acute (within 1 week of onset of illness) and convalescent (3 to 4 weeks after onset) serum specimens.

Reference

1. Centers for Disease Control and Prevention. Multistate Outbreak of Viral Gastroenteritis Related to Consumption of Oysters-Louisiana, Maryland, Mississippi, and North Carolina. MMWR 1993; 42:945-8.

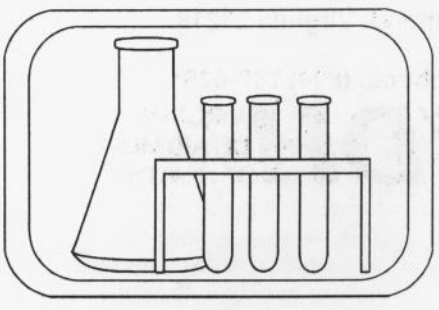
Rabies Antibody Testing (Animals & Human)

Two laboratories offer such testing. Note that one lab previously listed (Serologicals, Inc.) has moved and changed its name to Atlanta Health Associates, Inc. Both labs use the Rapid Fluorescent Focus Inhibition Test (RFFIT).

Atlanta Health Associates, Inc.
1100 Cambridge Square, Suite B
Alpharetta, GA 30201
(404) 667-8023
(800) 717-5612
(404) 667-8706 Fax

Kansas State University
Department of Veterinary Diagnosis
College of Veterinary Medicine
Veterinary Clinical Science Building
Manhattan, Kansas 66506-5600
(913) 532-5650

Please contact the respective labs for proper procedures for submitting specimens.



Cases of Selected Notifiable Diseases, Virginia, November 1 through November 31, 1993.*

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
		Regions							
	State	NW	N	SW	C	E	This Yr	Last Yr	5 Yr Avg
AIDS	92	6	40	5	32	9	1518	614	502
Campylobacteriosis	45	14	5	4	18	4	634	590	604
Gonorrhea†	742	-	-	-	-	-	10738	14049	15090
Hepatitis A	15	0	3	0	3	9	137	140	251
Hepatitis B	13	2	2	5	0	4	130	174	243
Hepatitis NANB	14	0	0	7	3	4	45	35	49
Influenza	10	0	2	0	3	5	1068	137	1245
Kawasaki Syndrome	1	0	0	0	0	1	23	21	21
Legionellosis	1	0	1	0	0	0	9	24	15
Lyme Disease	2	0	1	1	0	0	72	109	91
Measles	0	0	0	0	0	0	4	16	75
Meningitis, Aseptic	30	3	5	0	0	22	300	275	321
Meningitis, Bacterial‡	13	4	3	0	0	6	91	104	139
Meningococcal Infections	4	0	1	0	2	1	44	56	51
Mumps	8	1	3	2	0	2	36	52	94
Pertussis	1	1	0	0	0	0	59	15	24
Rabies in Animals	37	12	6	7	8	4	365	337	270
Reye Syndrome	0	0	0	0	0	0	3	0	1
Rocky Mountain Spotted Fever	2	0	1	1	0	0	12	25	21
Rubella	0	0	0	0	0	0	0	0	2
Salmonellosis	66	10	12	7	16	21	967	866	1288
Shigellosis	91	5	10	0	66	10	656	216	311
Syphilis (1° & 2°)†	63	1	0	6	4	52	606	672	684
Tuberculosis	22	0	8	3	4	7	399	313	323

Localities Reporting Animal Rabies: Albemarle 1 skunk; Amelia 1 raccoon, 1 skunk; Appomattox 1 raccoon; Augusta 1 cow, 2 skunks; Campbell 1 fox, 1 raccoon; Chesterfield 1 raccoon; Fairfax 4 raccoons; Frederick 1 bat; Goochland 1 cat; Halifax 1 raccoon; Henrico 1 cat; Lancaster 1 otter; Loudoun 1 fox, 1 raccoon; Lunenburg 1 raccoon; Madison 1 skunk; Page 3 skunks; Patrick 1 skunk; Prince Edward 1 raccoon; Pulaski 2 skunks; Roanoke City 1 cat; Rockingham 1 skunk; Spotsylvania 1 skunk; Suffolk 2 raccoons; Warren 1 skunk; Westmoreland 1 raccoon.

Occupational Illnesses: Asbestosis 5; Carpal Tunnel Syndrome 75; Coal Workers' Pneumoconiosis 8; Lead Poisoning 2; Loss of Hearing 8; Silicosis 1.

*Data for 1993 are provisional. †Total now includes military cases to make the data consistent with reports of the other diseases. ‡Other than meningococcal.

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