REVIEW

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Underused options for preventing and treating influenza

ABSTRACT

Both amantadine and rimantadine are effective for preventing and treating influenza A, particularly in high-risk patients. However, they should be used judiciously due to the risk of central nervous system side effects and drug interactions. Zanamivir, a new agent for treating influenza, offers promise but needs further study and approval by the Food and Drug Administration before it can be recommended for routine use. Influenza vaccine, the most effective preventive measure, is widely underused.

KEY POINTS

Trivalent parenteral influenza vaccine is highly effective and safe, but remains underused.

Intranasal live-attenuated influenza vaccine appears effective, but is not yet widely used.

Amantadine and rimantadine are effective in preventing and treating influenza A only.

Zanamivir, an experimental drug not yet approved by the US Food and Drug Administration, is a neuraminidase inhibitor that appears effective in treating both influenza A and B.

ALTHOUGH WE HAVE the means to prevent most cases of influenza, and to reduce the severity of cases that occur, these strategies are underused.

This article briefly reviews the use of the antiviral drugs amantadine and rimantadine to prevent and treat influenza, and discusses a new antiviral medication that is currently being tested. It outlines the use of vaccines as a preventive strategy, and discusses how to improve vaccination rates among high-risk patients.

THE INFLUENZA VIRUS CHANGES RAPIDLY

If this is a typical winter, 10% to 20% of the US population will come down with influenza, and 20,000 people—primarily elderly, chronically ill, or immunocompromised persons—will die of it.[1] Some years, the toll is substantially higher. Influenza is the fifth leading cause of death in people over age 65 and the most common infectious cause of death in the United States.

Influenza is caused by infection with an RNA virus, influenza type A or B. These viruses are highly infectious because they can rapidly change their surface antigens, presenting our immune systems with a new target every year. Each virion carries two antigenic surface glycoproteins: hemagglutinin (H) and neuraminidase (N). These molecules can change in two ways:

Antigenic drift. Minor changes in the glycoprotein molecules, often involving only one or two amino acids, occur nearly every year

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TABLE 1

Who should get a flu shot: CDC recommendations

All persons aged 65 years or older
All residents of long-term care facilities, regardless of age
Adults and children with chronic cardiac or pulmonary disorders
Adults and children with other chronic medical problems, such as diabetes mellitus
Immunosuppressed patients (whether due to disease or medications)
Children receiving long-term aspirin therapy, to reduce the risk of developing Reye syndrome
Women who will be in the second or third trimester of pregnancy during the influenza season
Health care providers
Members of households of persons at high risk for influenza
Travelers to parts of the world with known epidemics

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Schedule routine visits in the fall to vaccinate elderly patients

and account for the epidemics that occur yearly in the Northern Hemisphere between December and March. Drift can occur in influenza type A and type B.

Antigenic shift. Major changes in these surface glycoproteins occur less often but make the virus much more infectious, causing pandemics. Antigenic shift is much more frequent in influenza type A than in type B.

Because the virus is constantly changing, the Centers for Disease Control and Prevention must formulate a new vaccine every year. Annual changes in influenza vaccine should provide antigenic matches for viruses expected to circulate in the world through April of the coming year. Accordingly, the 1998–1999 vaccine includes the influenza types A/Beijing/262/95-like (H1N1), A/Sydney/5/97-like (H3N2), and B/Harbin/7/94.[2]

VACCINE IS EFFECTIVE BUT UNDERUSED

Influenza vaccine is safe and effective. Because the vaccine is formalin-killed, it can neither cause influenza nor produce viremia. Studies in the elderly[3] and in healthy, working adults[4] found that vaccination can reduce the number of cases of influenza by at least 70%, the number of hospitalizations for influenza-related pneumonia by 45%, and influenza-related deaths by 40%. It is cost-effective,[5] and it is covered by Medicare. Yet, only 60% of people age 65 and older and 30% of those under age 65 at risk for influenza receive the vaccine regularly.[3]

Why is it so underused? Health care providers are partially to blame by not consistently offering the vaccine, and patients may decline vaccination for fear of side effects. Physicians could perhaps increase the rate of vaccination by scheduling routine office visits for elderly patients early in the fall and providing appropriate education about the benefits of the vaccine.

Persons at high risk for influenza infection (TABLE 1) should be vaccinated, ideally starting in mid-October to provide maximum protection during the peak of the epidemic. The only contraindication to the vaccine is a known allergy to eggs or other vaccine components.

Those who receive vaccine start to develop an antibody response after about a week, but the maximum response may take 2 to 4 weeks and declines within 10 months.[6] Local soreness at the injection site is the most common side effect.[4,7] Fever and myalgia occur in about 10% of adults.

New developments in influenza vaccination

Intranasal vaccine. Live-attenuated trivalent influenza vaccine given intranasally has been shown to be 93% effective in children,[8] and has provided additional protection when added to the parenteral vaccine in the elderly.[9] However, children receiving the intranasal vaccine experienced transient rhinorrhea, fever, and decreased activity.

Adjuvants to vaccination. The protective effect of influenza vaccine is suboptimal in immunocompromised patients, mainly due to poor humoral immune responses.[10] Adjuvants currently being evaluated to boost the immune response to the influenza vaccine include granulocyte-macrophage colony stimulating factor[11] and Ginseng extract.[12]

AMANTADINE AND RIMANTADINE AS PREVENTIVE DRUGS

Influenza type A contains a transmembrane ion channel called M2. Amantadine and rimantadine inhibit this channel and block RNA encod-

ing of influenza A, thus inhibiting viral replication.[13] They have no effect on influenza B.

Indications. Amantadine and rimantadine are indicated for persons at high risk (TABLE 1) who have not received the influenza vaccine at the time of an outbreak, and for their health care providers.[1] Because of the cost and potential side effects, mass chemoprophylaxis of the general population against influenza is not recommended.

Efficacy. Both medications are 70% to 90% effective in preventing influenza A when given for 10 days after exposure, or longer if given during an outbreak. Unfortunately, resistance and cross-resistance to either drug may develop.[14]

Side effects. Amantadine seems to cause more central nervous system side effects such as anxiety, light-headedness, and difficulty concentrating than does rimantadine.[15] Concomitant use of antihistamines and anticholinergics may worsen these side effects, and the concurrent use of central nervous system stimulants should be avoided. If agitation, hallucination, or marked behavioral changes develop, the medication should be discontinued.

Dosage. 100 to 200 mg daily. While rimantadine is extensively metabolized in the liver, amantadine is largely excreted unchanged by the kidneys. Thus, the dose of amantadine should be reduced in patients with renal failure, and the rimantadine dose should be reduced in patients with hepatic failure.

In persons at high risk, give amantadine or rimantadine at the first sign of symptoms

TREATMENT OF INFLUENZA

Traditionally, treatments for influenza were aimed at the symptoms only. These measures are still valid and include:

- Bed rest
- Oral hydration
- Acetaminophen or nonsteroidal anti-inflammatory agents to reduce fever, headache, and muscle aches
- Menthol throat lozenges to ameliorate sore throat
- Intranasal anticholinergics such as ipratropium bromide to alleviate nasal congestion. (However, systemic antihistamines and anticholinergics should be used cautiously in elderly, frail patients, who are at increased risk of developing side effects such as confusion and urinary retention.)

Most patients recover within 5 to 7 days using these measures. However, we now have antiviral drugs that can shorten the course of the disease and possibly decrease its complications.

Amantadine and rimantadine as influenza treatment

Either amantadine or rimantadine should be started within 48 hours of the onset of symptoms in persons at high risk. Although I recommend starting these agents on the basis of symptoms alone, nasopharyngeal cultures should be obtained in an attempt to isolate influenza virus, and confirmed cases should be reported to US Centers for Disease Control and Prevention through local and state health departments.

Doses are the same as for prophylaxis, and the recommended duration of therapy is 5 to 7 days.

Zanamivir

Zanamivir, a new agent, is a sialic acid analogue that selectively inhibits neuraminidase in both influenza A and B, thus inhibiting viral replication. The optimum dose has not been established, but studies in adults and children used 3.6 to 16 mg intranasally two to six times daily for 5 days.[16,17]

The drug is well tolerated and is 85% effective in reducing the frequency of febrile illness. In one study,[17] duration of symptoms was shortened by 3 days when the drug was begun within 1 day of the onset of illness. However, pending further study and FDA approval, routine use of this agent cannot yet be recommended.

Aerosolized ribavirin

Aerosolized ribavirin, a purine nucleoside analogue, has a broad spectrum of activity against DNA and RNA viruses. It inhibits viral RNA polymerase and interferes with viral messenger RNA initiation and elongation, thus inhibiting viral protein synthesis.

Ribavirin is widely used to treat respiratory syncytial virus bronchiolitis in hospitalized children.

Studies of ribavirin for influenza in healthy adults have not been conclusive.[18] It is teratogenic and may worsen bronchospasm and cause hemolytic anemia. At present, it is not recommended for treating "regular" influenza in healthy adults, but rather for influenza-associated pneumonia.

THWARTING INFLUENZA EPIDEMICS IN NURSING HOMES AND SCHOOLS

If an outbreak of influenza A is suspected in a nursing home, school, or other semi-closed setting, chemoprophylaxis should begin as soon as possible. The influenza vaccine should be given to all residents not previously immunized that season. Amantadine and rimantadine do not interfere with the antibody response to the vaccine, which could take up to 2 weeks in adults and 6 weeks in children; therefore, they should be given for at least 2 weeks, or until 1 week after the end of the outbreak. Contact between people with confirmed influenza and those receiving chemoprophylaxis should be limited to avoid transmission of drug-resistant virus.

Chemoprophylaxis and vaccination should also be offered to all employees and health care providers of that institution.

Global influenza alert network

Influenza is common and may affect parts of the world simultaneously or sequentially. For this reason, the World Heath Organization (WHO) has developed an Internet application linking the global WHO network of influenza centers (FluNet; http://oms.b3e.jussieu.fr/flunet/).[19] This early-alert system provides international authorities with real-time epidemiologic and virologic information necessary for global monitoring, perhaps allowing for early intervention to stave off epidemics and pandemics.

Amantadine and rimantadine do not interfere with the antibody response to the vaccine

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