CME CREDIT

Antiviral agents for treating influenza

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ABSTRACT

The new neuraminidase inhibitors zanamivir and oseltamivir are important additions to the treatment of influenza, being the first class of agents active against both influenza A and influenza B. The decision to use these agents rather than amantadine or rimantadine, which are effective only against influenza A, should be based on the age of the patient, antiviral activity, side effect profile, ease of administration, drug interactions, and cost. All of these agents are effective only when started within 24 to 48 hours of onset of symptoms. To avoid inappropriate use of these agents, treatment should be continued only in patients with a confirmed diagnosis of influenza. Although effective in decreasing symptoms, none of these agents prevent pneumonia or hospitalization secondary to influenza.

Start antiviral agents within 48 hours of the onset of symptoms

RECENTLY TWO NEW DRUGS—zanamivir (Relenza) and oseltamivir (Tamiflu)—were approved for the treatment of influenza. These drugs are the first of a new class of drugs called neuraminidase inhibitors, and unlike the two other influenza antivirals amantadine (Symmetrel) and rimantadine (Flumadine), are effective against both influenza A and B.

This article discusses the role of these agents in treating and preventing influenza. Vaccination, still the first line of prevention, is also discussed.

*Disclosure: Dr. Mossad serves on the speakers' bureau of Roche Pharmaceuticals (which makes oseltamivir); Dr. Goldman serves on the speakers' bureau of Roche Pharmaceuticals and Glaxo Wellcome Inc. (which makes zanamivir).

ANTIVIRAL AGENTS

Most treatments for influenza address only the symptoms, with antiviral agents reserved for specific situations. Patients at high risk (eg, elderly, those on dialysis, immunocompromised) with signs and symptoms of influenza during an epidemic in a community should be given consideration for treatment with an antiviral agent.

Amantadine and rimantadine were the first antiviral agents approved for treating and preventing influenza. In 1999 zanamivir and oseltamivir were also approved for treating influenza. Several studies found the latter two agents effective in preventing influenza as well, but at this time only amantadine and rimantadine are FDA-approved for the prevention of influenza.

Mechanisms of action

Amantadine and rimantadine block the ion channel M2, which prevents the opening and cleaving of hemagglutinin, thereby blocking the encoding of RNA and inhibiting viral replication. They are also believed to inhibit uncoating of the virus particle early in the replicative cycle.[1,2]

In contrast, oseltamivir and zanamivir have a different mechanism of action: they block the viral neuraminidase enzyme, which is necessary for releasing virus from infected cells. In addition, they increase formation of viral aggregates and decrease viral spread.[3,4]

Efficacy

All of the antiviral agents for influenza tend to decrease the duration of symptoms by 1 to 2 days when started within 48 hours of the onset of symptoms. Starting therapy more

than 48 hours after symptom onset has not demonstrated clinical benefit. None of the agents decrease serious complications of influenza (ie, pneumonia or hospitalization).

DOES THE PATIENT TRULY HAVE THE FLU?

Although often confused with the common cold, influenza is a distinct syndrome, characterized by sudden onset, high fever, nonproductive cough with chest discomfort, and constitutional symptoms such as headache, myalgia, and fatigue. In contrast, the common cold is slower in onset, has a greater degree of upper respiratory symptoms (runny/stuffy nose, sneezing), and less-intense constitutional symptoms.

It is important to differentiate these diseases, as the antiviral drugs available for influenza are not effective against the common cold. Yet antiviral agents must be started soon after the onset of symptoms to be effective.

Our approach is to have the patient come in the same day he or she calls, obtain a nasopharyngeal swab for a direct fluorescent antigen test for the influenza virus, and in those high risk patients we believe truly have influenza, start an antiviral agent immediately. Depending on the result of the test, the agent can be stopped, continued, or changed (FIGURE 1).

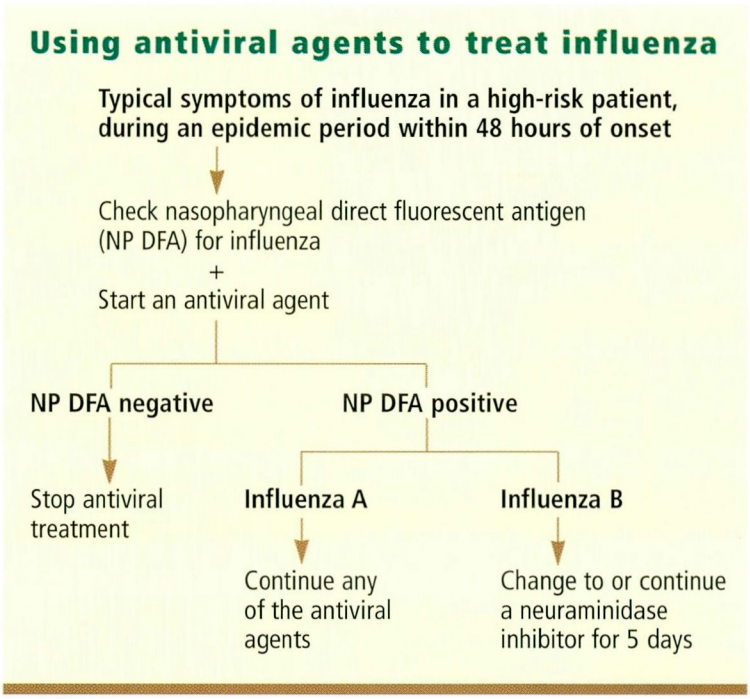

FIGURE 1. Approach to treating influenza with antiviral agents.

WHAT AGENT TO USE FOR TREATMENT?

The neuraminidase inhibitors may have some small advantages over the older agents, but no head-to-head comparisons of these agents have been conducted and there is no evidence that any agent is superior to another. Therefore, the choice of agent should be individualized. The following factors may affect the choice.[5–11]

Age of the patient. Amantadine is approved for use in children and adults, but rimantadine, zanamivir, and oseltamivir are approved for use in adults only.

Antiviral activity. Amantadine and rimantadine are active only against influenza A, but zanamivir and oseltamivir are active against both influenza A and influenza B. While most pandemics have been due to influenza A, in the 1998-1999 influenza season more than 20% of cases were due to influenza B.[12]

Side effect profile. The newer agents have fewer side effects than the older agents, especially amantadine. In particular, amantadine can cause central nervous system side effects including confusion and seizures (TABLE 1). These occur more frequently in the elderly and in patients with renal insufficiency. Rimantadine has side effects similar to amantadine's but to a much lesser extent.

We obtain a DFA when we start an antiviral agent

Zanamivir is available as an inhaled powder, which can cause throat discomfort and can exacerbate bronchospasm in patients with asthma. Patients with asthma or chronic obstructive pulmonary disease are advised to have a fast-acting bronchodilator available while using zanamivir. Patients should contact their physicians if they develop difficulty with breathing.[11]

Oseltamivir has relatively few side effects. Clinical trials did demonstrate an increased rate of nausea compared with placebo.

Ease of administration. Because zanamivir is an inhaled powder, it may be difficult for patients who have problems with dexterity to use this product. Oseltamivir is available as a capsule. Rimantadine and amantadine are available as tablets and in liquid dosage forms,

TABLE 1

Antiviral agents approved for treating influenza

ION CHANNEL M2 BLOCKERS

Amantadine (Symmetrel)

Indications
Prophylaxis and treatment of influenza A in adults and children

Dosage
Prophylaxis, adults: 200 mg daily or 100 mg twice a day*
Prophylaxis, children (1 to 9 years): 5 mg/kg daily in 1 to 2 divided doses (maximum 150 mg)
Treatment, adults: 200 mg daily or 100 mg twice a day* for 24 to 48 hours after symptoms disappear
Treatment, children (1 to 9 years): 5 mg/kg daily in 1 to 2 divided doses (maximum 150 mg) for 24 to 48 hours after symptoms disapppear

Adverse effects
CNS: Dizziness, insomnia, anxiety, impaired concentration, seizures (occur more frequently and severely in geriatric patients)
GI: Nausea, vomiting

Drug interactions
Anticholinergic agents, CNS stimulants, and antihistamines may worsen CNS side effects of amantadine; hydrochlorothiazide, quinidine, and quinine may decrease the renal clearance of amantadine

Cost (5-day course)
$3.50§

Rimantadine (Flumadine)

Indications
Prophylaxis of influenza A in adults and children
Treatment of influenza A in adults

Dosage
Prophylaxis, adults: 100 mg twice a day†
Prophylaxis, children (< 10 years): 5 mg/kg daily
Treatment: 100 mg twice a day† for 5 to 7 days

Adverse effects
Similar to amantadine but with less frequency and severity

Drug interactions
Acetaminophen and aspirin reduce the peak levels and area under the curve of rimantadine
Cimetidine increases the renal clearance of rimantadine

Cost (5-day course)
$8.75§

NEURAMINIDASE INHIBITORS

Zanamivir (Relenza)

Indications
Treatment of influenza A and B in adults and children >12 years

Dosage
10 mg twice a day for 5 days (two inhalations twice a day with the Diskhaler inhalation device)

Adverse effects
Nasal and throat discomfort, cough, headache
Bronchospasm has occurred in patients with asthma

Drug interactions
No drug interactions have been observed

Cost (5-day course)
$44.00

Oseltamivir (Tamiflu)

Indications
Treatment of influenza A and B in adults

Dosage
75 mg twice a day for 5 days‡

Adverse effects
Nausea, vomiting, headache

Drug interactions
No drug interactions have been observed

Cost (5-day course)
$53.00

*Preferred dosing regimen for elderly patients; patients with renal dysfunction may require 100 mg once daily
† Elderly patients and those with severe renal dysfunction should receive 100 mg once daily
‡ Patients with a creatinine clearance less than 30 mL/minute should receive 75 mg once daily
§Cost based on actual wholesale price as listed in Drug Topics Red Book, Montvale, NJ: Medical Economics, 1999.

TABLE ADAPTED FROM REFERENCES 11,20–25

which is easier for children and adults who have trouble swallowing pills.

Drug interactions. The neuraminidase inhibitors have not been shown to have significant drug interactions. The interactions of rimantadine and amantadine are listed in TABLE 1.

Cost. The new agents are as much as 15 times as expensive as amantadine.

VACCINATION STILL THE BEST STRATEGY

Each year, influenza kills from 20,000 to 40,000 people in the United States,[13] and necessitates more than 100,000 hospitalizations, mostly in people older than 65 years.

Our best option in preventing influenza epidemics is to improve the vaccination rate. Vaccination rates have doubled from 33% to 66% in the last 10 years in persons 65 years of age and older. However, persons younger than 65 who have medical conditions that place them at high risk should also be vaccinated, and in this group the rate is still 30% or less. Other groups that should be vaccinated, according to the Advisory Committee on Immunization Practices, are health care providers, all close contacts of patients at high risk for influenza complications, and any person who wishes to reduce the chances of contracting influenza.

Multiple studies have confirmed the efficacy and cost-effectiveness of the inactivated influenza vaccine in various risk groups.[14,15] Fortunately, this protection does not decrease with annually repeated influenza vaccination.[16]

Suggested measures to improve vaccination rates include:

- Automatic reminders to patients and health care providers that vaccinations are due.
- Educational programs for the public and patients that emphasize that the vaccine cannot cause influenza since it does not contain live virus, and that minor illnesses do not contraindicate the use of the vaccine.
- Easier access to vaccination in medical or public health settings.[17] Reducing out-of-pocket costs is also an incentive—when Medicare started reimbursing for vaccination in 1993, the vaccination rate increased in people 65 and older.

A live-attenuated, cold-adapted, trivalent, intranasal influenza vaccine has also shown promise[18,19] and will probably be approved for the 2000-2001 flu season.

None of the antiviral agents is proven superior to the others

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