Prophylaxis and Treatment for Influenza among the Elderly

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Hajime GOTO
Professor, The First Department of Internal Medicine, Kyorin University School of Medicine

Abstract: The treatment for influenza has undergone drastic changes in the last two years. The important changes are summarized below: 1) Introduction of accurate, simple and quick diagnostic techniques, 2) Introduction of novel anti-influenza virus drugs, 3) Reevaluation of influenza vaccination as a prophylaxis. Outbreaks of influenza are a matter of particular concern for the elderly because the elderly form a high-risk group for influenza. According to the data obtained in the epidemic season between 1998 and 1999, over 90% of influenza-related deaths in Japan occurred among persons aged 65 and older. The present review summarizes prophylaxis and treatment for influenza in the elderly focusing on the following: the efficacy of the influenza vaccine, the efficacy of single dose influenza vaccines, and the properties of anti-influenza virus drugs including amantadine, oseltamivir, and zanamivir, and antimicrobial treatment for influenza.

Key words: Amantadine; Oseltamivir; Zanamivir; Influenza vaccine

Introduction

The news of the emergence of a new influenza virus (influenza A: H5N1) in Hong Kong swept through the world in May 1997. This event has completely changed the understanding of doctors for influenza.

Since this world-shaking event, influenza is no longer regarded as a type of common cold syndrome and the necessity to implement countermeasures on a national scale has been recognized.

Consequently, the clinical approaches applied to the diagnosis, treatment, and prevention of influenza have undergone drastic changes in the last two years.

The important changes are summarized as follows:

1) Introduction of accurate, simple and quick diagnostic techniques
2) Introduction of novel anti-influenza virus drugs
3) Reevaluation of influenza vaccination as a prophylaxis

A clear line had not been drawn between influenza and the common cold syndrome pro-
duced mainly by rhinovirus. However, in those years, the conception has changed. Influenza has come to be considered as an independent disease requiring immediate virological diagnosis and specific antiviral treatment, and this infection can be prevented by vaccination.

Why Has the Occurrence of Influenza among the Elderly Become an Issue?

The occurrence of influenza among the elderly has become an issue because they form a high-risk group for influenza.

In Japan, epidemiological surveys of influenza are generally confined to epidemics among school-age children and less information is available on epidemics among the elderly. Since the influenza pandemic of 1998–1999, a project of fixed point observation has been promoted and a system to investigate the actual conditions of influenza among the elderly has been established. However, so far, there is insufficient information available on influenza activity among this population and further effort is necessary to obtain more data.

In the US, which has a population approximately double that of Japan, influenza deaths exceed the predicted number by twenty to forty thousand during the epidemic season, and accordingly, the number of influenza-related deaths in Japan can be estimated at ten to twenty thousand. Special attention should be directed to the fact that most of these deaths occur among the elderly. Taniguchi et al. assessed the data obtained between 1998 and 1999 and reported that over 90% of influenza-related deaths occurred among persons aged 65 and older in Japan. Thus, this population can be categorized as a high-risk group in Japan.

Countermeasures for Influenza Epidemics among the Elderly

I. Vaccination

(1) Influenza vaccination in Japan

In Japan, a system of group influenza vaccination for school-age children is adopted and this vaccination had been in practice for many years. Up to 1987, the number of vials of vaccines used annually per 1,000 population exceeded 200, indicating that the quantity of influenza vaccine used in Japan was consistently more than double that used in the US.

In subsequent years, however, doubts had been expressed over the efficacy of the influenza vaccine and since the revision of the Preventive Vaccination Law in 1994, the vaccination has been administered on a voluntary basis. At the time of this revision, no recommendation was made to encourage elderly individuals to receive influenza vaccination, which resulted in a significant reduction of influenza vaccination rates.

On the other hand, the efficacy of the influenza vaccine has been considered as established in foreign countries and many medical care providers have endeavored to introduce a practical method to improve influenza vaccination rates. So, nowadays, significant differences exist in the number of vials of vaccines used annually per 1,000 population in Japan and foreign countries. The statistics obtained are as follows: US (239), Canada (150), France (119), UK (102), and Japan (8).

(2) Is the influenza vaccine effective?

In 1973, Sugiura et al. conducted a comparative study using tetanus toxoid as a control to evaluate the efficacy of influenza vaccine at the Institute of Public Health, Japan. According to their results, the vaccine provided 80% protection against influenza virus A and 43% protection against influenza virus B. In 1997, Sugaya et al. conducted a controlled study on infants and reported that the vaccine was effective in preventing influenza virus A in 67.5% and in preventing influenza virus B in 43.7%.

These figures do not directly indicate the effective rates of the influenza vaccine, and do not therefore mean that 67.5% of those who underwent the vaccination were free from infection. They indicate that, of those who did not receive the vaccination who suffered the infec-
tion, 67.5% could have been free from the infection if they had undergone the vaccination.

The effective rate of the vaccine can be calculated by the following formula:

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\text{Effective rate of vaccine (\%) = } [1 - (\text{morbidity among the vaccinated/ morbidity among the unvaccinated})] \times 100
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The results obtained in the above controlled studies are considered to demonstrate the effectiveness of the influenza vaccine among infants and normal adults.

Among cases of influenza in the elderly, the following points require consideration:

a. Does the vaccine provide a similar rate of protection among the elderly as among younger adults?

b. If the vaccine fails to prevent the occurrence of infection, does it contribute to the amelioration of influenza symptoms?

c. Does the vaccine prevent the development of influenza complications, especially pneumonia?

d. Does vaccination contribute to a reduction in influenza-related deaths?

The problem lies in the fact that insufficient data has been accumulated giving answers to these questions, and more data will be needed before the clinical implications of influenza vaccination for the elderly can be clarified.

(3) Is one dose of the influenza vaccine sufficiently effective in preventing the infection?

As mentioned above, the influenza vaccination was first introduced as group immunization for school-age children in Japan and two doses have routinely been indicated for all individuals including school-age children and adults. In foreign countries including the US, one dose has routinely been indicated and the efficacy of this immunization technique has been evaluated.

In this situation, doctors have evaluated the effectiveness of single dose vaccinations in Japan. Horie et al. measured the elevation of serum antibody levels after one and two doses for comparative study. They observed no difference in the elevation of serum antibody levels between the one dose group and two dose group. They divided the subjects into two groups according to their ages and recognized no significant difference in the elevation of serum antibody levels between those aged 40 and above and those under 40.

The Council for Public Health, the Ministry of Health and Welfare, Japan, considered these scientific data and finally concluded, on October 18, 2000, that a single dose of the influenza vaccine was to be indicated for elderly individuals aged 65 and over. Accordingly, one dose will be routinely indicated, at least among the elderly, in Japan.

2. Amantadine

The target-site of amantadine is the M2 protein which has the functions of an ion channel and virus uncoating. Amantadine shows antiviral effects by affecting this ion channel and inhibiting virus uncoating. This drug has been used as an anti-Parkinson agent in Japan, although it is widely used as an effective anti-influenza virus drug in foreign countries, including the US. Amantadine is ineffective for influenza B because the M2 protein exists only in influenza virus A.

Influenza viruses are regarded as a group of viruses with certain mutations (quasispecies), and amantadine resistant viruses are detected with a frequency of 1/10^4. In the course of antiviral treatment, resistant strains are selected and increases in accordance with the duration of treatment. Therefore, the recommended duration of amantadine treatment is less than five days.

When amantadine is given orally in a dose of 50mg, its peak blood level is 0.12µg/ml, and it has a comparatively long half-life of 12.3 hours. The usual dosage is 50mg per dose, twice daily. Influenza viruses proliferate rapidly and the viral amount reaches its peak within two days of infection. Accordingly, the beneficial effects of amantadine can not be obtained if 24–48 hours have passed before the administration. Thus, the fundamental problem of treating influenza patients with amantadine is the timing of
its administration. A person may catch a cold and decide to rest at home for a few days; if the symptoms persist it may lead him/her to consult his/her physician. Amantadine therapy is not indicated for this type of patient, as it is too late for such patients to start this antiviral treatment. It is necessary for physicians to educate the public so that they can have correct knowledge about antiviral treatment for influenza.

Amantadine is approved both as a drug to treat influenza and as a drug to prevent influenza. For preventive purposes, amantadine can be administered by the following two methods.

1) Consecutive administration following influenza vaccination for two weeks till the elevation of the antibody titer
2) Prolonged consecutive administration to persons who are unable to undergo vaccination because of, for example, anaphylactic hypersensitivity to (chicken) eggs

Adverse reactions of amantadine include digestive symptoms such as anorexia and nausea, and psychiatric symptoms such as insomnia, easy fatigability and depression.

3. Neuraminidase inhibitors

(1) Oseltamivir

Oseltamivir displays its antiviral activity by inhibiting the neuraminidase of the influenza virus. It is a synthesized antiviral agent, which has been designed in a completely novel manner.

After proliferation in the cells, influenza viruses are released from the infected cells. In the process of acceleration of the infection, sialic acid is to be incised by neuraminidase and influenza viruses are to be released from infected cells. Oseltamivir, which is similar in structure to sialic acid, blocks the activity of neuraminidase and finally inhibits the release of viruses from the infected cells. Because neuraminidase exists both in influenza virus A and in influenza virus B, oseltamivir is effective for influenza caused by these two viruses.

During the period between 1997 and 1998, a clinical trial was conducted in the US to evaluate the efficacy of oseltamivir as a treatment for influenza. Regarding the morbid period as one of the main endpoints, oseltamivir showed a significant reduction in morbid period when administered orally in a dose of 75 mg twice daily (placebo administration group 124.2 hours vs. oseltamivir administration group 93.9 hours).

In 1998, the use of oseltamivir as a prophylactic drug was evaluated in the US. When oseltamivir was orally administered in a dose of 75 mg once a day, the incidence of influenza was 25/519 in the placebo administration group and 6/520 in the oseltamivir administration group. Thus, oseltamivir provided protection against influenza at the significantly high rate of 76%.

Oseltamivir is effective both in treating influenza and in preventing the disease but its beneficial effects are considered to be shown more significantly in patients with influenza virus A than in those with influenza virus B.

The frequency of oseltamivir resistant strains was lower than that of amantadine resistant strains. The infectivity of oseltamivir resistant strains is definitely lower than that of original strains because the resistant strains possess weaker activity of neuraminidase.

The advantages of oseltamivir are summarized as follows:

a. Effective both for influenza virus A and for influenza virus B
b. Lower frequency of resistant strains
c. Reduction of infectivity of resistant strains

Like amantadine, oseltamivir shows minimum therapeutic effects unless the administration is started within 24 to 48 hours. This disadvantage remains as the most important issue to be resolved in the future.

Oseltamivir has been approved in fourteen countries including the US, Canada and Switzerland. In Japan, it was approved in February 2001.

(2) Zanamivir

Like oseltamivir, zanamivir is a neuraminidase inhibitor. The antiviral activity of zanamivir in vitro is as strong as that of oseltamivir. Zanamivir is inhaled through the respiratory tract using a special inhaler. This inhaler is the
same as that used for fluticasone treatment. It was approved in February 2001.

As in the case of amantadine, these neuraminidase inhibitors are considered to be effective for the influenza viruses which possess new assortment of hemagglutinines and neuraminidases, they therefore play important roles in treating and preventing such new influenza viruses.

4. Antimicrobial treatment

The complication of bacterial pneumonia and resulting death are serious problems among elderly patients with influenza. The impairment of the epithelium of the respiratory tract due to influenza facilitates the development of pneumonia. The major causative bacteria include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*.

Considering the risks of complicated bacterial pneumonia is indispensable in treating elderly patients with influenza. Although antimicrobial treatment is not necessarily indicated in younger adult patients, the use of antimicrobials agents is recommended in older adult patients.

The following antimicrobials are available:

(1) β-lactam: Since β-lactamase producing bacteria such as *Haemophilus influenzae* and *Staphylococcus aureus* are frequently detected, the β-lactamase inhibitor containing penicillins or cefems are to be selected.

(2) Macrolides: The existence of macrolide resistant strains of *Streptococcus pneumoniae* and *Staphylococcus aureus* and insufficient antimicrobial effects on *Haemophilus influenzae* are pointed out as disadvantages, therefore available macrolides are limited.

(3) New quinolones: Since the antimicrobial effects on *Streptococcus pneumoniae* present a problem, so-called respiratory quinolones including sparfloxacin, which are effective for *Streptococcus pneumoniae*, are to be selected.

Conclusion

Remarkable improvements have been made in the clinical treatment for influenza during the last two years and this marked progress has caused clinicians to change their recognition of this disease.

An influenza epidemic immediately causes large numbers of patients to visit clinics within a short period of time, and respiratory internists can not manage all patients when an influenza outbreak occurs like a storm. In this situation, all physicians regardless of their specialist field, are expected to have an up-to-date knowledge of the treatments available for influenza and of the modalities involved.

REFERENCES


