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Charles Feldman obtained his undergraduate and postgraduate degrees at the University of the Witwatersrand. He spent 18 months undertaking research at the Brompton Hospital in the United Kingdom on a Medical Research Council (SA) postdoctoral scholarship. His main research interest has always been in the field of pulmonary infections and the title of his PhD was Aspects of Community-acquired Pneumonia. *He was co-author of the guidelines on* Influenza Vaccination *published in the* South African Medical Journal. *He is currently President of the South African Thoracic Society.*

Antiviral agents for prevention and/or treatment of influenza virus infections: old and new

Influenza continues to be a cause of significant morbidity and mortality around the world each year, but advances in its treatment and prophylaxis mean that it no longer needs to be such a headache for the GP.

Epidemics of influenza A and/or B typically occur every year during the winter months and are a cause of considerable morbidity and even mortality worldwide.[1,2] While influenza may occur at any age, it is more frequent in children and more serious in the elderly, the latter because of the presence of underlying diseases that are associated with more complicated infection.[1]

Uncomplicated influenza is characterised by the abrupt onset of constitutional and respiratory symptoms and signs.

Influenza is spread from person to person by sneezing and coughing.[1] The incubation period is short, usually 1 - 4 days, with an average of 2 days. Patients are infectious from the day before the onset of symptoms until 5 days after symptoms start. Uncomplicated influenza is characterised by the abrupt onset of constitutional and respiratory symptoms and signs. On the basis of symptoms alone, respiratory illness due to influenza is difficult to distinguish from illness caused by a wide range of other respiratory pathogens. Ideally, therefore, a definitive laboratory diagnosis of influenza would be used to guide the use of antiviral agents. In practice, laboratory confirmation by rapid shell vial culture has a 48-hour turnaround time, which exceeds the window of opportunity for instituting anti-influenza therapy in an individual patient. Routine laboratory surveillance for influenza in major centres can provide information on community influenza activity and allow a presumptive diagnosis of influenza in an individual when community activity is high.

Symptoms of infection usually resolve in a limited number of days in most individuals. In some cases exacerbation of prior co-morbid conditions (cardiac and respiratory) may occur and influenza can cause primary viral pneumonia or lead to secondary bacterial pneumonia. A number of other local and systemic complications have been described.[1,2]

PREVENTION AND TREATMENT OF INFLUENZA INFECTION

The main option for the prevention of influenza and its complications is yearly vaccination with the appropriate formulation of inactivated vaccine (killed vaccine) before the seasonal increases in influenza virus circulation.[1] Antiviral agents are an adjunct to vaccination for the control and prevention of influenza infection, but should never be used as a substitute for vaccination.[1] Two different classes of

Table I. Treatment and prophylaxis dosages for anti-influenza drugs

Drug	Subject	Dose
Amantadine*/rimantadine†	adult	100 mg bd
	adult > 65 yrs	50 mg bd or lower
	child 1 - 9 yrs (< 40 kg)	5 mg/kg/day (max. 150 mg) divided into bd dosages
	child ≥ 10 yrs (> 40 kg)	100 mg bd
Zanamivir	adult	10 mg (2 inhalations) bd (once daily for prophylaxis)
	child ≥ 12 yrs	10 mg (2 inhalations) bd (once daily for prophylaxis)
Oseltamivir*	adult	75 mg bd (once daily for prophylaxis)
	child ≥ 13 yrs	75 mg bd (once daily for prophylaxis)
	child 1 - 12 yrs (< 40 kg)	< 15 kg: 30 mg bd 16 - 23 kg: 45 mg bd 24 - 40 kg: 60 mg bd

* Dosage adjustment advised for impaired renal function.
† Dosage adjustment advised for impaired renal or hepatic function.

antiviral agents are available, the adamantanes (older agents) and the neuraminidase inhibitors (newer agents). In South Africa, only one of the adamantanes (amantadine) and one of the neuraminidase inhibitors (zanamivir) are currently licensed for use. However, for completeness, all the different agents will be discussed below.

Adamantanes[1-5]

These agents were described more than 30 years ago. Amantadine and rimantadine are chemically related antiviral agents that are active against influenza A virus, but not against influenza B virus. Both agents are administered orally and rimantadine is better tolerated. They act by blocking the M2 protein channels of influenza A virus. Once influenza A is taken up into a cell through receptor-mediated endocytosis, the M2 channel's hydrogen ion transport function ordinarily facilitates acidification of the virus's interior, a process essential for viral uncoating and release of the nucleic acid for transcription and translation. Adamantanes therefore prevent uncoating of the virus, and this is inhibitory to viral replication.

These agents are about 70 - 90% effective as prophylaxis against influenza A infections. Also, when administered within 48 hours of onset of illness, they can reduce the duration of uncomplicated influenza A virus infection.They have not been clearly demonstrated to be effective in preventing serious influenza-related complications. Moreover, most studies of the benefit of all the antiviral agents have been conducted in uncomplicated influenza.When used as prophylaxis, they may also prevent illness while permitting subclinical infection and the development of protective antibodies against circulating influenza virus. This means that some patients on prophylaxis with these agents will develop protective immune responses to the virus. They also do not interfere with the antibody response to the vaccine.

One problem with the use of the adamantanes is the potential for rapid development of influenza virus resistance. To reduce the emergence of resistance, these agents should be discontinued as soon as clinically warranted, which is typically 3 - 5 days after initiation of therapy or 24 - 48 hours after disappearance of symptoms/signs.

Dosage recommendations vary according to age and associated medical conditions (Table I).

Both the adamantane agents can cause central nervous system (CNS) and gastrointestinal (GIT) side-effects. The CNS side-effects include nervousness, anxiety, insomnia, difficulty in concentrating and light-headedness. It is recommended that patients with seizure disorders be observed carefully during treatment. Amantadine should be used with caution when administered concurrently with drugs that affect the CNS, particularly stimulants. Concurrent administration of antihistamines and anticholinergics increases the risk of adverse CNS reactions. GIT side-effects include nausea and anorexia. Side-effects are usually mild and stop soon after the drugs are discontinued. Because amantadine has anticholinergic effects, it should not be given to anyone with untreated angle closure glaucoma. In acute overdose of amantadine, CNS, renal, respiratory and cardiac side-effects, including arrhyth-

mias, have been noted. No studies have been undertaken regarding their safety in pregnant women. Both amantadine and rimantadine have been shown to be teratogenic and embryotoxic in large doses in animal studies.

Neuraminidase inhibitors[1-4,6-8]

Viral neuraminidase, a surface glycoprotein of influenza A and B, aids the release of newly formed virus particles from infected cells. Neuraminidase may also counteract viral inactivation by respiratory mucus, thus facilitating cell-to-cell spread of the virus. Neuraminidase inhibitors block the activity of neuraminidase and selectively reduce the replication of influenza A and B viruses.

Zanamivir and oseltamivir are chemically related antiviral agents, known as neuraminidase inhibitors, which have activity against both influenza A and B. Oseltamivir is administered orally and zanamivir by oral inhalation. These agents can reduce the duration of uncomplicated infection by approximately 1-2.5 days compared with placebo. However, they have not been shown to be effective in preventing serious influenza-related complications. Both agents are effective in preventing febrile, laboratory-confirmed influenza illness and have been reported to be effective as prophylaxis after a household member has been diagnosed as having influenza.

Zanamivir has been approved in South Africa for the treatment of people ≥ 12 years of age. Oseltamivir has been approved in the USA (but has not been licensed yet in South Africa) for treatment of children ≥ 1 year of age and for chemoprophylaxis of anyone ≥ 13 years (see Table I for neuraminidase inhibitor dosages).

In some studies, zanamivir was associated with respiratory symptoms, including airway hyperresponsiveness and/or deterioration of lung function, including a decrease in FEV_1 of > 20%, particularly in patients with asthma or obstructive airway disease. Subsequently zanamivir was shown to be safe and beneficial in patients with asthma and chronic obstructive pulmonary disease. Nonetheless, all patients with airway disorders taking this agent should have a fast-acting bronchodilator available. Other side-effects noted with both these agents have been relatively uncommon. No clinical studies have been undertaken of safety in pregnant women. Very limited clinical data are available about drug interactions with these agents.

Anti-influenza drugs as chemoprophylaxis[1-3,9,10]

Factors such as cost, compliance, and side-effects need to be considered when determining the agent of choice, timing and duration of therapy. To be maximally effective the drugs should be taken daily for the entire duration of the influenza season; however, to be more cost effective, one study of amantadine or rimantadine prophylaxis suggested that these drugs should be taken only during the period of peak influenza activity. Individuals who should be considered for prophylaxis include the following:

- Persons at high risk who have not been vaccinated or are vaccinated after influenza activity has begun. Persons at high risk of influenza complications can still be vaccinated after an outbreak of influenza has begun. Since the development of antibodies takes approximately 2 weeks, high-risk cases could receive prophylaxis from the time of vaccination until antibodies develop.
- Unvaccinated persons who provide care to those at high risk. To reduce the spread of the virus to persons at high risk during community or institutional outbreaks, those who provide care and are unvaccinated could receive prophylaxis. They include employees of hospitals, clinics, and chronic-care facilities, household members, district nurses, and volunteer workers.
- Persons who have immune deficiency. Chemoprophylaxis could be considered for persons with immune deficiency, who may be expected to have an inadequate antibody response after vaccination.
- Persons in whom vaccination is contraindicated (e.g. those with severe hypersensitivity to egg protein). Chemoprophylaxis throughout the influenza season or during peak viral activity could be considered for high-risk cases who should not be vaccinated.
- Other persons wishing to prevent infection with influenza (e.g. persons who are to travel from one area to another, such as from the southern hemisphere to the northern hemisphere).

Control of institutional outbreaks of influenza[1,9]

Use of antiviral agents is a key component in the treatment and prevention of institutional outbreaks of influenza infection, and is combined with other outbreak control measures. Most published studies have reported on influenza A outbreaks among nursing home populations using the adamantanes. Less information is available on the neuraminidase inhibitors and influenza A or B outbreaks. According to the Centers for Disease Control and Prevention, Atlanta, USA, during outbreaks chemoprophylaxis should be given to all residents irrespective of their vaccination status for ≥ 2 weeks. If surveillance indicates ongoing

occurrence of new infections, prophylaxis should be continued until 1 week after the last infection. Chemoprophylaxis can also be offered to unvaccinated staff looking after persons at high risk. In addition to nursing homes, similar recommendations are made for control of outbreaks in closed or semi-closed settings, such as dormitories or large businesses. These agents have also been used for control of household outbreaks of influenza infection.

References available on request.

IN A NUTSHELL

Yearly epidemics of influenza are a cause of considerable morbidity and mortality worldwide.

Influenza vaccination is the primary means of prevention of infection and its complications.

Antiviral agents are an adjunct to vaccination for control and prevention of influenza infection, but should never be used as a substitute for vaccination.

Two classes of antiviral agents are available for the prevention and treatment of influenza infection, the adamantanes and the neuraminidase inhibitors.

Adamantanes block the M2 protein channels of the influenza A virus and prevent uncoating of the virus inside the cells, so inhibiting replication.

The neuraminidase inhibitors block the activity of viral neuraminidase, so preventing the release of newly formed viruses from cells.

Amantadine, an adamantane available in South Africa, is 70 - 90% effective in preventing illness caused by influenza A infection, and when administered within 2 days of onset of illness can reduce the duration of uncomplicated influenza A infection.