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Antiviral Drugs for Treatment and Prophylaxis of Influenza

By Daniel Hartung, Pharm.D., MPH Candidate, OSU College of Pharmacy

The annual influenza epidemic, which is responsible for approximately 36,000 deaths annually in the US, is a predictable source of morbidity and mortality worldwide. Immunization is the primary method for preventing infection and complications due to influenza virus. The US Centers for Disease Control (CDC) guidelines for use of the influenza vaccine are summarized in Table 1 below.[1] There are also four antiviral drugs available for the treatment and prevention of influenza. While not a substitute for vaccination, these drugs are an important adjunct for managing influenza epidemics. This article will summarize the current role of antiviral drugs for the treatment and prophylaxis of influenza.

Table 1: CDC Influenza Vaccination Recommendations (2005-2006)

High Risk Groups	LAIV	IIV
Persons > 65 years of age	No	Yes
Residents of long-term care facility	No	Yes
Persons with chronic pulmonary, cardiovascular, metabolic, renal, immunologic, or hemoglobin-related disease	No	Yes
Persons with conditions compromising respiratory function or handling of secretions	No	Yes
Children <18 years on long-term aspirin therapy	No	Yes
Pregnant women	No	Yes
Children 6-23 months	No	Yes
Other recommended groups		
Persons 50-64	No	Yes
Persons who are in contact with high risk individuals or children < 6 years	Yes*	Yes
Persons who fulfill essential public services	Yes*	Yes
Students and others residing in institutional settings	Yes*	Yes

IIV=inactivated influenza virus;
LAIV= live, attenuated influenza virus (Flumist™)
*LAIV is NOT appropriate for persons aged <5, persons with a history of Guillain-Barre syndrome, those with an egg allergy, or those with close contact to high risk individuals with immunosuppressive disease

There are two types of influenza, A and B. Influenza A is further classified according to surface proteins, hemagglutinin (H) and neuraminidase (N), displayed on its viral coat. H and N facilitate the movement of influenza virus from a host cell and are important targets for both antiviral drugs and vaccines. The extent of an influenza epidemic is determined largely by the antigenic variation in these proteins that occurs from year to year. During most years, there are only slight changes in the surface proteins. These minor changes are "antigenic drift" and are the reason why yearly reformulation of the influenza vaccine is needed. Occasionally, a significant antigenic change will occur resulting in a virus with a novel H and/or N subtype leaving much of the population immunologically naïve. These changes are called "antigenic shift" and have been strongly associated with past influenza pandemics.[2] All characterized influenza A H and N subtypes have been found in water fowl, but only H1, H2, and H3 have established stable transmission mechanisms in humans.[3] Transition from birds to humans occurs when differing strains co-infect an intermediate species susceptible to human strains, and genetic material is allowed to mix. This is not always the case, as there have been recent cases of bird to human transmission of H5N1("Avian Flu"), an aggressive subtype which has circulated among birds in Asia since 1997.[4] There is concern that H5N1 influenza virus will mutate to a form that allows sustained human to human transmission. Although Influenza B circulates to some extent during most yearly epidemics, it is not a major cause of severe outbreaks because it does not undergo extensive antigenic change.

M2 ion channel blockers (adamantanes)

Amantadine and Rimantadine belong to a class of antivirals called the M2 ion channel blockers, or adamantanes. The M2 blockers exert their antiviral effect by inhibiting the M2 ion channel which interferes with viral uncoating inside the host cell.

Prophylaxis: A recent Cochrane Collaborative Review evaluated the effectiveness and safety of amantadine and rimantadine for the treatment and prophylaxis of influenza A.[5] The evidence indicates both drugs are 60%-70% effective at preventing clinical illness when taken during epidemic periods (6-8 weeks). Both drugs appeared to be equally effective when used for prophylaxis. The effectiveness of rimantidine for prophylaxis among elderly nursing home patients was also established in one randomized, placebo controlled study of 328 mostly vaccinated nursing home residents, where rimantidine (100 or 200mg) continued to lower the risk of influenza infection by almost 60%.[6]

Treatment: The M2 blockers are effective at reducing the severity and duration of influenza A illness. It has been shown that M2 blockers can reduce the duration of influenza illness, specifically fever, by about 1 day, if administered within the first 48 hours of ilness.[5] These drugs also reduce the symptoms of influenza infection such as fever severity, cough, and malaise.[5, 7] However, it is not known if the M2 blockers can prevent serious influenza-related complications, such as pneumonia.

The M2 blockers have three important limitations. First, they have no activity against influenza B virus. Second, resistance can occur after spontaneous mutation in one nucleotide during therapy and is not uncommon.[8, 9] Finally, the M2 blockers can cause significant central nervous side effects such as insomnia, confusion, dizziness, and hallucinations. Amantadine is also known to have potent anticholinergic properties that may limit its use, particularly in elderly patients. The side effect profile of rimantadine has been shown to be significantly better tolerated.[5] Both amantadine and rimantadine are eliminated through the kidneys and therefore doses should be adjusted for patients with renal insufficiency. Both agents are pregnancy category C and should be avoided in pregnancy.

Neuraminidase Inhibitors

The neuraminidase inhibitors (NI), oseltamivir (*Tamiflu*) and zanamivir (*Relenza*), are a relatively new class of antivirals active against both influenza A and B. The NI are potent neurominidase substrate analogues that prevent cleaving of replicated viruses from the host cell, limiting replication and further cellular infection.

Prophylaxis: Oseltamivir is the only NI approved by the FDA for prevention of influenza. However, published data from randomized clinical trials indicate that both oseltamivir and zanamivir reduce the risk of symptomatic influenza by between 70%-90%, depending on the underlying population.[10, 11] Overall, both drugs appear to be similar in efficacy when studied in healthy populations. In one large randomized clinical trial, prophylaxis with oseltamivir among mostly vaccinated elderly nursing home patients reduced the incidence of laboratory-confirmed influenza from 4.4% to 0.4% (relative risk reduction 92%).[12] Oseltamivir was also effective at reducing the incidence of influenza-related complications, defined as otitis media, sinusitis, or chest infection, by 86%. Both drugs were studied and shown to be protective among persons exposed to a household member with an existing influenza infection.[13-15] However, unlike the M2 blockers, the emergence of resistance during therapy is far less common.[9, 16]

Treatment: Simliar to the M2 blockers, the NI have been shown to be effective at reducing the duration and severity of illness caused by influenza infection in healthy individuals.[10,11] When administered within 48 hours of symptom onset, NI can reduce the time to fever resolution by about 1 day. However, several randomized trials have shown that the sooner influenza is recognized and treatment is initiated, the faster symptoms will resolve.[17-19] There is limited evidence on the impact of treatment on the incidence of influenza-related complications. In an analysis of pooled data from 10 placebo-controlled randomized trials that included 769 high-risk individuals,

treatment with oseltamivir was associated with a 50% relative risk reduction in all-cause hospitalizations (1.6% versus 3.2%; p=0.17).[20] Another trial in children ages 5–12 suggests that treatment with zanamivir can reduce the incidence of complications requiring antibiotic use (15% versus 12%, p=ns) compared to placebo.[21]

The NI are generally well tolerated with a side effect profile similar to placebo.[11] Nausea and vomiting will occur with 10%-15% of patients treated with oseltamivir.[22] Zanamivir is delivered as a dry powder inhaler and has been associated with bronchospasm and should be used with caution in individuals with underlying respiratory disease.[23, 24] Unlike M2 blockers, for which resistance can emerge during therapy, antiviral resistance to the NI has not been a major problem.[11] Animal studies have suggested these agents are harmful to the fetus and have been rated pregnancy category C.

Guidelines for the Use of Antivirals[25]

None of the antivirals are a substitute for annual influenza vaccination. The CDC recommends the NI be reserved for treatment of patients who are experiencing a life-threatening influenza-related complication or in individuals who are at high risk for influenza-related complications. Because of resistance issues, the M2 blockers should only be used for prophylaxis. For institutional outbreaks, prophylaxis should be initiated in all residents, regardless of vaccination status, and unvaccinated workers (if only recently vaccinated, workers should receive antivirals for 2 weeks following vaccination to allow time to mount an immune response). Prophylaxis should be continued in all residents for a minimum of 2 weeks. If additional cases continue to occur, prophylaxis should continue for 1 week following the last case. Persons who are at high risk for complications should be given prophylaxis if they are likely to be exposed to others who are infected. When a high risk individual is part of a household containing an infected individual, prophylaxis should be continued for 7 days. The CDC recommendations also suggest considering prophylaxis for individuals in a community affected by influenza who are at high risk and not able to receive vaccine, at high risk who have not had enough time to mount a sufficient immune response (2 weeks in adults), immunosuppressed and not able to mount vaccine antibody response, and health care workers unable to obtain vaccine. While the CDC does not specifically address prophylaxis of influenza B virus outbreaks, it is important to remember that only the NI are active against influenza B. Table 2 shows pertinent prescribing information for the four antiviral drugs.

Until recently, most of the emphasis on planning for yearly epidemics was focused correctly on formulating the yearly vaccine and encouraging vaccination in high-risk individuals. The eventual emergence of a new influenza subtype, not covered by vaccine, could make antivirals a more important component of influenza management. Antiviral drugs will be needed for both general prophylaxis and treatment until vaccine for the new subtype can be developed and produced in sufficient quantities. The H5N1 virus is currently a top candidate for the next pandemic because there is little natural immunity in the population and it has exhibited a high case fatality rate.[4] A vaccine for this subtype has been developed and is currently in clinical trials. While the M2 blockers are the preferred option for prophylaxis during most influenza seasons, the H5N1 currently exhibit resistance to this class.[11] Thus, the NI would be the only option for prophylaxis and treatment in the event of a H5N1 pandemic. During normal years, influenza causes the most complications in individuals with pre-existing comorbidities (i.e. high risk groups), however experience with past pandemics indicate that emerging subtypes may exhibit virulence properties that make otherwise healthy individuals susceptible to severe complications.[26] Thus, the prioritizing of therapy for individuals may change depending on virulence characteristics of the virus.

Table 2: Antiviral Prescribing Information In Adults and Children

	Adults		Children		
Drug*	**Prophy-laxis♠**	**Treat-ment♣**	**Prophylaxis♠**	**Treatment♣**	**Cost♦ (10 days)**
Amantadine*	100 mg BID	100 mg BID	5 mg/kg/d in DD Max 150 mg/d	Same as prophylaxis	$9
Rimantadine*	100 mg BID	100 mg BID	5 mg/kg/d in DD Max 150 mg/d	NA Same as proph.	$19
Oseltamivir*	75 mg QD	75 mg BID	FDA-approved >13 yrs Same as adult	FDA-approved >1yr ≤ 15 kg: 30 mg bid 16-23 kg: 45 mg bid 24-40 kg: 60 mg bid >40 kg: 75 mg bid	$133
Zanamivir*	NA 10 mg inhaled QD	10 mg inhaled BID	NA 10mg inhaled QD	FDA-approved ≥13yr 10 mg inhaled BID	$57

NA = not FDA approved

*Doses need to be adjusted for renal dysfunction

♠Institutional outbreaks require at least 2 weeks of prophylaxis (1 week after end of last case), within household, prophylaxis requires 7-10 days

♣Treatment course is typically 5 days

♦Cost based on average ingredient cost for 10 day course FFS OHP 1/1/05 -7/1/05 (rebates excluded)

Reviewed by: Ann Thomas, M.D., DHS Public Health Physician and David Bearden, Pharm.D., OSU College of Pharmacy

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Managing Editor: Kathy L. Ketchum
ketchumk@ohsu.edu or 503-947-5220