Drugs for Influenza

One flu over …

September, 2000

Influenza continues to be a significant cause of morbidity and mortality in North America. In Canada during any given flu season, 25% or more of the general population will be infected and 500-1500 deaths may result.[1] Of the two main flu viruses, influenza A is the more frequent and severe. Persons living in a close environment with others are particularly vulnerable as the virus spreads by person-to-person contact, contaminated articles, and airborne droplets. People of all ages can be affected but influenza's severity is greatest among the very young, the elderly and those whose health is compromised.

Influenza A has a 48 hour incubation period followed by abrupt onset of fever, chills, myalgia, headache, and extreme fatigue over the next 24 hours. These symptoms persist for 2-3 days and are often accompanied by respiratory tract symptoms such as sore throat, runny nose, and non-productive cough. The infectious stage is 3-5 days from onset in adults but up to 7 days in young children. Symptoms generally resolve in 5-7 days but some, like cough and fatigue, may persist for weeks. In Canada, the impact of influenza can be reduced through two measures:

- **prophylaxis** through immunization or alternately with antivirals such as amantadine
- **treatment** of active illness when indicated

HIGHLIGHTS

- **Immunization is the most effective means of preventing and controlling spread of influenza**
- **Immunization of health care workers is primarily for the protection of the patient although reduced absenteeism due to illness may be an added benefit**
- **Bacterial infections should be considered and treated appropriately**
- **Antiviral agents are of little value if prescribed ≥48hr after onset of illness**
- **Amantadine side effects are almost always related to failure to reduce dosage for age and decline in renal function**

VACCINATION AGAINST INFLUENZA

Immunization with inactivated viral vaccine is the **most effective** method of prevention. Trivalent vaccine is produced annually to cover the two main subtypes of influenza A as well as influenza B. Because these viruses undergo continuous mutation, new vaccine must be produced each year to combat both the previous and newly emergent strains. Revaccination should also occur yearly due to the antigenic drift and since previously formed antibodies are relatively short-lived with titres falling below protective levels within a few months after immunization.

Influenza hits from November to April with peak incidence between late December and early March. Since it takes 1-2 weeks following vaccination for antibodies to develop and provide protection, **the optimal time to immunize is October through mid-November**. However, once vaccine is available, **immunization can begin in September or early October** to ensure good coverage prior to significant circulation of influenza. Antibody titres begin to fall below protective levels after 6 months. Since this can occur in <4 months in the elderly, immunization in this group may be preferred in November.

Efficacy is dependent upon a person's age and immune response and on the similarity between the vaccine and the actual strains in circulation. Since vaccine components must be chosen 9 months in advance, there is potential for considerable antigenic drift to occur prior to the flu season. In the elderly and those with chronic medical conditions, the vaccine may be less effective due to a reduced immune response with fewer antibodies produced and a shorter period of protection prior to levels falling off. Generally **in healthy adults the vaccine is 70-90% effective** in preventing illness[2]; this is reduced to 30-40% in the frail elderly[3] although hospitalization is reduced by 50% and death by 80%[4]. In non-institutionalized elderly and chronically ill, vaccine can reduce hospitalization by 70% and death by 85%[5].

Side effects: The vaccine does not contain live virus and cannot produce active illness. The most common complaint is mild soreness at the injection site for up to 2 days. In children not previously exposed to influenza or with use of whole rather than split virus vaccine, fever and myalgia may occur within 6-12 hours of vaccination and last 1-2 days; prophylaxis and treatment with acetaminophen may be helpful. Severe allergic reactions are rare and related to the egg protein or the thimersol preservative. Although very rare cases of Guillain-Barre Syndrome have been reported, the rate is no different (1-2 per million) than that seen in the unvaccinated population.

Indications: Immunization is **strongly recommended** and provided **free of charge** to select **groups at high risk** of complications or death:

- all adults ≥ 65yrs old (The American ACIP recommends ≥50yrs[6])
- residents of long-term care facilities and group homes for the elderly or chronically ill
- adults or children ≥ 6months old with chronic pulmonary, cardiovascular, renal, metabolic, or immunocompromised conditions
- children ≥ 6months - 18yrs on chronic ASA therapy (to prevent complication with Reye's Syndrome)

**Hospitalized high risk patients should be vaccinated prior to discharge if not already immunized*

➽ **It is strongly recommended that health care givers and cohabitants who have regular contact with these groups also be vaccinated**. ***Saskatoon District Health offers vaccination at no charge to all its employees regardless of site or occupation*.**

...Vaccination of staff in Long Term Care can reduce patient morbidity and mortality...

Vaccine is available at most physicians' offices and community health units at a cost to the client of up to **$15.00 / dose** (includes variable administration fee). Others groups recommended for vaccination include:

- essential service workers
- students in institutional settings (e.g. dorms)
- travelers (check with Public Health regarding destination)
- pregnant women who will be in 2nd or 3rd trimester during flu season (vaccine considered safe for administration at any time)
- anyone wanting it

The greatest barrier to vaccination remains public education. Many people think they do not need immunization, believe it lacks efficacy, or fear adverse effects.[7]

Contraindications: Vaccine should not be given to people who:

- have had anaphylactic reactions to previous doses or to eggs
- are acutely ill and febrile until their symptoms resolve

AMANTADINE PROPHYLAXIS:

Amantadine (Symmetrel®) is the only antiviral drug approved for prophylaxis in Canada for adults and children ≥ 1year old. Amantadine prevents viral uncoating by blocking the ion channel activity of viral M2 protein. It is **70-90% effective in preventing influenza A** but is ineffective against influenza B which lacks the M2 protein substrate. **Amantadine should not replace immunization unless the vaccine is contraindicated**.

Prophylaxis with amantadine is indicated for:

- control of influenza A outbreaks in chronic care facilities (should be given to **all residents and unvaccinated staff**)
- prophylaxis for high risk patients when vaccine is unavailable, contraindicated or unlikely to be effective due to antigenic drift
- adjunctive treatment for late vaccination in high risk patients during the 2 week interval prior to adequate antibody production
- adjunctive therapy in patients with immune deficiency who may not have adequate antibody response to vaccine (e.g. HIV)
- health care workers in contact with high risk patients during community outbreaks

Dosage is dependent on age and renal function (>80% eliminated unchanged in the urine) and is outlined in Table 1. Prophylaxis should be continued for 7-8 days following onset of the last case in an outbreak or possibly the entire flu season depending on the indication. Treatment is discussed later in this paper.

Side effects: **Side effects are most often related to failure to adjust dosage for age related decline in renal function**. CNS disturbances are most common with 5-10% of healthy adults reporting difficulty concentrating, insomnia, lightheadedness, and irritability. Nausea and vomiting can also occur. High serum levels have been associated with agitation, seizures, hallucinations, and marked behavioral changes; this is particularly problematic in the elderly and debilitated if the dose has not been adjusted. Patients with previous psychiatric conditions, seizure disorders, or on concurrent anticholinergic drugs may also be at increased risk of adverse CNS effects. They should receive a reduced dose or alternately, a neuraminidase inhibitor may be considered.[8]

ANTIVIRALS FOR INFLUENZA TREATMENT

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza can help reduce the inappropriate use of antibiotics as well as optimize antiviral therapy. However, some bacterial infections can produce symptoms similar to influenza or result as a complication, and should be treated appropriately if suspected. Recently the FDA issued a warning that some patients who died of serious bacterial complications of influenza were prescribed only antivirals and failed to receive appropriate antibiotic therapy.[9]

Three antiviral agents are approved in Canada for treatment of influenza: amantadine (Symmetrel®) and two neuraminidase inhibitors, oseltamivir (Tamiflu®) and zanamivir (Relenza®).

◆**Amantadine** can reduce the duration and severity of **uncomplicated influenza A** if given within 24-48 hours of illness. It is ineffective against influenza B. Dosages and side effects are compared in the chart following. Treatment should be discontinued after 3-5 days or within 48 hours of symptom resolution.

◆**Neuraminidase inhibitors (NI)** represent a new class of antivirals. **Oseltamivir (Tamiflu®)** and **zanamivir (Relenza®)** inhibit neuraminidase, the enzyme responsible for cleaving sialic acid on the surface of host cells and virus envelopes to allow release of viral progeny. The result is a reduction in the amount of virus particles released to infect other cells. These drugs are effective for both influenza A and B. **To be effective for treatment, NIs must be initiated within 48 hours of onset of symptoms.** Earlier administration is associated with greater improvements although benefits are modest.

Studies show a reduction in severity of symptoms and earlier resolution of uncomplicated influenza but results have been variable. Major North American and European zanamivir studies have shown an average reduction in median time to alleviation of major symptoms of 1-1.5 days.[10,11] The MIST Study[12] in the Southern hemisphere reported greater reductions of 1.5-2.5 days. When study populations were subgrouped in a recent pooled analysis, clinical benefit was greatest in those who started treatment within 36 hours of symptom onset, were febrile, and/or had laboratory-confirmed influenza.[13] One zanamivir study showed no detectable benefit in patients who started treatment after 30 hours of onset of symptoms.[7] Although some studies show reductions in subsequent antibiotic use, **neither drug has shown effectiveness in preventing serious influenza related complications** (e.g. viral and bacterial pneumonia or exacerbation of chronic diseases). Additionally, data on efficacy of treatment in children and high risk groups is limited as studies do not usually include these populations in their treatment groups; most reported results have been obtained in otherwise healthy adults. These agents may have a more promising role in prophylaxis although they are not yet approved for this indication. They may be preferred in patients with a history of seizures or those on anticholinergic medications.[8] Oseltamivir and zanamivir are compared in Table 2.

Considerations before prescribing NIs:

- ◆vaccination is still the primary method of preventing and controlling influenza
- ◆a typical influenza patient receiving a NI within 48 hours of the onset of influenza symptoms could expect to shorten the duration of symptoms by 1 day, and gain 1/2 day in getting back to normal activity (at a cost of ≥ $50)[14]
- ◆some patients may not get any benefit, especially if influenza A or B is not confirmed or if treatment is started after 36 hours of symptom onset
- ◆as with all drugs, these agents are not free of adverse effects… **oseltamivir can cause nausea and vomiting**; taking doses with food may alleviate this…**zanamivir may cause bronchospasm, especially in patients with asthma or COPD**
- ◆the potential for bacterial infection should be considered for patients who become severely ill; NIs will not be effective in patients who go on to develop bacterial infections

TIPS in Preparing for the Influenza Season

- ◆Public and health professional education regarding role and benefit of immunization are key to success
- ◆ Immunization Drives in early fall for those at:
  - High risk ~September-October
  - Low risk ~October-November
- ◆For residents in long term care: have estimated CrCl determinations in patient charts prior to influenza season (Oct.); write orders for amantadine to be given upon confirmation of an outbreak (dose adjusted for age/renal function)
- ◆Emphasis on Staying Healthy;
  - IF SICK, STAY HOME - !!!!

We wish to acknowledge those who have assisted in the development and review of this newsletter: Dr. K. Williams (Inf. disease) , Dr. T. Laubscher & Dr. M. Jutras (Family Medicine), Dr. E. Berman (LTC), Dr. C. Neudorf (MHO), Yvonne Shevchuk (U. of S. - C. of Pharmacy) members of the SDH - Influenza in LTC working group, & the RxFiles Advisory Committee. *Sharon Downey BSP & Loren D. Regier BSP, BA*

References available on request, or on line
www.sdh.sk.ca/RxFiles

Table 1: AMANTADINE (Symmetrel ®) Dosage by Age and Renal Function [8,15]

	DOSAGE
No recognized renal dysfunction	
Children 1-9 yrs old[a]	5mg/kg OD or divided BID (total daily dose not to exceed 150mg)
Children >10 yrs old	200mg OD or divided BID[b] (if less than 40 kg, give 5mg/kg per day)
Adults ≤ 64 yrs old	200mg OD (or 100mg BID)[b] Note: **100mg OD** adequate/better tolerated for prophylaxis
Adults ≥ 65 yrs old	100mg OD
Renal dysfunction: CrCl* in ml/second (ml/min in brackets)	
>1.33ml/s (≥80 ml/min)	100mg po OD
1.00-1.32 ml/s (60-79 ml/min)	Alternating daily doses of 100mg & 50mg
0.67-0.99 ml/s (40-59 ml/min)	100mg every 2 days
0.50-0.66 ml/s (30-39 ml/min)	100mg twice weekly
0.33-0.49 ml/s (20-29 ml/min)	50mg three times per week
<0.32 ml/s (10-19 ml/min)	Alternating weekly doses of 100mg & 50mg
Hemodialysis	200mg every 7 days

* **Calculation of creatinine clearance (CrCl):**

- CrCl ml/second = $\frac{(140\text{-age}) \times \text{weight (kg)}}{\text{serum creatinine (umol/L)} \times 50}$
- Females: CrCl = 0.85 x CrCl (male)

Watch units for ml/second !!!

[a] **Use in children** < 1yr old has not been evaluated

[b] **Patients with history of seizures**: consider reduction in amantadine dose or use alternate neuraminidase inhibitor

Table 2: Antiviral Agents for Treatment of Influenza

	M2 INHIBITORS	NEURAMINIDASE INHIBITORS	
	Amantadine ***SYMMETREL®***	**Oseltamivir** ***TAMIFLU®***	**Zanamivir** ***RELENZA®***
Influenza coverage	Influenza A only	Influenza A & B	Influenza A & B
Route of administration	Oral	Oral	Oral Inhalation (<2 % oral bioavailability)
Dosage forms available	100mg **capsules** 10mg/ml **syrup**	75 mg **capsules**	5mg per inhalation via **Diskhaler** [d]
Approved for prophylaxis	YES - ≥ 1yr old	NO [c]	NO [c]
Approved age for treatment	≥ 1yrs old	≥ 18 yrs old	≥ 12 yrs old
Dosage [a]	**see Table 1**	75 mg po BID x 5 days	2 inhalations's (10mg) q12h x 5days [e]
Adjustment for renal failure	YES - see Table 1	YES - if CrCl < 0.33ml/sec 75 mg po OD	NO
Side Effects	CNS - lightheadedness, insomnia, irritability (less common when dose adjusted for age & renal function) GI upset	**Nausea**, vomiting Insomnia Vertigo Bronchitis	Nasal/throat irritation Headache GI upset Bronchitis, Cough
Cost in Saskatchewan [b]	**~$10.00 (cap); $18.00 (syrup)**	**~ $54.00**	**~ $66.00**
Comments/ Precautions	◆Adverse CNS effects related to and progressive with high serum concentrations ◆Reduce dosage for age, renal function and seizure history	◆ Prodrug requiring hepatic activation ◆ ~ 10% incidence of **nausea** +/- vomiting; taking with food may help	◆may cause **bronchospasm** ◆in people with asthma or COPD avoid or use cautiously with access to a SABA (such as salbutamol *Ventolin®*)

[a] Treatment must be initiated **within 48 hrs** of symptoms onset

[b] **Cost** based on 5 day course of treatment for otherwise healthy adult <65 yrs old; includes acquisition cost, mark-up and dispensing fee

[c] New NIs not presently approved for prophylaxis although recent and ongoing trials show promising efficacy rates of 80-85% at 1/2 of the usual dose.

[d] Instructions included with Diskhaler, however patient should be shown how to use device properly

[e] **Zanamivir - Recommended on first day**: 2 inhalations stat; repeat after 2 hours then begin 2 inhalations q12h the next day for 4 days

[f] **COPD** = chronic obstructive pulmonary disease **SABA** = short acting beta agonist

The Rx Files – Drugs for Influenza
References

[1] Health Protection Branch. Flu Information, 2000.
[2] Palanche AM. Influenza Vaccine: a reappraisal of their use. Drugs 1997; 54: 841-56.
[3] Arden NH et al. Experiences in the use and efficacy of inactivated influenza vaccine in nursing homes in Kendal AP, Patriarca PA, eds. Options for the control of influenza. New York, NY: Alan R. Liss Inc, 1986: 155-68.
[4] Patriarca PA et al. Efficacy of influenza vaccine in nursing homes: reduction in illness and complications during an Influenza A (H3N2) epidemic. JAMA 1985; 253: 1136-9.
[5] National Advisory Committee on Immunization's Statement on Influenza Vaccination for the 2000-2001 Season. Health Protection Branch - Laboratory Centre for Disease Control (Ottawa, Canada), Vol 26 (ACS-2), June 1, 2000.
[6] Advisory Committee on Immunization Practices. Prevention and Control of Influenza. Center for Disease Control. Atlanta, Georgia. April 14, 2000 / 49 (RR03); 1-38.
[7] Fowles JB, Beebe TJ. Failure to immunize the elderly: a systems problem or statement of personal values? Jt Comm J Qual Improv 1998; 24:704-10.
[8] McGeer A, Sitar D, Tamblyn S, et al. Use of antiviral prophylaxis in influenza outbreaks in long term care facilities. Can J Infect Dis 2000; 11(4): 187-192.
[9] FDA reminds prescribers of important considerations before prescribing flu drugs. FDA Talk Paper. FDA, US Dept of Health and Human Services, Rockville, MD; January 12, 2000.
[10] Hayden FG et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. N Engl J Med 1997; 337: 874-80.
[11] Monto AS et al. Efficacy and safety of neuraminidase inhibitor zanamivir in treatment of influenza A and B virus infections. J Infect Dis 1999; 180:254-61.
[12] MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet 1998; 352: 1877-81.
[13] Monto AS et al. Randomized, placebo-controlled studies of inhaled zanamivir in treatment of influenza A and B: pooled efficacy analysis. J Antimicrob Chemother 1999; 44:23-9.
[14] Jeffeson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults (Cochrane Review). In *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.
[15] Adapted from the National Advisory Committee on Immunization's Statement on Influenza Vaccination for the 2000-2001 Season. Health Protection Branch - Laboratory Centre for Disease Control (Ottawa, Canada), Vol 26 (ACS-2), June 1, 2000.