disease prevention news

December 18,2000

Vol. 60 No. 26

Treatment and Chemoprophylaxis of Influenza

Influenza viruses circulate every winter and during most winters cause substantial morbidity and mortality. The first influenza isolate for the 2000-2001 season in Texas was identified in October, and influenza activity has increased steadily since that time. To date, the highest level of activity in the state has been detected in the Austin area. Most isolates have been influenza type A(H1N1), the strain represented in the 2000-2001 influenza vaccine by the A/New Caledonia/20/99-like virus. Isolates for 2 influenza cases in Central Texas were identified as influenza B. See DPN *Vol. 60, No. 16 and* DPN *Vol 60,No. 21 for information on this season's influenza immunization campaign. Antiviral agents can be important adjuncts to influenza vaccine for prevention and control of influenza.[1] This article describes the 4 currently available antiviral agents against influenza.*

Annual influenza vaccination is recommended for persons at high risk for severe complications following influenza infection and for their caregivers and household contacts. During most years, influenza vaccine becomes available to providers by October; however, this year distribution of vaccine has been delayed nationwide because of manufacturing problems. Although a substantial amount of vaccine has been distributed, some providers have still not received vaccine. As a result, public and private vaccination programs have been delayed this season, and individuals who would otherwise have been vaccinated by this time remain unprotected.

Elderly persons and persons of all ages with certain chronic medical conditions are more likely than those who are younger and healthier to develop serious complications as a result of influenza infection. Even individuals with uncomplicated influenza infection stand to miss work and school days. It has been estimated that the cost of a severe influenza epidemic in the United States may be as high as 12 billion dollars. The greatest total costs of influenza are not due to the direct costs of inpatient and outpatient medical care, but to lost productivity.[2]

The symptoms of uncomplicated influenza can usually be managed with bed rest, fluids, and simple home remedies or over-the-counter medications such as antipyretics, analgesics, and cough suppressants. The choice of antipyretic and analgesic is important for children and teenagers, who, because of the risk of developing Reye's syndrome, should never be given aspirin when influenza is suspected.[3]

Antiviral agents offer another option for treating influenza. There are now 4 different antiviral drugs available with specific activity against influenza (Table 1). Two of these drugs, amantadine and rimantadine, are effective only against influenza type A. Two recently approved drugs, zanamivir and oseltamivir, are effective against both influenza types A and B. Amantadine and rimantadine can reduce the severity and duration of influenza A infections when administered within 48 hours of illness onset, but have not been proven to prevent complications.[4,5] Zanamivir and oseltamivir have been shown to reduce the duration of uncomplicated influenza illness when administered within 30 to 36 hours of illness onset. These drugs also can reduce the severity of uncomplicated influenza illness; there is evidence from clinical studies that they also can reduce the incidence of influenza-associated complications and the use of antibiotics. However, larger studies are needed to confirm these findings and to determine the extent to which they can reduce severe complications.[6-9]

Amantadine and its closely related analogue rimantadine have been studied since the 1960s and were approved for treatment and prophylaxis of all type A

Continued ☞

Also in this Issue:

TABLE 1. Comparison of Antiviral Agents for Influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Types of Influenza Virus Inhibited	Influenza A	Influenza A	Influenza A&B	Influenza &B
Route of Administration	Oral	Oral	Oral inhalation	Oral
Ages for which Treatment Approved	≥1 yr	≥14 yrs	≥12 yrs	≥18 yrs
Ages for which Prophylaxis Approved	≥1 yr	≥1 yr	Not approved for prophylaxis	≥13 yrs
Cautions	Dosage adjusted for renal insufficiency; ages < 10 yrs and > 64 yrs	Dosage adjusted for renal and hepatic insufficiency; ages < 10 and frail elderly	Not recommended for patients with airway disease	Dosage adjusted for renal insufficiency

Adapted from: CDC. Neuraminidase inhibitors for treatment of influenza A and B infections. MMWR 1999;48(RR14).

influenza viruses in 1976 and 1993, respectively. Both drugs prevent influenza A virus replication by the same mechanism, and viruses are cross-sensitive and cross-resistant. However, the pharmacokinetics of these drugs differ markedly. Both drugs have high oral bioavailability, but amantadine is largely unmetabolized and is associated with a higher incidence of central nervous system and neuropsychiatric side effects, especially among the elderly. Both drugs require dosage adjustments for patients with renal insufficiency, and rimantadine requires adjustment in patients with severe hepatic dysfunction.[4,5]

Zanamivir and oseltamivir interfere with the replication of both influenza type A and type B viruses by inhibiting enzymatic activity of the viral neuraminidase, which plays an important role in the release of virus from infected cells. Zanamivir is administered as a fine powder directly to the respiratory tract by oral inhalation using a specially designed breath-activated plastic device. Only about 4% to 17% of the inhaled dose is absorbed systemically and is excreted unchanged in the urine.[9] Pharmacokinetic studies have concluded that the potential for drug interactions is very low. [10] In clinical trials adverse events were uncommon, and the incidence of adverse events was similar in treatment and placebo groups. However, after zanamivir was approved for marketing in 1999, cases of bronchospasm and respiratory function deterioration following inhalation of zanamivir were reported; most, but not all, were among patients with underlying asthma or chronic obstructive pulmonary disease.[1] Therefore, zanamivir is not recommended for treatment of patients with underlying airways disease.

Oseltamivir is well-absorbed after oral administration and is metabolized in the liver to the active compound GS4071. Because GS4071 is excreted in the urine by glomerular filtration and tubular secretion, a reduction in dosage is recommended for patients with creatinine clearance <30 mL/min. Since oseltamivir is metabolized by high capacity esterases, no dosage adjustment has been recommended for patients with liver disease. In clinical trials, mild and transient gastrointestinal disturbances, primarily nausea and vomiting, were reported more frequently among subjects receiving oseltamivir than those receiving placebo. These events generally occurred on initiation of treatment and resolved within two days; dropout rates

Continued ☞

were low and similar between treatment and placebo groups. There is also some evidence that taking the drug with food may reduce the incidence of these side effects. [9,11]

Amantadine and rimantadine are also approved for prevention of influenza type A. Oseltamivir was approved for prevention of influenza types A and B in November 2000 after it was shown to be effective in preventing influenza illness and infection in studies of naturally occurring and experimental influenza A and B infections.[11] There is evidence that zanamivir is also effective as prophylaxis, and it may be approved for this indication in the future. [12]

Many studies have shown amantadine and rimantadine to be 70% to 90% effective in preventing illness caused by naturally occurring strains of type A influenza viruses; chemoprophylaxis with these drugs has been effective in stopping outbreaks in long-term-care facilities and boarding schools and in limiting transmission within households.[4,5] However, efforts should be made to isolate persons who are being treated from those who are taking drug for prophylaxis because individuals who are treated with either amantadine or rimantadine may shed resistant virus during the course of therapy.[13] Although emergence of resistance during treatment has not been shown to reduce therapeutic efficacy in persons shedding resistant virus, resistant viruses can be transmitted to contacts, whether or not they are undergoing chemoprophylaxis. Apparent transmission of resistant virus has been described in nursing homes and within households.[14,15]

The extent of transmission of resistant viruses is unknown. Most amantadine- and rimantadine-resistant viruses have been isolated from persons undergoing drug treatment or, less often, from their contacts. In situations when only prophylaxis has been used, isolation of resistant virus has been uncommon. International surveillance for drug-resistant influenza A viruses has shown that few isolates obtained from patients with no known history of antiviral treatment are resistant.[13-16]

Studies to date suggest that resistant virus does not readily emerge during treatment with zanamivir and oseltamivir, although strains of influenza virus resistant to these compounds have been identified both *in vitro* and *in vivo*. However, resistant viruses do not emerge as rapidly during passage in tissue culture in the presence of zanamivir and oseltamivir as they do in the presence of amantadine and rimantadine; in clinical trials resistant strains have rarely been isolated from subjects taking these drugs for treatment of influenza infection. Furthermore, laboratory studies to date suggest that, compared with wild type virus, most viruses that have developed resistance to zanamivir or oseltamivir may be at a growth disadvantage.[17-20] *In vitro* studies have shown that amantadine- and rimantadine-resistant viruses are sensitive to zanamivir and oseltamivir.

Use of rapid diagnostic testing can greatly facilitate early detection and confirmation of influenza in the community and help determine treatment options for patients who present with influenza-like illness.[20] It is not necessary to test every patient once a community outbreak of influenza has been detected and confirmed. There are a number of commercially available assays that can be used to rapidly detect influenza from nasopharyngeal, nasal or throat swab specimens. One enzyme immunoassay, Directigen Flu A®, will detect only influenza type A.[21] A new enzyme immunoassay, Directigen Flu A&B® detects both influenza A and B, and indicates a positive or negative result for each influenza virus type.[22] Other available rapid diagnostic tests for point-of-care use detect both influenza

Continued ☞

types A and B but do not distinguish between the two. The ZstatFlu® test is a colorimetric enzyme assay that detects activity of the influenza neuraminidase enzyme.[23] AB FLU OIA® is an optical immunoassay that detects antibody-antigen interactions that are registered visually on a slide.[24] QuickVue® is an immunoassay using monoclonal antibodies; a color indicator on a test strip is used to determine if influenza virus antigens are present in throat swab, nasal wash, or nasal aspirate specimens.[25]

Knowledge of national, state, and local influenza surveillance data--disseminated by the Centers for Disease Control and Prevention and by state and local health departments--can be used to determine which rapid assays are best to use in a given influenza season. During most influenza seasons, only one influenza virus type predominates in any given geographic area at any given time during the season. During the more unusual seasons when both influenza types A and B circulate simultaneously, 2 tests or the single test that distinguishes type A from B, may be needed to determine the etiology of the outbreak. When suspected or confirmed influenza outbreaks occur, specimens also should be sent to state or local health departments for viral culture, which is necessary to characterize the virus and determine how similar it is to the vaccine strains or to test for other agents if influenza is not detected This is also an important contribution to the accumulation of virologic data needed for annual influenza vaccine strain selection.

Prepared by Nancy Arden, MN, Department of Microbiology and Immuniology, Baylor College of Medicine.

References

1. Advisory Committee on Immunization Practices. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(RR03):1-38.

2. Schoenbaum SC. Economic impact of influenza: the individual's perspective. Am J Med 82(suppl 6A):26-30, 1987.

3. Hurwitz E.S. Reye's syndrome. Epidemiol Rev 1989;11:249-253.

4. Tominack RL, Hayden FG. Rimantadine hydrochloride and amantadine hydrochloride use in influenza A virus infections. Infect Dis Clin North Am 1987;1:459-78.

5. Douglas RG. Drug therapy: prophylaxis and treatment of influenza. N Eng J Med 1990; 322:443-450.

6. Hayden FG, Osterhaus ADME, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. N Engl J Med 1997;337:874-880.

7. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. JAMA 2000;283(8):1016-24

8. The Mist Study Group. Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet 1998;352:1877-1881.

9. Relenza [package insert]. Research Triangle Park, NC: Glaxo Wellcome Inc; 1999.

10. Daniel MJ, Barnett JM, Pearson BA. The low potential for drug interactions with zanamivir. Clin Pharmacokinet 1999;36((Suppl 1):41-50.

11. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase in inhibitor oseltamivir to prevent influenza. NEJM 1999; 341(18):1336-43.

12. Monto AS, Robinson DP. Herlocher ML, Hinson JM, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy healthy adults: a randomized controlled trial. JAMA 1999;282:31-35.

13. Monto AS, Arden NH. Implications of viral resistance to amantadine in control of influenza A. Clin Infect Dis 1992;15:362–367.

14. Mast EE, Harmon MW, Gravenstein S, Wu SP, Arden NH, Circo R, Tyszka G, Kendal AP, Davis JP. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of influenza A(H3N2). Am J Epidemiol 1991;13:988-997.

15. Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, SooW. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. N Engl J Med 1989;321:1696-1702.

16. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. Curr Top in Microbiol and Immunol 1992;176:120–130.

17. Colacino JM, Laver WG, Air GM. Selection of influenza A and B viruses for resistance to 4-guanidino-Neu5Ac2en in cell culture. J Infect Dis 1997;176:S66-S68.

18. Gubareva LV, Bethell R, Hart GJ, Murti KG, Penn CR, Webster RG. Characterization of mutants of influenza A virus selected with the neuraminidase inhibitor 4-guanidino-Neu5Ac2en. J Virol 1996;70:1818-1827.

19. Blick TJ, Tiong T, Sahasrabudhe A, et al. Generation and characterization of an influenza virus neuraminidase variant with decreased sensitivity to the neuraminidase-specific inhibitor 4-guanidino-Neu5Ac2en. Virology 1995;214:475-484.

Continued on back page ☛

Disease Prevention News
2000 Annual Index

Continued ☞

TOPIC **ISSUE**

Continued ☞

Errata

Several typographical errors appeared in the print copies of DPN Vol. 60, No. 24. The Internet version was corrected prior to its appearance online and its delivery via the list servers. The corrections are as follows:

In the second paragraph on page 1, "The main incubation..." should read, "The mean incubation...." In the first paragraph of the second column on page 1, p+0.008 should be p=0.008. The second sentence in the second paragraph of column 2, page 1, should read, "Of the 67 people who consumed most or parts of the meal, 83% were interviewed.

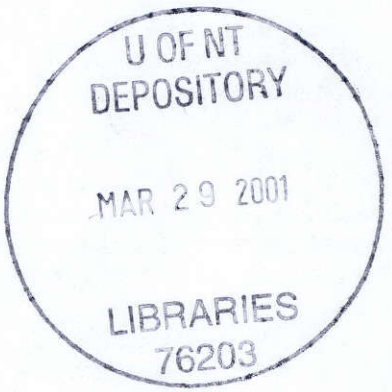
DPN staff apologize for any problems these errors may have caused our readers.

Disease Prevention News (ISSN 1068-7920) is a biweekly newsletter published by the Texas Department of Health, Public Health Professional Education, at 1100 West 49th Street, Austin, TX 78756-3199, (512) 458-7677, FAX (512) 458-7340, email: dpn@tdh.state.tx.us.
Periodicals Postage Paid at Austin, TX
POSTMASTER: Send address changes to Disease Prevention News, 1100 West 49th Street, Austin, TX 78756-3199.
The electronic version of *Disease Prevention News*, the subscription form, and a searchable index of issues from 1995 are available at the followingwebsite: http://www.tdh.state.tx.us/phpep/

Disease Prevention News
Texas Department of Health
1100 West 49th Street
Austin, TX 78756-3199

Address Service Requested

Periodicals Postage Paid at Austin, TX



Continued from page 4

20. Tai CY, Escarpe PA, Sidwell RW, et al. Characterization of human influenza virus variants selected in vitro in the presence of the neuarminidase inhibitor GS 4071. Antimicrob Agents Chemother 1998;42:3234-3241.

21. Directigen Flu A [product package insert] Becton Dickenson & Co, Cockeysville, MD, 1996.

22. Directigen Flu A&B [product package insert] Becton Dickenson & Co., Sparks, MD., 2000.

23. Zstat flu [product package insert]. Oklahoma City, Oklahoma: ZymeTx Inc, 1998.

24. Flu OIA [product package insert]. Boulder, Colorado: BioStar, Inc, 1999.

25. QuickVue [product package insert]. San Diego, CA: Quidel, 2000.

Attention *DPN* Print Subscribers!

The deadline to renew print subscriptions without interruption of service is December 31, 2000. All subscription renewal packets were mailed out last month. You can subscribe to *Disease Prevention News* print or electronic services at any time online: http//www.tdh.state.tx.us/phpep/, click on *Disease Prevention News*.

If you did not receive your renewal materials in the mail and cannot subscribe online, *contact Linda Darlington by* ***phone:*** **(512) 458-7677** ***or*** **(800) 252-8239 (press 4)**, *or by* **FAX: (512) 458-7340.**