Antiviral Agents for Seasonal Influenza: Side Effects and Adverse Reactions

Note: On December 19, 2008, CDC issued Interim Recommendations for the Use of Influenza Antivirals for the 2008-09 Season.

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When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (See Table); presence of other medical conditions; indications for use (i.e., chemoprophylaxis or therapy); and the potential for interaction with other medications.

Zanamivir

Limited data are available about the safety or efficacy of zanamivir for persons with underlying respiratory disease or for persons with complications of acute influenza, and zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease. In a study of zanamivir treatment of ILI among persons with asthma or chronic obstructive pulmonary disease in which study medication was administered after use of a B2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a greater than 20% decline in forced expiratory volume in 1 second (FEV1) after treatment. However, in a phase-I study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir. In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Because of the risk for serious adverse events and because efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease. Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance.

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving placebo (i.e., inhaled lactose vehicle alone). The most common adverse events reported by both groups were diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose, and throat infections. Each of these symptoms was reported by less than 5% of persons in the clinical treatment studies combined. Zanamivir does not impair the immunologic response to TIV.

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%). Among children treated with oseltamivir, 14% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect, and a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms. Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis. Nausea and vomiting might be less severe if oseltamivir is taken with food. No published studies have assessed whether

oseltamivir impairs the immunologic response to TIV.

Transient neuropsychiatric events (self-injury or delirium) have been reported postmarketing among persons taking oseltamivir; the majority of reports were among adolescents and adults living in Japan. FDA advises that persons receiving oseltamivir be monitored closely for abnormal behavior.

Amantadine and Rimantadine

Both amantadine and rimantadine can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, incidence of CNS side effects (e.g., nervousness, anxiety, insomnia, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine. In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced one or more CNS symptoms, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo. A study of older persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine. Gastrointestinal side effects (e.g., nausea and anorexia) occur among approximately 1%--3% of persons taking either drug, compared with 1% of persons receiving the placebo.

Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week, despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among older persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day. Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects. In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported. Because rimantadine has been marketed for a shorter period than amantadine, its safety among certain patient populations (e.g., chronically ill and older persons) has been evaluated less frequently. Because amantadine has anticholinergic effects and might cause mydriasis, it should not be used among patients with untreated angle closure glaucoma.

Use During Pregnancy

Oseltamivir, zanamivir, amantadine and rimantadine are both "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. Only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus; the manufacturers' package inserts should be consulted. However, no adverse effects have been reported among women who received oseltamivir or zanamivir during pregnancy or among infants born to such women.

Drug Interactions

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data.

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential

exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate.

Careful observation is advised when amantadine is administered concurrently with drugs that affect CNS, including CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions (248). No clinically substantial interactions between rimantadine and other drugs have been identified.

No published data are available concerning the safety or efficacy of using combinations of any of these influenza antiviral drugs. Package inserts should be consulted for more detailed information about potential drug interactions.

NOTE: The text above is taken from Prevention & Control of Influenza - Recommendations of the Advisory Committee on Immunization Practices (ACIP) 2008. MMWR 2008 Jul 17; Early Release:1-60.

The text on amantadine and rimantadine is taken from Prevention & Control of Influenza – Recemmendations of the Advisory Committee on Immunization Practices (ACIP) 2004. MMWR 2004 May 28; 53(RR06);1-40.

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