‘Alarming’ adamantane resistance threatens influenza control

**By Jeff Evans**  
Senior Writer

Evidence of widespread resistance of influenza against amantadine and rimantadine has prompted calls for restraint in the use of antivirals in order to preserve the therapeutic value of these adamantanamines as well as newer generation agents. Investigators at the Centers for Disease Control and Prevention detected an “alarmingly high” resistance rate of 92% to the adamantane antiviral drugs amantadine and rimantadine in an analysis of 209 influenza A(H1N2) isolates from patients in 26 states from Oct. 1 through Dec. 31, 2005 (JAMA doi:10.1001/jama.295.8.jelic6009, published Feb 2, 2006). An earlier CDC analysis that found adamantane resistance in 10% of 120 influenza A(H1N2) isolates from patients in 23 states from Oct. 1 to Oct. 31, 2004, through Jan. 12, 2006, led the CDC to issue a Health Alert on Jan. 14, 2006. The alert recommended that neither amantadine nor rimantadine be used for the treatment or prophylaxis of influenza A infections in the United States, the remainder of the 2005-2006 influenza season.

“If antiviral use is curtailed, susceptible strains could emerge and adamantanes could regain their utility against both epidemic and pandemic influenza,” Dr. David M. Weinstock and Dr. Gianna Zuccotti of Memorial Sloan-Kettering Cancer Center, New York, wrote in an editorial (JAMA doi:10.1001/jama.295.8.jelic6009, published Feb 2, 2006). In the report, Rick A. Bright, Ph.D., and his colleagues at the CDC noted that adamantane resistance in the United States increased from 1.9% in 2003-2004 to 11% in 2004-2005 to 11% in 2005-2006 to 92%. The CDC study also noted that 100% of influenza A(H1N2) isolates obtained from 10 patients in Mexico and 3 patients in Canada were resistant to amantadine and rimantadine. A recent report on influenza A(H1N2) isolates from the 2005-2006 influenza season in Canada found that 43 (91%) of 47 isolates showed resistance to those drugs.

The CDC report “is a clarion call for action from the medical community,” the editorial said. “Physicians and other health care providers, (2) recognize the powerful influence that affect prescribing practices before assigning culpability to those who have inappropriately used adamantanes.”

In a related report that appeared just before the CDC report, a systematic review of 52 randomized, controlled trials of the adamantane drugs and the newer generation neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza) also raised serious doubts about the wisdom of using the four drugs for routine control of seasonal influenza.

Amantadine and rimantadine neither prevent infection nor affect viral shedding. And even though they shorten the duration of fever, the drugs also have potentially serious adverse effects and promote the rapid emergence of resistance strains. “The evidence does not support” their use for seasonal or pandemic influenza outbreaks, reported Dr. Tom Jefferson of Cochrane Vaccines Field, Alessandria, Italy, and his associates.

Zanamivir and oseltamivir should be used only “in a serious epidemic or pandemic” alongside other public-health measures such as [the] use of masks, gowns, gloves, quarantine, and handwashing,” Dr. Jefferson said in a statement. The investigators drew their conclusions from a review of 52 trials of either prevention or treatment of influenza-like illness involving otherwise healthy subjects aged 16-65 years. Resistance to oseltamivir therapy among adults infected with influenza A(H1N1) or influenza A(H2N2) virus has been rare, but resistant strains have been reported in up to 18% of Japanese children receiving oseltamivir, Dr. Weinstock and Dr. Zuccotti noted in their editorial. Zanamivir and oseltamivir should be used only “in a serious epidemic or pandemic” alongside other public-health measures such as [the] use of masks, gowns, gloves, quarantine, and handwashing,” Dr. Jefferson said in a statement. The investigators drew their conclusions from a review of 52 trials of either prevention or treatment of influenza-like illness involving otherwise healthy subjects aged 16-65 years. Resistance to oseltamivir therapy among adults infected with influenza A(H1N1) or influenza A(H2N2) virus has been rare, but resistant strains have been reported in up to 18% of Japanese children receiving oseltamivir, Dr. Weinstock and Dr. Zuccotti noted in their editorial.

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