Drug Monitor

Effects of Neuraminidase Inhibitors on Influenza

Despite their global use, neuraminidase inhibitors may not be the best option for preventing or treating the symptoms of influenza, say researchers for the Cochrane Acute Respiratory Infections Group. In updating a 2005 Cochrane review, they found that neuraminidase inhibitors have only a modest effect on influenza symptoms and that evidence about their benefits and risks is limited.

The researchers conducted an updated search of the Cochrane central register of controlled trials, Medline, Embase, and postmarketing pharmacovigilance data to assess the effects of the neuraminidase inhibitors oseltamivir and zanamivir. They were interested in the drugs' effectiveness at preventing or ameliorating the symptoms, transmission, and complications of influenza in otherwise healthy adults, as well as the frequency of adverse effects. The search resulted in 1,416 trials, 20 of which were included in the review: four on prophylaxis, four on postexposure prophylaxis, and 12 on treatment.

Of the four prophylaxis trials, two compared a total of 697 patients treated with inhaled zanamivir 10 mg daily and 602 patients given placebo, while the other two compared 675 patients treated with oral oseltamivir 75 mg daily and 413 patients given placebo. Zanamivir and oseltamivir showed similar reductions of symptomatic, laboratory-confirmed influenza (risk ratio, 0.38 and 0.39, respectively), but neither drug protected against asymptomatic influenza. Two postexposure prophylaxis studies using zanamivir and two using oseltamivir reported significant protection for households. Researchers found insufficient evidence, however, to support or refute their prophylactic effects.

The review included eight trials of zanamivir treatment and five trials of oseltamivir treatment. The researchers found that the neuraminidase inhibitors had low effectiveness and reduced the length of illness by about one day if taken within 48 hours of symptom onset. Data on the drugs' effectiveness against the complications of influenza (such as pneumonia, bronchitis, sinusitis, and otitis media requiring antibiotics or hospital admission) are "confusing," they say, with insufficient evidence to support any one conclusion.

When studying the safety evidence from the trials, the researchers identified only one serious adverse event: Oseltamivir induced nausea, especially at the higher dose of 150 mg daily. The researchers also obtained data from the FDA's adverse event reporting system (AERS), which contained 2,275 adverse event reports for oseltamivir and 453 for zanamivir generated worldwide between December 1999 and July 2009. Eight cases from AERS suggest that oseltamivir may cause sudden behavioral changes, including hallucinations, suicidal tendencies, and sudden death while asleep. The researchers note that evidence about the toxicity of neuraminidase inhibitors is likely underreported.

Neuraminidase inhibitors appeared to have some—albeit low—effectiveness at preventing and treating seasonal flu. The researchers found no direct comparative evidence of their role in the avian or H1N1 influenza pandemics, however. They acknowledge that evidence was lacking and call for independent, randomized trials "to resolve the uncertainties surrounding effectiveness."

Source: *BMJ.* 2009;339:b5106. doi:10.1136/bmj.b5106.

Early Combination Treatment for Severe Acute Respiratory Syndrome: Is It Effective?

The combination treatment of ribavirin and corticosteroids was used commonly during worldwide outbreaks of severe acute respiratory syndrome (SARS) in 2002 and 2003. Ribavirin (and other broad-spectrum antibiotics) was used because of its in vitro activity against a wide range of viral agents, and early in the epidemic, the infecting agent remained unidentified. Ribavirin also was believed to suppress acute viral replication early in the disease process. Early treatment was considered important since the viral load peaked 10 days after symptoms first presented. Corticosteroids were administered to protect patients from inflammatory lung damage.

Studies on the combination treatment's effectiveness during the outbreak have been uncontrolled and inconclusive. After analyzing data on 1,934 patients in two SARS epicenters (Hong Kong and Toronto, Canada), however, researchers from The University of Hong Kong, the Department of Health, and Hospital Authority, all in Hong Kong, and Canadian Severe Acute Respiratory Syndrome Research Network, Toronto conclude that initial combination treatment had no significant benefit.

The researchers analyzed an integrated database and conducted a retrospective cohort study of 1,755 patients in Hong Kong and 191 patients in Toronto who were diag-

nosed with SARS during the outbreak. Among the patients in this cohort, 301 (17%) of those in Hong Kong and 25 (13%) of those in Toronto died. Crude case-fatality ratios were higher in patients who did not receive treatment with either ribavirin or corticosteroids within two days of admission compared with patients treated with both drugs within two days of admission (23.3% and 20% versus 12.6% and 12.8% among patients in Hong Kong and Toronto, respectively). The researchers did find, however, that younger patients and those with a longer delay between symptom onset and hospital admission were more likely to receive the combination treatment.

After adjusting for these and other patient characteristics, they predict that the case-fatality ratio would have been highest (19.2%) if all patients in Hong Kong had been treated with both ribavirin and corticosteroids and that the ratio would have been the lowest (15.4%) if no patients had received ribavirin or corticosteroids. The 3.8% difference in ratios suggests, at most, no effectiveness of combination therapy, they say. Similar results were found for Toronto: The adjusted excess case-fatality ratio for combination treatment versus neither treatment was 2.1%.

The researchers say the in vivo inhibitory effect of ribavirin at clinically achievable doses remains controversial, and the drug is associated with significant adverse effects. They also say the effectiveness of corticosteroids in SARS has not been established, and they surmise that, when corticosteroids are given during the early stage of viral replication, the drugs may suppress immune response and allow for a higher peak viral level. Corticosteroids also were associated with adverse effects in patients with SARS, including avascular necrosis, aspergillus superinfection, and reduced bone mineral density. The researchers advise that, in the absence of further evidence, clinicians should not use ribavirin and corticosteroids to treat SARS: "To the best of our knowledge, they provide no benefit in terms of survival."

Source: *Am J Med.* 2009;122(12):1150.e11–1150.e21. doi:10.1016/j.amjmed.2009.07.018.

Prophylactic Beta-Blockers: Timing and Dosage Are Key

Studies have produced conflicting results on the benefits, if any, of giving beta-blockers in the perioperative period to patients at risk for cardiovascular complications. The Perioperative Ischemic Evaluation (POISE) trial was started in 2002 in an attempt to resolve the inconsistencies. In the trial, 8,351 patients were assigned randomly to receive either extended-release metoprolol succinate (n = 4,174) or placebo (n = 4,177). The metoprolol was administered in high doses (up to 400 mg) starting two to four hours before surgery and continued for 30 days. At 30 days postsurgery, cardiac events were reduced significantly in the treatment group compared with the control group, but the incidence of total mortality and stroke was significantly increased in the treatment group.

The high incidence of stroke in the POISE trial prompted researchers at Leiden University Medical Center, Leiden and Erasmus Medical Center, Rotterdam, both in The Netherlands, to "question the liberal use" of beta-blockers during the perioperative period. Individual results of three Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) trials showed that a low-dose, long-acting beta-blocker titrated to effect at least 30 days before surgery was not associated with postoperative stroke. To see if a pooled analysis would change these findings, the researchers analyzed combined data from DECREASE trials I, II, and IV.

They found that, at 30 days postsurgery, 18 (0.46%) of 3,884 patients had ischemic strokes, and 12 (67%) of these 18 patients had been given a beta-blocker (bisoprolol). They determined that the average dose of bisoprolol administered to patients was 15% of the maximum recommended therapeutic dose (MRTD). Patients with a history of stroke were most at risk for postoperative stroke, but there was no association between stroke and statin, anticoagulant, or bisoprolol therapy.

The researchers propose that timing of beta-blocker therapy may be a key element in lowering the risk of postoperative stroke. Evidence suggests that the anti-inflammatory and plaque stabilizing properties of beta-blockers may take days to develop. They point out that the incidence of postoperative stroke was higher in studies that initiated beta-blockers "hours before surgery" as opposed to a week or more beforehand.

Dose may be another key element, say the researchers. The POISE trial used 50% to 100% of the metoprolol MRTD, while the DECREASE trials used 10% to 20% of the bisoprolol MRTD. Investigators in the DECREASE trials also titrated beta-blocker therapy gradually, whereas investigators in the POISE trial used a high dose from the outset.

The authors of this pooled analysis also suggest that the type of beta-blocker used may lead to different outcomes. They note one study's results, which suggest that longer acting agents demonstrate greater cardioprotection than shorter acting agents. Bisoprolol (used in the DECREASE trials) has been associated with better results, and metoprolol (used in the POISE study) and atenolol have shown mixed results in clinical trials.

Continued on page 32

Continued from page 30

Although all of the trials demonstrated the cardioprotective effects of beta-blockers, the researchers conclude that the protocol used in the DECREASE trials "is associated with an overall benefit compared to the risk [of stroke]," whereas "high-dose therapy started the morning of surgery is associated with an increased risk rather than benefit."

Source: *Am J Cardiol.* 2010;105(1):43–47. doi:10.1016.j.amjcard.2009.08.646.