PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Niacin is Ineffective for Preventing CV Disease

In this issue: Niacin — No Benefit for the Heart; Letrozole for Infertility in PCOS; Panel Recommends FluMist for Children; and FDA Actions.

Niacin — No Benefit for the Heart

A new study confirms the lack of effectiveness of niacin for reducing major vascular events, essentially putting the nail in the coffin for use of this once-popular drug. Researchers in the United Kingdom randomized more than 25,000 high-risk patients (those with evidence of vascular disease) to 2 g of extended-release niacin along with 40 mg of laropiprant (given with niacin to reduce flushing) or placebo. All patients were already being treated with a statin. The primary outcome was first major vascular event (nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization). After a median follow-up of nearly 4 years, niacin was effective at lowering low-density lipoprotein (LDL) cholesterol by an average of 10 mg/dL and raising high-density lipoprotein (HDL) cholesterol by an average of 6 mg/dL. However, niacin had no effect on major vascular events (patients with an event: 13.2% niacin vs 13.7% placebo, rate ratio 0.96; 95% confidence interval, 0.90-1.03; $P = 0.29$). Niacin-laropiprant was associated with worsening of diabetes control and an increased incidence of diabetes as well as other serious adverse events, including gastrointestinal, musculoskeletal, skin rashes, increased rate of infections, and bleeding. The authors conclude that adding niacin-laropiprant to a statin did not reduce the risk of major vascular events but did increase serious adverse events in high-risk vascular patients (*N Engl J Med* 2014;371:203-212). The authors suggest that these findings are consistent with trials of niacin alone and are likely to be generalizable to all high-dose niacin formulations. An accompanying editorial extends niacin's complete failure in all efforts to raise HDL cholesterol, pointing out the failure of other drugs that raise HDL to reduce the risk of vascular events — findings that "undermine the hypothesis that HDL cholesterol is a causal risk factor" for cardiovascular disease (*N Engl J Med* 2014;371:271-273). Niacin-laropiprant is a combination that Merck has tried to get approved in this country for years. It was approved in Europe in 2008. However, based on this study and others, Merck has withdrawn the product from the market worldwide. ■

Letrozole for Infertility in PCOS

In women with polycystic ovary syndrome (PCOS), the aromatase inhibitor letrozole (Femara) results in better pregnancy outcomes than the current first-line treatment clomiphene (Clomid), according to a new study. Researchers randomly assigned 750 women with PCOS to letrozole or clomiphene for up to five treatment cycles with the primary outcome of live birth during the treatment period. Women treated with letrozole had more cumulative live births than those receiving clomiphene (27.5% vs 19.1%, $P = 0.007$) with no significant differences in congenital abnormalities (although there were four major congenital abnormalities in the letro-

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zole group and one in the clomiphene group). The cumulative ovulation rate was higher with letrozole (61.7% vs 48.3%, $P < 0.001$). There was no difference in the rate of pregnancy loss or rate of twins, and side effects were slightly different (more hot flushes with clomiphene and more fatigue and dizziness with letrozole), although there was no difference in incidence of side effects. The authors conclude that, compared to clomiphene, letrozole was associated with higher live-birth and ovulation rates among women with PCOS. The safety and teratogenic risks with letrozole compared to other infertility therapies need further study (*N Engl J Med* 2014;371:119-129). ■

Panel Recommends FluMist for Children

This fall, the Centers for Disease Control and Prevention (CDC) is likely to recommend that children receive live attenuated vaccine nasal spray rather than the traditional flu shot. The nasal spray, marketed as FluMist, will likely become first-line for healthy children ages 2-8. The move is anticipated after the CDC's Advisory Committee on Immunization Practices voted unanimously to recommend FluMist for children after reviewing evidence that the nasal spray vaccine is more effective than injectable flu vaccine in preventing flu. Some critics suggest that the recommendation is coming too late in the year to have an impact this year, since many practices have already ordered their flu vaccine. Others are concerned about the significantly increased cost of FluMist vs traditional vaccine. Although the CDC has yet to act officially on the Advisory Committee's findings, it usually endorses the committee's recommendations. ■

FDA Actions

The FDA has approved a new inhaled insulin. Human insulin Inhalation Powder is a rapid-acting insulin used to improve glycemic control in adults with type 1 and type 2 diabetes. The drug is to be used at mealtime and is not a substitute for long-acting insulin. The drug was approved on the strength of studies of more than 3000 patients, of which one-third were type 1 diabetics and two-thirds were type 2 diabetics. For type 1 diabetics, inhaled insulin was non-inferior to insulin aspart when combined with a long-acting insulin, although HbA1c was significantly higher with inhaled insulin compared to aspart. For type 2 diabetics, inhaled insulin was combined with an oral agent and compared to a placebo inhaled agent plus an oral agent. By 24 weeks, inhaled insulin showed a significantly greater reduction in HbA1c than placebo. Inhaled insulin comes with a boxed warning regarding risk of acute bronchospasm in patients with asthma and chronic obstructive pulmonary disease. The warning also states that the drug should not be used in patients with chronic lung disease. The warning further states that spirometry should be performed prior to starting inhaled insulin, as well as 6 months into therapy and every year thereafter. The drug is also approved with a Risk Evaluation and Mitigation Strategy requiring a plan to inform health care professionals about the risk of bronchospasm. Insulin inhalation powder is manufactured and marketed by MannKind Corporation as Afrezza. This product is the second inhaled insulin after Exubera, which was approved in 2006, but then removed from the market in 2007 due to poor sales.

The FDA has approved a new topical agent for treating toenail fungus (onychomycosis). Tavaborole 5% is applied daily for 48 weeks. It was approved on the basis of two trials of nearly 1200 patients who did not have lunula involvement showing a 7-9% complete cure rate at 1 year compared to a 0.5-1.5% cure rate for placebo. Tavaborole will be marketed by Anacor Pharmaceuticals as Kerydin.

The FDA has issued a Consumer Alert about powdered pure caffeine that is being marketed directly to consumers over the Internet. The product is sold in bulk bags and contains pure powdered caffeine, with each teaspoon containing the equivalent amount of caffeine found in 25 cups of coffee. There has been one reported death of an Ohio teenager who used these products. Powdered caffeine is becoming increasingly popular with teens and young adults who see it as an inexpensive form of caffeine with a quick onset of action. Overdose can cause tachycardia, seizures, nausea, diarrhea, stupor, disorientation, and death. The FDA recommends avoiding powdered pure caffeine and reporting adverse effects to its hotline at CAERS@cfsan.fda.gov. ■