PHARMACOLOGY WATCH

Evidence-Based Updates in Clinical Pharmacology

Digoxin May Increase Mortality in AF Patients

In this issue: Digoxin may increase mortality in patients with atrial fibrillation; daily low molecular weight heparin may not be an effective intervention of recurrent pregnancy loss; treating CDI with fecal microbiota transplantation; ramelteon may be effective for treating delirium in older hospitalized patients; and FDA actions.

Digoxin May Increase Mortality in AF Patients

Digoxin may increase mortality in patients with atrial fibrillation (AF) and congestive heart failure (CHF), according to the new a meta-analysis. Researchers combined 19 studies, which included more than 235,000 patients with AF and 91,000 patients with CHF. Based on the analysis of adjusted mortality results from all 19 studies, digoxin use was associated with an increased relative risk of all-cause mortality (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.07-1.38; $P < 0.01$). Among AF patients alone, digoxin compared to no glycosides was associated with a 29% increased mortality risk (HR 1.29, 95% CI, 1.06-1.22). The hazard ratio for CHF was 1.14 (1.14; 95% CI, 1.06-1.36, $P < 0.01$). Among the 19 studies, there was only one randomized controlled trial of digoxin in CHF patients that did not show either a benefit or risk of the drug, although there was a reduced risk of hospitalization for CHF. The mechanism for the increased risk is unknown, but it may be due to a narrow therapeutic window for digoxin, as well as the drug's proarrhythmic effects. The authors conclude that digoxin therapy, especially without proper serum level control, is associated with an increased mortality risk in patients with AF and CHF, with a higher risk in AF. They further state "digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control and in AF." (Published online *Eur Heart J* 4 May 2015; doi: http://dx.doi.org/10.1093/eurheartj/ehv143). ■

Low Molecular Weight Heparin and RPL

The common practice of giving daily low molecular weight heparin (LMWH) to women to prevent recurrent pregnancy loss (RPL) may not be an effective intervention, according to a new study. In a randomized, controlled trial from Germany and Austria, some 450 women with at least two consecutive early miscarriages or one late miscarriage were randomized to dalteparin (Fragmin) injections for up to 24 weeks' gestation, while the control group received only prenatal vitamins. At 24 weeks, there was no difference in the percentage of pregnancies between the two groups (86.8% LMWH group vs 87.9% control group), and the live birth rates were also similar (86.0% LMWH vs 86.7% control, absolute difference -0.7 percentage points; 95% confidence interval, -7.3 to 5.9 percentage points). The rates of pregnancy complications were similar in the two groups. The authors conclude that LMWH injections "do not increase ongoing pregnancy or live-birth rates in women with RPL. Given the burden of injections, they are not recommended for preventing miscarriages." (*Ann Intern Med* 2015;162:601-609; doi:10.7326/M14-2062). An accompanying editorial suggests that the future of LMWH in RPL is not clear. It should not be prescribed before 12 weeks' gestation based on this current study, but "we should

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seek to understand the pathophysiolocgic molecular backbone of this syndrome. This may enable relevant and targeted therapeutic inteventions." (*Ann Intern Med* 2015;162:658-659; doi:10.7326/M15-0564). ■

Treating CDI with Fecal Microbiota Transplantation

Recurrent *Clostridium difficile* infection (CDI) is defined as the recurrence of infection after successful initial therapy. Recurrent CDI occurs up to 20% of the time after initial treatment and up to 60% after one recurrence. Fecal microbiota transplantation (FMT), the introduction of healthy donor stool into the patient's colon via enema or colonoscopy or the upper GI tract via endoscopy, has become a promising new therapy for this debilitating disease. A new review looks at the effectiveness of FMT for CDI infections. Two, randomized control trials, 28 case-series studies, and five case reports were included, of which 516 patient were treated with FMT for recurrent CDI. Across all studies for recurrent CDI, symptom resolution was seen in 85% of cases. One trial compared FMT route (n = 20) and found a resolution rate of 60% in the nasogastric tube group vs 80% in the colonoscopy group although the difference was not significant ($P = 0.63$). The authors suggest that FMT may have a substantial beneficial effect with few short-term adverse effects for recurrent CDI. Evidence is insufficient for FMT use for refractory or initial treatment of CDI infections. They were unable to detect a difference in efficacy based on donor, preparation, or delivery method (*Ann Intern Med* 2015;162:630-638; doi:10.7326/M14-2693). An accompanying editorial brings up several intriguing questions about FMT, including how to regulate the procedure and donor sources (*Ann Intern Med* 2015;162:662-663; doi:10.7326/M15-0609).

Recently, a nonprofit called OpenBiome, based in Medford, MA, created a commercially available product with screened, filtered, and frozen material ready for clinical use. The company provides fecal microbiota preparations for both colonic and duodenal delivery. Another approach has been transplantation of nontoxigenic *C. difficile* strains. In a recent study, preparations of nontoxigenic *C. difficile* M3 (NTCD-M3) were given orally in three different concentrations, along with a placebo group, to patients with first CDI infections or recurrent CDI. Fecal colonization with the NTCD-M3 occurred in 69% of the patients in the treatment group. Recurrence of CDI occurred in 30% of placebo patients and 11% of treatment patients (odds ratio 0.28; 95% CI, 0.11-0.69; $P = 0.006$). Only 5% of patients receiving the highest concentration of spores had a recurrent CDI. The authors conclude that NTCD-M3 was well-tolerated and safe while significantly reducing CDI recurrence (*JAMA* 2015;313:1719-1727; doi:10.1001/jama.2015.3725). ■

Ramelteon May Be Effective for Treating Delirium

Ramelteon may be effective for treating delirium in older hospitalized patients, according to the findings of a new study. There is currently no effective treatment for delirium, which can affect up to 30% of patients older than 65 years of age at some time during a hospitalization. In a small study, 67 patients ages 65-89 years who were newly admitted to the hospital for serious medical problems were randomized to ramelteon 8 mg per day or placebo every night for 7 nights. Ramelteon was associated with a lower risk of delirium (3% vs 32%; $P = 0.003$). Kaplan-Meier estimates of time to development of delirium were about a day longer with ramelteon (6.94 vs 5.74). The authors feel that ramelteon administered nightly to elderly patients admitted for acute care may provide protection against delirium. Since ramelteon is a melatonin agonist, these findings support possible pathogenic role of melatonin neurotransmission in delirium (*JAMA* 2015;313:1745-1746; doi:10.1001/jama.2014.17394). ■

FDA Actions

The FDA has approved the first spray-dried fibrin sealant to help control bleeding during surgery. The product contains fibrinogen and thrombin obtained from human blood products. The approval of fibrin sealant was based on a study of 719 participants undergoing different types of surgical procedures showing a reduction in the time needed for bleeding to stop compared to using absorbable sponges alone. Fibrin sealant (human) is manufactured by ProFibrix BV and marketed as Raplixa.

The FDA has issued a warning regarding a class of type 2 diabetes medications and the risk for ketoacidosis. The drugs are SGLT2 inhibitors and include canagliflozin (Invokana), dapagliflozin (Farixga), and empagliflozin (Jardiance). SGLT2 inhibitors block the sodium glucose co-transporter-2, which allows sugar to be excreted in the urine, thus lowering blood sugar levels. The FDA Adverse Event Reporting System database identified 20 cases of acidosis reported as diabetic ketoacidosis, ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014. The FDA is warning patients who take these medications to look for signs and symptoms of ketoacidosis. The agency is also asking physicians to report adverse effects through the MedWatch program. ■