Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Online Supplement to *Clinical Cardiology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Integrative Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports*

AHCMedia.com August 2016

CDC Advisory Committee Recommends Against Live Attenuated Influenza Vaccine

In a rather dramatic decision affecting this year's flu season, the CDC's Advisory Committee on Immunization Practices (ACIP) has voted that the live attenuated influenza vaccine (LAIV, FluMist) should not be used this fall. The decision came after ACIP reviewed data showing vaccine effectiveness for LAIV of only 3%. This means that use of the vaccine resulted in no measurable protective benefit last year. In comparison, injectable flu vaccine resulted in a 63% rate of vaccine effectiveness. The committee issued a statement on June 22 that concluded, "In light of the evidence for poor effectiveness of LAIV — the live attenuated influenza vaccine, otherwise known as FluMist — in the United States over the last three influenza seasons, for the upcoming 2016-2017 season, the ACIP makes the interim recommendation that FluMist should not be used." ACIP continues recommending annual flu vaccination, with either the inactivated influenza vaccine or recombinant influenza vaccine for everyone ≥ 6 months of age. The CDC has yet to issue a final ruling on flu vaccines this year, but usually follows the ACIP's guidance.

Safe, Effective Alternatives to Warfarin

The non-vitamin K antagonist oral anticoagulants (NOACs) are safe and effective alternatives to warfarin, according to a new study from investigators in Denmark. In a database of more than 61,000 patients, the NOACs (dabigatran [Pradaxa], rivaroxaban [Xarelto], and apixaban [Eliquis]) were compared to warfarin in patients with atrial fibrillation. In an observational cohort study, more than half of the patients took warfarin, while nearly 13,000 took dabigatran, more than 7,000 took rivaroxaban, and 6,300 took apixaban. The NOACs were similar to warfarin in preventing ischemic stroke, although rivaroxaban was better than warfarin in preventing stroke or systemic embolism (3.0% vs. 3.3%, respectively; hazard ratio, 0.83; 95% confidence interval, 0.69-0.99). The annual risk of death and overall rate of bleeding was significantly lower with apixaban and dabigatran compared to warfarin, while rivaroxaban was comparable to warfarin for both endpoints. The authors concluded that the NOACs are safe and effective alternatives to warfarin in the routine care setting (*BMJ* 2016;353:i3189).

Drug May Slow Renal Disease Progression

Empagliflozin (Jardiance), an SGLT2 inhibitor used to treat type 2 diabetes, may slow the progression of renal disease in diabetics at risk for cardiovascular disease. In a recently published, industry-sponsored study, patients with type 2 diabetes and a glomerular filtration rate of at least 30 mL/min/1.73 m^2 were randomly assigned to empagliflozin (10 or 25 mg/day) or placebo. Incident or worsening nephropathy occurred in 12.7% of the empagliflozin group (525 of 4,124) and 18.8% of the placebo group (388 of 2061; hazard ratio, 0.61; 95% confidence interval, 0.53-0.70; $P < 0.001$). Doubling of serum creatinine occurred, and renal replacement therapy was twice as common in the placebo group. The authors concluded, "In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care." (*N Engl J Med*. Published online June 14, 2016. DOI: 10.1056/NEJMoa1515920). Interestingly, two other SGLT2 inhibitors are the subject of a new FDA

warning regarding worsening renal function (see FDA actions below).

Good News for Type 2 Diabetics

Liraglutide (Victoza) may reduce cardiovascular risk in type 2 diabetics, according to a new study. In a double-blind trial, 9,340 patients were randomized to liraglutide or matching placebo and followed for an average of 3.8 years. The primary outcome was time to first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome occurred in 13% of the liraglutide group and 14.9% of the placebo group (hazard ratio [HR], 0.87; 95% confidence interval, 0.78-0.97; $P < 0.01$ for superiority). Fewer patients died from cardiovascular disease (HR, 0.78) and death from any cause (HR, 0.85) in the liraglutide group. Gastrointestinal events were the most common side effect with liraglutide, but interestingly, the incidence of pancreatitis was lower with the drug. The authors concluded that the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo (*N Engl J Med*. Published online June 13, 2016. DOI: 10.1056/NEJMoa1603827).

Patients Need More Education on Opioid Storage, Disposal

What happens to opioid medications once they are in patients' medicine cabinets? A recently published research letter examined sharing, storage, and disposal of opioid medications among nearly 3,300 respondents who had received an opioid prescription. About 21% reported sharing their medication with another person, primarily to help the other person manage pain. More than half of respondents reported they had leftover medication, of which 60% reported keeping the medication for future use. Nearly half did not recall receiving information on safe storage or disposal of opioids. The authors recommended reducing the prescribed quantity of opioids and improving education about storage and disposal (*JAMA Intern Med*. Published online June 13, 2016. DOI:10.1001/jamainternmed.2016.2543).

FDA Actions

The FDA has approved sofosbuvir/velpatasvir to treat chronic hepatitis C virus (HCV) infection in patients with and without cirrhosis. It is the first drug or drug combination that is approved to treat all six major genotypes and, as such, has been widely anticipated for patients with genotype 2-6 HCV infections. It is approved in combination with ribavirin for patients with decompensated cirrhosis. Sofosbuvir/velpatasvir was approved on the strength of three studies of more than 1,500 patients with and without cirrhosis or compensated cirrhosis, which showed 95-99% of patients had no detectable virus at 12 weeks post treatment (SVR12). In combination with ribavirin for patients with decompensated cirrhosis, the SVR12 was 94%. Sofosbuvir/velpatasvir is marketed as Epclusa. Twelve weeks of therapy will be priced at $74,760, less than other HCV treatments.

The FDA has approved obeticholic acid for the treatment of primary biliary cirrhosis in combination with ursodeoxycholic acid. Obeticholic acid increases bile flow from the liver and suppresses bile acid production. The drug was granted fast-track designation, a process that facilitates development and expedites review of drugs intended to treat serious conditions for which there is no adequate treatment. The drug also received Orphan drug designation, which includes financial incentives for drug development, and it was approved under the accelerated approval program, which features less stringent requirements for endpoints of efficacy. Approval was based on a controlled clinical trial of 216 participants in which the biomarker alkaline phosphatase was lower at one year, a surrogate marker of efficacy. Improvement in survival or progression to cirrhosis has not been shown. Obeticholic acid is marketed as Ocaliva. It is expected to cost nearly $70,000 per year.

The FDA has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Both medications are SGLT2 inhibitors that lower blood sugar by increasing renal excretion of glucose. The FDA has received 101 reports of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use. There were four deaths and 15 cases requiring dialysis. The FDA recommends considering risk factors for acute kidney injury prior to starting canagliflozin or dapagliflozin, including dehydration, chronic kidney disease, congestive heart failure, and concomitant medications such as diuretics, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs. Assess renal function periodically. Patients should seek medical attention immediately if they experience signs and symptoms of acute kidney injury (www.fda.gov/Safety/MedWatch). ■

PHARMACOLOGY WATCH™
is published monthly by AHC Media, LLC.

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