Pharmacology Watch

Evidence-based updates in clinical pharmacology

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California Becomes Third State to Eliminate Personal Vaccination Exemption

Liraglutide Helps Non-diabetics Lose Weight

Liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, is an effective weight loss agent in non-diabetics, according to a new study. The drug was approved last year for long-term treatment of obesity (Saxenda) and previous to that for the treatment of type 2 diabetes (Victoza). In this new study, 3731 non-diabetic patients with a BMI of at least 30, or at least 27 with dyslipidemia or hypertension, were randomized in a 2:1 ratio to liraglutide 3.0 mg subcutaneously once a day or placebo. Both groups received counseling on lifestyle modification. By week 56, patients in the liraglutide group lost a mean of 8.4 ± 7.3 kg body weight, while those in the placebo group lost a mean 2.8 ± 6.5 kg (a difference of -5.6 kg; 95% confidence interval [CI], -6.0 to -5.1; $P < 0.001$). Almost two-thirds of patients in the liraglutide group lost at least 5% body weight compared to 27% of the placebo group ($P < 0.001$), and 33% and 10.6%, respectively, lost more than 10% body weight ($P < 0.001$). The most frequent adverse effects with liraglutide were nausea and diarrhea, occurring in 6.2% of the treatment group and 5% of the placebo group. HgbA1c levels, fasting glucose, and fasting insulin levels were also lower in the treatment group, and both systolic and diastolic blood pressures were also lower in the treatment group. Patients in the liraglutide group also reported higher scores on assessment of overall physical and mental health. Pancreatitis was about five times more common in the liraglutide group, with an incidence of 0.4 events per 100 patient-years at risk. There was also a slightly higher incidence of breast cancer in the treatment group, although there was no evidence of thyroid cancer — a concern that has been raised regarding GLP-1 mimetics based on rat data. The authors conclude that 3.0 mg of liraglutide given subcutaneously once daily as an adjunct to diet and exercise was associated with clinically meaningful weight loss, along with reductions in glycemic variables and multiple cardiometabolic risk factors (*N Engl J Med* 2015; 373:11-22DOI: 10.1056/NEJMoa1411892). ■

California Mandates Vaccinations for Children

California has passed one of the strictest school vaccination laws in the country, banning the "personal exemption" option for school-aged children. The bill leaves the medical exemption in place. The hotly contested bill comes in the wake of a pertussis epidemic in 2010, with nearly 10,000 confirmed cases in the state, including the death of 10 infants. Last year, a highly publicized measles outbreak occurred at Disneyland, which led to more than 100 new measles cases.

The new law will require all school-aged children to be vaccinated prior to starting school, effective 2016-2017. The law applies to both public and private schools as well as day care centers. This leaves home schooling as the only option for parents who refuse to vaccinate their children. California is the third state to eliminate the personal exemption option, behind Mississippi and West Virginia. The effort to pass the new law was led by Democratic State Sen. Richard Pan, a pediatrician from Sacramento. Opposition to the bill was vigorous

and at times very emotional, with some opponents of the bill considering a class action lawsuit and a voter referendum. Gov. Jerry Brown noted as he signed the bill, "The science is clear that vaccines dramatically protect children against a number of infectious and dangerous diseases." ■

New Drug Reverses Anticoagulant Effect of Dabigatran

Idarucizumab, an antibody fragment, shows promise in reversing the anticoagulant effect of dabigatran (Pradaxa). Researchers looked at 90 patients who needed reversal of dabigatran because of serious bleeding (n = 51) or needed an urgent procedure (n = 39). The endpoint was the reversal of the anticoagulant effect at 4 hours. In patients with testing validating an anticoagulant effect at baseline, all were reversed at 4 hours (100%; 95% confidence interval, 100 to 100). Idarucizumab normalized test results in 88-98% of patients, and the effect was evident within minutes of administration of the drug. The authors conclude that idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes (published online June 22, 2015. DOI: 10.1056/NEJMoa1502000).

This is a Phase 3 trial for idarucizumab, which is manufactured by Boehringer Ingelheim. The company received a priority review by the FDA, clearing the way for approval later this year. It will be the first reversal agent for any of the new oral anticoagulants, which may give dabigatran a competitor against rival drugs rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa), which do not have reversal agents. ■

FDA Actions

The FDA is warning that the methylphenidate patch (Daytrana) can lead to permanent depigmentation of the skin (chemical leukoderma). The patch is used to treat ADHD. The area of depigmentation can range up to 20 cm (8 inches) in diameter. Chemical leukoderma is not physically harmful but can be disfiguring. The FDA is warning patients or caregivers to watch for areas of lighter skin, especially under the patch, and report it immediately to their healthcare provider.

The FDA has approved cangrelor, an intravenous antiplatelet drug that is used as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural thrombotic events such as myocardial infarction (MI) or stent thrombosis. Approval was based on a trial of more than 10,000 patients undergoing PCI in which cangrelor was compared to clopidogrel. Cangrelor reduced the incidence of MI and the need for further PCI or stent thrombosis, but was also associated with significantly more serious bleeding events. Cangrelor is manufactured by the Medicines Company and marketed as Kengreal.

The FDA has approved a novel new drug to treat cystic fibrosis (CF). Lumacaftor/ivacaftor is approved for CF patients 12 years and older who have two copies (homozygous) of the F508del gene mutation, the leading cause of CF. Having two copies of the mutation (one from each parent) leads to disruption in how water and chloride are transported. The drug was given breakthrough status and priority review as well as designation as an orphan drug, all of which speed the approval process for the drug and reduce the cost of development. Approval was based on two double-blind, placebo-controlled trials of more than 1100 patients with CF and the F508del mutation. In both studies, patients who took lumacaftor/ivacaftor (2 pills every 12 hours) demonstrated improved lung function compared to those who took placebo. Lumacaftor /ivacaftor is manufactured by Vertex Pharmaceuticals and is marketed as Orkambi. The drug is expected to cost more than $250,000 per year.

The FDA has approved a new combination drug for the treatment of heart failure. The new drug combines valsartan, an angiotensin II receptor antagonist, and the new chemical entity sacubitril, which exerts its action by inhibiting neprilysin, an enzyme that degrades atrial and brain natriuretic peptide. Sacubitril/valsartan was studied in the PARADIGM-HF trial of more than 8000 patients with symptomatic heart failure and was shown to reduce the rate of cardiovascular death and hospitalization related to heart failure when compared to the ACE inhibitor enalapril. Most patients were also receiving other drugs for heart failure, including beta-blockers, diuretics, and mineralocorticoid antagonists. The most common side effects were hypotension, hyperkalemia, and renal impairment. Like valsartan and other ARBs and ACEIs, the drug was also associated with angioedema. Sacubitril/valsartan is manufactured by Novartis as Entresto. *The New York Times* reports that the drug will cost about $4500 per year, and Novartis is telling shareholders the drug could eventually achieve more than $5 billion in sales. ■

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