PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

No Link Between MMR and Autism

In this issue: Prevention of Type 1 Diabetes in Children ; Early Initiation of HPV Vaccine; Effects of Antibiotic Exposure Early in Life; ED-initiated Buprenorphine for Opioid-dependent Patients; and FDA Actions.

Link Between MMR Vaccine and Autism?

Another large study has shown no link between the MMR (measles, mumps, and rubella) vaccine and autism, even in children at high risk for autism. Nearly 96,000 privately insured children, all of whom had older siblings, were evaluated. About 2% of the younger children had an older sibling with autism spectrum disorder (ASD) and were considered high risk.

Over a 5-year follow-up, MMR vaccine was not associated with an increased risk of ASD at any age. For children with older siblings with ASD, at age 2, the adjusted relative risk (RR) of ASD for one dose of MMR vaccine vs no vaccine was 0.76 (95% confidence interval [CI], 0.49-1.18; P=0.22), and at age 5, the RR of ASD for two doses compared with no vaccine was 0.56 (95% CI, 0.31-1.01; P=0.052). For children whose older siblings did not have ASD, the RR at age 2 for one dose was 0.91 (95% CI, 0.67-1.20; P=0.50) and at age 5, the RR for two doses was 1.12 (95% CI, 0.78-1.59; P=0.55).

The authors conclude that in this large sample of children with older siblings, the receipt of MMR was not associated with increased risk of ASD, regardless of whether the older sibling had ASD, indicating no harmful association between MMR and ASD, even among high-risk children (JAMA 2015;313:1534-1540. doi:10.1001/jama.2015.3077). As an accompanying editorial points out, about a dozen studies have now shown no link between vaccination and age of onset of ASD, severity, or risk of ASD recurrence in families (JAMA 2015;313:1518-1519. doi:10.1001/jama.2015.2628). n

Prevention of Type 1 Diabetes in Children

Could oral insulin help prevent type 1 diabetes in children at high risk for the disease? A new study published in JAMA shows promise that exposing the oral mucosa to insulin may induce a protective immune response. In a double-blind, placebo-controlled study, 25 islet autoantibody-negative children who were at risk for type 1 diabetes (family history and susceptible genotypes), aged 2 to 7 years, were randomized to oral insulin (n = 15) or placebo (n = 10) once daily for 3-18 months. Nine of the 16 active treatment-group children received escalating doses of oral insulin. Lower doses of insulin showed modest immune responses, but in the highest-dose group, five of six children showed increases in IgG binding to insulin, IgA binding to insulin, and CD4 T-cell responses to insulin (P = 0.02), immune responses that could potentially prevent autoimmunity to islet cells. No hypoglycemia was noted, and there were no serious reactions to oral insulin. These data "support the need for a phase 3 trial to determine whether oral insulin can prevent islet automimmunity and diabetes in such children." (JAMA 2015;313(15):1541-1549. doi:10.1001/jama.2015.2928). n

Early Initiation of HPV Vaccine

Start HPV vaccine early for the highest likelihood of protection is the message of a new study from Canada. Using data from Ontario's grade 8 quadravalent HPV vaccine (qHPV) program in girls, rates

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of cervical dysplasia and anogenital warts (AGW) were assessed before and after initiation of the program. The cohort included more than 240,000 girls. Vaccination completion by grade 8 and 9 significantly reduced the incidence of dysplasia by 5.70 cases per 1000 (RR 44%, 0.56; 95% CI, 0.36-0.87). There was also a suggestion of decreases in the rate of AGW due to vaccination. The authors suggest that these data offer "additional justification for not delaying vaccination…" in girls aged 14-17 years (Pediatrics published online doi: 10.1542/peds.2014-2961). The qHPV may be cost-effective in boys as well. A recent cost-effectiveness study from Canada looked at the vaccine for the prevention of oropharyngeal cancer. Even assuming a low vaccine efficacy of 50%, immunizing boys was cost effective, saving millions of dollars over the lifetime of a theoretical cohort (Cancer published online: 13 APR 2015, DOI: 10.1002/cncr.29111). n

Effects of Antibiotic Exposure Early in Life

Antibiotics early in life may contribute to overweight toddlers, according to a study from Finland. We know that giving antibiotics to livestock makes them gain weight for some unknown reason, perhaps by altering bowel microflora. It now appears that the same may be the case for humans. More than 12,000 healthy children were assessed for antibiotic use in the first 24 months of life. Children who were exposed to antibiotics were, on average, heavier than unexposed children (SD for boys 0.13 [95% CI, 0.07-0.19; P < 0.001] and SD for girls 0.07 [0.01-0.13, P < 0.05]). The effect was most pronounced for macrolide exposure in the first 6 months of life. The data suggest that antibiotic exposure before 6 months of age, or repeatedly during infancy, is associated with increased body mass in otherwise healthy children (Pediatrics 2015;135:617-626 doi: 10.1542/peds.2014-3407). With other studies showing a link between early exposure to antibiotics and asthma and allergies, health care providers need to carefully weigh the risks vs benefits of antibiotic treatment in infants, especially use of macrolides. n

ED-initiated Buprenorphine for Opioid-dependent Patients

Should opioid-dependent patients in the emergency department (ED) be offered buprenorphine/naloxone (Suboxone) at discharge? A new study suggests that initiation of the drug may increase the likelihood of participation in an addiction treatment program. Opioid-dependent patients often use emergency services for medical care. In a trial of 229 such patients presenting to an urban teaching hospital ED, subjects were randomized to one of three groups: 1) screening and referral to treatment (referral); 2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and 3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine). After 30 days, 78% of the buprenorphine group remained engaged in addiction treatment vs 37% in the referral group and 45% in the brief intervention group (P < 0.001). Those in the buprenorphine group were less likely to use illicit opioids (P = 0.02) and less likely to require inpatient addiction treatment services (11% vs about 35% in the other two groups, P < 0.001). The authors conclude that ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services. There was no difference in HIV risk or rate of positive urine samples for opioids. Although ED-initiated treatment is promising, these findings should be replicated before widespread adoption (JAMA 2015;3133:1636-1644. doi:10.1001/jama.2015.3474). n

FDA Actions

The FDA has approved ivabradine for the treatment of heart failure. The drug is indicated for patients with low ejection fractions who are on the maximum tolerated dose of a beta-blocker and have a heart rate of at least 70 beats per minute. In a trial of 6500 such patients, ivabradine reduced the time to first hospitalization for heart failure from 9.2% patient-year to 12.7% patient-year. There was no benefit in overall mortality or cardiovascular mortality. The drug was reviewed under the FDA's priority review programs and granted fast-track designation. Side effects include bradycardia, hypertension, afibrillation, and visual disturbance. Ivabradine is marketed by Amgen as Corlanor.

Sandoz has received approval to market generic glatiramer (Copaxone) for the treatment of relapsing forms of multiple sclerosis. Teva has held the patent on Copaxone, and it is the company's best-selling drug. Sandoz is the only company to apply for a generic of Copaxone, so it is unclear whether a single generic will create cost competition.

The FDA has also approved a generic version of aripiprazole (Abilify), Bristol-Myers Squibb's blockbuster, second-generation antipsychotic drug. Abilify had sales of more than $2 billion last year. Four companies (Alembic Pharmaceuticals, Hetero Labs, Teva, and Torrent) received approval to market generic versions that will be available soon. It is expected that competition will result in significant cost reductions. n