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FDA Drug Safety Update: Implications for Pediatric Health Care Providers

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The Food and Drug Administration (FDA) has issued several drug safety communications and made a number of labeling changes of importance to pediatric health care providers during the past six months. Some of these changes are the result of accumulated post-marketing surveillance data while others represent findings from recent clinical research. For more information on safety alerts or to subscribe to the FDA e-mail update service for health care professionals, go to <http://www.fda.gov/ForHealthProfessionals/default.htm>.

Codeine Toxicity in Children

On August 15, 2012, the FDA issued a drug safety communication on the risk for adverse effects from codeine use in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnea (OSA).¹ The communication and accompanying consumer update were prompted by the reports of four children (ages 2-5 years) who developed severe adverse effects after receiving standard doses of codeine for post-operative analgesia.^{2,3} Three of the patients died, while the fourth developed life-threatening respiratory depression. Three of the children were found to be cytochrome P450 2D6 (CYP2D6) ultra-rapid metabolizers. Patients with CYP2D6 polymorphisms are able to convert codeine to morphine more rapidly and to a greater extent than the normal population, and as a result, are at a greater risk for opioid adverse effects.^{4,5} Prevalence of CYP2D6 ultra-rapid metabolizer genotypes varies among different populations, ranging from 1-2% in Asian, Hungarian, and Northern European populations to 29% in African populations.

These reports add to the growing concern for morphine toxicity following codeine use. In 2006, a case report in *Lancet* described the death of a breastfeeding infant whose mother was receiving codeine for post-partum pain.⁶ The

mother was found to be an ultra-rapid metabolizer, and her breast milk contained higher concentrations of morphine than expected. Publication of that case led to a 2007 FDA Public Health Advisory warning of the risk to infants of codeine administration to breastfeeding mothers.⁷

As a result of these new pediatric cases, the FDA is conducting a thorough safety review of codeine to identify other potential cases of toxicity related to the CYP2D6 ultra-rapid metabolizer genotype. The FDA recommends caution in prescribing codeine-containing products to children, especially in those who have had a tonsillectomy and/or adenoidectomy for OSA, use of the lowest effective dose, and avoidance of standing or "around the clock" schedules. Parents and caregivers should be aware of the need to monitor the child for symptoms associated with opioid toxicity, including lethargy, confusion, or difficulty breathing, and understand the need to seek medical attention immediately if symptoms occur.

Health care providers who identify potentially life-threatening or fatal codeine-related adverse effects are asked to report them to the FDA MedWatch program. Information can be submitted on-line via the MedWatch website at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, by printing a form and sending it by fax or mail, or by calling 1-800-FDA-1088.

Opioid REMS Program

In 2009, more than 400,000 patients were seen in emergency departments throughout the United States for non-medical opioid use resulting in toxicity. That same year, there were more than 15,000 deaths related to opioid use. The National Prescription Drug Abuse Plan was announced in 2011 in an effort to reduce

prescription opioid abuse and educate patients about the risks of opioid misuse. In July, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for long-acting opioids as part of the 2011 National Plan.⁸ Opioid preparations included in the program include:

- Buprenorphine transdermal system
- Fentanyl transdermal system
- Hydromorphone extended release products
- Methadone products
- Morphine extended-release products
- Morphine and naltrexone extended-release products (not currently available)
- Oxycodone controlled-release products
- Oxymorphone extended-release products
- Tapentadol extended-release products

The program requires manufacturers to provide training and educational materials for health care providers regarding safe prescribing practices. It is anticipated that this training will take the form of voluntary continuing education programs. Educational materials must also be made available for prescribers to distribute to their patients. An updated Medication Guide will be available for pharmacists to give to their patients when a long-acting opioid is dispensed in the outpatient setting or if requested in the inpatient setting. It is anticipated that the educational programs and materials will be in place by all manufacturers, for both brand and generic products, by March 1, 2013. The FDA has provided information on the REMS program at <http://www.er-la-opioidrems.com>

Pediatric Sildenafil Use

On August 30, 2012, the FDA issued a drug safety communication recommending that sildenafil not be used in children with pulmonary arterial hypertension (PAH).⁹ Sildenafil, a phosphodiesterase 5 inhibitor, has been used for more than a decade in the management of children and adults with pulmonary hypertension.¹⁰ Although never approved for use in children by the FDA, a number of papers in the medical literature have suggested a positive benefit from its use. The lack of effective alternatives, particularly oral therapies that can be made into a liquid dosage form for young children, has made sildenafil a frequent part of the management of infants and children with primary or secondary PAH.

The recent safety communication was based on interim results from the second Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, with Pulmonary Arterial Hypertension Study (STARTS-2), a long-term continuation of the STARTS-1 trial.¹¹ The first study was a 16-week

randomized, double-blind, placebo-controlled dose-ranging trial of sildenafil in 234 children with PAH. The children were randomized to receive high dose (20-80 mg depending on weight), medium dose (10-40 mg), or low dose (10 mg) sildenafil, based on weight stratification, or placebo given orally 3 times daily for 16 weeks. Percent change from baseline peak oxygen consumption (PVO₂) served as the primary outcome. The estimated mean (\pm SE) percent change for the three groups combined versus placebo was 7.7 \pm 4.0% (95% CI, -0.2% to 15.6%, p=0.056). Although the combined result was small, both medium and high dose sildenafil produced significantly greater improvement in PVO₂, hemodynamics, and functional class than placebo. Low-dose therapy showed no benefit. No serious adverse effects were reported.

All patients were eligible for the STARTS-2 continuation study. Those receiving sildenafil started on the same dose, while the placebo patients were randomized to one of the three treatment groups. An interim analysis, at a mean follow-up of 3 years, revealed a higher mortality rate in the children receiving high dose treatment. The hazard ratio for the high dose group compared to the low dose group was 3.5 (p = 0.015). The first deaths came after a 1 year of treatment; the difference between treatment groups began to occur after 2 years of treatment. All deaths were related to progression of PAH. The majority of patients who died had baseline hemodynamic values above the study median. Based on the data available to date, the authors concluded that the medium dose produced favorable results and recommended further study to determine an optimal dosing strategy.

The FDA has required information from the study to be included in the Warnings section of the prescribing information for sildenafil, but has differed from the authors in recommending that it not be used at any dose. Further evaluation of the study results is needed to compare the relative risk to benefit of therapy and to explore other viable treatment options. At this time, there is no clear guidance for the management of infants and children with PAH.

Risk for Drug-induced QTc Prolongation

Two commonly used drugs, ondansetron and clarithromycin, have received additional safety labeling in response to new information on their potential to produce prolongation of the corrected QT interval (QTc) on electrocardiogram (ECG) and place patients at risk for the development of torsades de pointes. While the prescribing information for both of these drugs already included this adverse effect, this

new information has prompted a strengthening of the warning.

On June 29, 2012, the FDA issued a drug safety communication to inform prescribers of the results of a recently completed study from GlaxoSmithKline suggesting that one of the current ondansetron dosing options for prevention of chemotherapy-induced nausea and vomiting, a single 32 mg IV dose, was associated with an unacceptable prolongation of the QTc.¹² The study, requested by the FDA to assess the drug's potential to cause arrhythmias, demonstrated a dose-dependent prolongation of the QTc. A single IV dose of 32 mg, the highest dose studied, produced a maximum mean difference in QTc from baseline of 20 msec. In comparison, an 8 mg IV dose produced only a 6 msec difference. As a result of these findings, the manufacturer has voluntarily removed this dose from the product's prescribing information. The recommended IV dosing for adults and children remains 0.15 mg/kg given every 4 hours for three doses, with a single IV dose maximum of 16 mg. Oral dosing recommendations were not altered.

Although ondansetron produced no significant effect on the QTc interval in two pediatric clinical studies,^{13,14} there have been cases of ventricular tachycardia resulting from ondansetron use in children with underlying congenital QTc prolongation. In 2010, McKechnie and Froese described a previously healthy 11-year-old girl who developed polymorphic ventricular tachycardia within minutes of receiving ondansetron 0.1 mg/kg and dimenhydrinate 0.4 mg/kg IV for prevention of post-operative nausea and vomiting.¹⁵ An ECG revealed a significantly prolonged QTc of 590 msec that decreased to 490 msec by the following day, but did not normalize after the drugs had been eliminated. The patient was subsequently diagnosed with congenital QT prolongation.

Clarithromycin received new labeling in July 2012 to strengthen the warning regarding QTc prolongation, making the use of this drug in patients with a known history of QTc prolongation or ventricular arrhythmias a contraindication.¹⁶ This follows the announcement of a similar change to the prescribing information for azithromycin earlier this year.¹⁷

QTc prolongation resulting from clarithromycin use has been reported in children as well as adults. In 2006, Germanakis and colleagues studied the effect of clarithromycin on the QTc interval in 28 children being treated for

respiratory tract infections.¹⁸ The QTc was measured prior to starting clarithromycin and again 24 hours after the initiation of therapy. There was a statistically significant increase of 22 msec in the mean QTc after treatment (95% CI 14-30 msec, $p < 0.001$), but the results were not felt to be clinically significant overall. However, there were seven cases of clinically significant prolongation of the QTc (> 440 msec) identified.

Seizures Associated with Cefepime

On June 26, 2012, the FDA issued a drug safety communication to alert prescribers to changes in the Warnings and Precautions and Adverse Reactions sections of the prescribing information for cefepime.¹⁹ These changes call attention to the risk for nonconvulsive status epilepticus (NCSE) in patients with kidney impairment who receive cefepime without adequate dosage adjustment. In a recent review of the FDA's Adverse Event Reporting System database, there were 59 reports of NCSE linked with cefepime use from the time of the drug's approval in 1996 to February 2012. While the majority of patients were more than 65 years of age, the reports included children as young as 7 years of age. In 56 of the reports, the cefepime dose had not been appropriately adjusted based on the patient's degree of kidney impairment. Symptoms resolved in 43 (73%) of the patients.

NCSE was first linked to cefepime shortly after its introduction and a number of case reports have been published in the medical literature. In addition to the cases in the database, there are two reports of this adverse effect in pediatric patients. In 2004, a 15-year-old boy on ambulatory peritoneal dialysis developed acute confusion, ataxia, and difficulty reading and writing while receiving cefepime.²⁰ The dose, 12.5 mg/kg/day, had been adjusted for his end-stage renal disease. Electroencephalography (EEG) revealed NCSE. He responded to treatment with anticonvulsants, and all symptoms resolved within 24 hours of discontinuing cefepime. A similar case in a 15-year-old girl on hemodialysis was published in 2009.²¹ She was being treated with cefepime at a standard dose of 100 mg/kg/day. On the 4th day of therapy, she developed confusion and lethargy, followed a day later by myoclonic jerks. NCSE was diagnosed by EEG. The patient's symptoms and EEG findings improved within 48 hours after cefepime was stopped.

Summary

The FDA has recently issued several important drug safety communications and changed the prescribing information for a number of drugs used in children. This information, based on

both new clinical research and post-marketing surveillance data, will be of use to health care providers in prescribing and monitoring the efficacy and safety of drug therapy in children.

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Formulary Update

The following actions were taken at the September meeting of the Pharmacy and Therapeutics Committee:

1. Carfilzomib (Kyprolis™) was added to the formulary for treatment of patients with refractory multiple myeloma.
2. Nalbuphine injection, an opioid with agonist effects at kappa receptors and partial antagonist effects at mu receptors, was added for the treatment of neuraxial opioid-induced pruritus. Use of this agent is restricted to Anesthesiology.
3. The restriction on nitric oxide (INOMax®) was amended to include use as a second-line agent for intraoperative management of pulmonary hypertension in cardiac transplant patients, use during cardiac catheterization to determine vasodilator responsiveness in patients with pulmonary arterial hypertension, treatment of primary pulmonary hypertension in neonates, and use by Pediatric intensivists.

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