PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 16 Number 9 September 2010

Adverse Drug Events in Children: Recent Cases from the Medical Literature

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Avoidance or prevention of adverse drug events (ADEs) is a significant issue for pediatric health care providers. There is often little pediatric-specific ADE information on medications commonly used in children, as the result of the limited number of pediatric clinical trials being conducted and the use of smaller sample sizes, which makes identifying rare events difficult. As a result, pediatric health care providers must often turn to the medical literature to learn of new ADEs reported in children. This issue of *Pediatric Pharmacotherapy* provides a brief overview of ADE case reports and clinical trials published within the past year.

Adverse Events in Pediatric Intensive Care

A collaborative group of 15 PICUs published a retrospective evaluation of adverse events documented during the last four months of 2005. A total of 734 patient records were evaluated; 1,488 adverse events were identified, including 256 adverse drug events (ADEs). This resulted in a rate of 4.9 ADEs per 100 patient-days, or an adjusted cumulative risk for an ADE of 1.6% per PICU day. Surgical patients had a higher incidence of both adverse events and ADEs. There was also a relationship between the risk for ADEs and age, with a 4% increase in the adjusted ADE rate for every year increase in age. The authors suggest that these data may be useful in developing areas of focus for prevention strategies. **Agarwal S, Classen D, Larsen G, et al. Prevalence of adverse events in pediatric ICUs in the United States. Pediatr Crit Care Med 2010; (epub ahead of print).**

Analgesics and Anti-inflammatories in Sports

The June 2010 issue of *Pediatric Clinics of North America* includes an extensive review of the benefits and risks of analgesics and anti-inflammatory medications in young athletes. The authors describe the mechanism of action, pharmacokinetic and pharmacodynamic properties, and dosing recommendations for these drugs, as well as their adverse effect profiles. They include both oral agents and topical products. This article, with its extensive tables and bibliography, will be a useful reference for health care providers who provide care for adolescents with sports-related injuries. **Feucht CL, Patel DR. Analgesics and anti-inflammatory medications in sports: use and abuse. Pediatr Clin N Am 2010;57:751-74.**

Antiepileptic Safety Monitoring

Anderson and Choonara have studied the methods for ADE reporting during randomized controlled trials (RCTs) of antiepileptic drugs in children over the 10-year period from 1998 to 2007. Of the 29 RCTs identified, only three analyzed data from pediatric patients separately. Six of the trials (20%) described a standardized method for obtaining and documenting ADE information. Only three studies utilized an independent safety monitoring committee to ensure thorough, unbiased assessment of adverse event reports. Based on their assessment, the authors recommend significant changes in antiepileptic study design to improve safety monitoring and ADE reporting. **Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomized controlled trials of antiepileptic drugs in children over a 10-year period. Arch Dis Child 2010; (epub ahead of print).**

DRESS-syndrome with Sulfasalazine/Naproxen

DRESS-syndrome (drug rash with eosinophilia and systemic symptoms) was first described in patients treated with aromatic antiepileptics, but has subsequently been associated with several other drugs, including sulfonamides and non-steroidal anti-inflammatory drugs. The authors of this case report describe an 11-year-old boy who developed rash followed by systemic illness after being treated with sulfasalazine and naproxen for juvenile idiopathic arthritis. He had received naproxen 500 mg twice daily for 8 weeks and sulfasalazine 500 mg twice daily for 4 weeks when the rash first developed. Within a week, the rash had progressed and the patient developed lymphadenopathy, acute hepatitis with coagulation abnormalities and hyponatremia with

signs of renal tubular dysfunction. Both medications were discontinued and supportive therapy was initiated. After an extensive work-up, the diagnosis of DRESS-syndrome was made. Symptoms began to improve after 6 days of hospitalization, and the patient was discharged after three weeks. In addition to providing extensive details from this case, the authors review the literature on DRESS-syndrome and current recommendations for treatment. **Piñana E, Lei SH, Merino R, et al. DRESS-syndrome on sulfasalazine and naproxen treatment for juvenile idiopathic arthritis and reactivation of herpevirus 6 in an 11-year-old caucasian boy. J Clin Pharm Ther 2010;36:365-70.**

Drug-induced QT Interval Prolongation

A new review of drug- and non-drug-associated QT interval prolongation is now available which provides an excellent overview of this phenomenon. The authors discuss both genetic and acquired risk factors for repolarization disturbances, focusing the latter section on drugs known to produce QT prolongation and the potential mechanisms underlying this adverse effect. In addition to addressing drug-drug interactions, the article also includes a section on the potential for gene-drug interactions in which genetic polymorphism may result in pharmacokinetic differences that produce drug accumulation and a greater risk for arrhythmias. The article also provides a table of drugs known to induce torsade de pointes, based on data from the University of Arizona College of Pharmacy's website, www.qtdrugs.org, as well as an extensive reference list. **van Noord C, Eijgelsheim M, Stricker BHC. Drug- and non-drug-associated QT interval prolongation. Br J Clin Pharmacol 2010;70:16-23.**

Drug Safety Oversight Board Review

The Food and Drug Administration (FDA) formed the Drug Safety Oversight Board (DSB) in 2005 to focus its efforts to evaluate serious drug safety issues and educate health care providers and the public. In this review, published in the August 2010 issue of *Clinical Pharmacology and Therapeutics*, Grandinetti and Osborne describe the development of the DSB and its role in addressing medication safety issues. They include an extensive table listing recent issues and outcomes stemming from DSB recommendations. For readers interested in the FDA's drug oversight policies, this article sheds light on one of their primary mechanisms for educating health care providers about medication risks. **Grandinetti CA, Osborne SF. The Food and Drug Administration's Drug Safety Oversight Board: an evolving paradigm for clinical input on drug safety topics. Clin Pharmacol Ther 2010;88:269-74.**

Guillain-Barré Syndrome after H1N1 Vaccine

Tremblay and colleagues describe a case of Guillain-Barré Syndrome (GBS) in an 11-year-old boy after administration of the H1N1 vaccine during the fall of 2009. The patient presented to the hospital with facial diplegia, abdominal, forehead, neck, and thigh pain 13 days after receiving a subcutaneous injection of the Arepanrix® H1N1 vaccine. Neurologic examination demonstrated symmetric paralysis of the eighth cranial nerve, along with proximal weakness of the shoulder and pelvis. After exclusion of alternative diagnoses and further investigation, the authors concluded that there was a probable relationship between the patient's condition and the vaccine. While the CDC reports only 12 probable cases of GBS from approximately 46 million doses of vaccine administered during 2009 (MMWR 2009;58:1-6), this case serves as a reminder of the potential for this condition in children. **Tremblay M, Closon A, D'Anjou G, et al. Guillain-Barré syndrome following H1N1 immunization in a pediatric patient. Ann Pharmacother 2010;44:1330-3.**

Infliximab Adverse Events

Infusion-related reactions have been reported to occur in up to 20% of patients receiving infliximab. The majority of these reactions are mild and transient; less than 1% of patients experience a severe hypersensitivity reaction. Premedication with an antipyretic and/or an antihistamine has been recommended as a means of minimizing these infusion-related reactions. To test the utility of premedication in pediatric infliximab patients, investigators at the University of Helsinki administered oral acetaminophen (20 mg/kg) and cetirizine (10 mg) prior to the start of infusion. A total of 64 children (mean age 13 years) were studied. Twelve infusion reactions were observed in eight children (12.5%). Four reactions were categorized as mild, while eight were severe. The authors compared this value to data from the previous year when no premedication was given and found no difference in the rate of reactions (8.3%, $p > 0.05$). They concluded that premedication did not prevent acute infusion-related reactions to infliximab and recommended consideration of other potential mechanisms for these reactions. **Lahdenne P, Wikström AM, AaltoK, et al. Prevention of acute adverse effects related to infliximab infusions in**

pediatric patients. Arthritis Care Res 2010;62:785-90.

Lopinavir-induced SIADH

Lopinavir has become a common component of therapy in the management of children with HIV infection. Syndrome of inappropriate antidiuretic hormone (SIADH) has previously been reported in adults taking lopinavir, but this is the first report in a child. The authors of this case describe SIADH in a 13-year-old boy with perinatally acquired HIV infection who developed fever, nausea, vomiting, diarrhea and abdominal pain one week after starting an antiretroviral regimen consisting of tenofovir-emtricitabine and lopinavir-ritonavir. He had been placed on antibacterial prophylaxis with trimethoprim-sulfamethoxazole 2 months earlier. On admission, the patient was found to be hyponatremic, with a serum sodium of 132 mmol/L and hypokalemic with a serum potassium of 3.1 mmol/L. Other electrolytes and serum transaminases were normal.

Despite electrolyte and fluid replacement, his hyponatremia continued. Serum sodium eventually fell to 128 mmol/L with a serum osmolality of 267 mmol/kg. The diagnosis of SIADH was made at that time. Three weeks later, the patient developed a maculopapular rash suggesting drug hypersensitivity and his antiretroviral regimen was stopped. His fever and rash resolved within 24 hours of discontinuation and his serum sodium returned to normal. He was placed on an alternative regimen of atazanavir, ritonavir, and tenofovir-emtricitabine without recurrence of symptoms. **Yeong MM, Palasanthiran P, Ziegler JB, et al. Syndrome of inappropriate antidiuretic hormone associated with lopinavir therapy [letter]. Pediatr Infect Dis J 2010;29:678-9.**

Periocular Reactions to Gentamicin

In the fall of 2009, a shortage of erythromycin ophthalmic ointment led to the use of gentamicin ointment as an alternative for newborn prophylaxis. Most institutions switched to azithromycin, but some chose gentamicin as a readily available, less expensive option. This report describes 26 newborns with periocular ulcerative dermatitis after receiving gentamicin in two hospitals in Philadelphia. In all cases, the rash occurred within one to two days after gentamicin administration, strongly suggesting the drug as a cause. In addition, changing to a policy of wiping away excess ointment on the skin after application resulted in a decrease in the severity of the rash, indicating a probable dose-related response. Gradual resolution occurred within 1 to 2 weeks in all patients. Based on the number of newborns given prophylactic gentamicin at these two institutions, the authors calculated an incidence of 5.6 cases per 100 newborn treated. The authors reported their findings to the Centers for Disease Control and Prevention (CDC), and this information was added to the instructions for responding to the erythromycin shortage on the CDC website. This case serves as an example of the impact of drug shortages on patient safety and an excellent reminder of the value of ADE reporting by health care providers. **Binenbaum G, Bruno CJ, Forbes BJ, et al. Periocular ulcerative dermatitis associated with gentamicin ointment prophylaxis in newborns. J Pediatr 2010;156:320-1.**

Risk Evaluation and Mitigation Strategy Program

This recent editorial provides a concise overview of the background and implications of the FDA's Risk Evaluation and Mitigation Strategy (REMS) program. This program gives the FDA a legal mandate for requiring manufacturers to implement steps to reduce ADEs, including added labeling requirements, development of patient medication guides, post-marketing studies, or restriction of drug distribution. There are now over 100 medications with REMS, including several drugs used in children. **Baker DD. REMS-one year later. Hosp Pharm 2010;45:348-51.**

Safety of a Levetiracetam Loading Dose

Levetiracetam has become a commonly used option for treating partial onset and primary generalized tonic-clonic seizures in children, as well as myoclonic seizures associated with juvenile myoclonic epilepsy. In 2006, the Food and Drug Administration approved an intravenous (IV) form of levetiracetam for patients temporarily not able to take the oral preparation. Although currently approved only for adults, use of the IV formulation in children has been described in several case reports and small case series. In order to provide more definitive information on this product, Ng and colleagues conducted a prospective study of IV levetiracetam safety in 30 children between 6 months and 15 years of age who were hospitalized for seizures. All patients received a single 50 mg/kg loading dose (maximum 2,500 mg) over 15 minutes and then continued on either IV or oral levetiracetam. The mean levetiracetam blood concentration 10 minutes after the infusion of the loading dose was 83.3 mcg/mL (range 47-128 mcg/mL).

The IV levetiracetam loading dose was well tolerated and produced no serious adverse reactions. Three patients experience sleepiness or fatigue, two had fevers (not thought to be drug-related), and three were restless or crying at the time of the infusion. One patient had a seizure two hours after the levetiracetam dose. The frequency of seizures in the 24-hour period after administration of levetiracetam was decreased from the 24-hour period prior to treatment in 25 of the 30 children. The authors concluded that the 50 mg/kg IV levetiracetam dose used in this study was well tolerated and provided a safe and appropriate loading dose. **Ng YT, Hastriter EV, Cardenas JF, et al. Intravenous levetiracetam in children with seizures: a prospective safety study. J Child Neurol 2010;25:551-5.**

Trimethoprim-sulfamethoxazole (TMP-SMX)-induced Hepatotoxicity

The authors of this report describe hepatotoxicity in a 9-year-old boy being treated with TMP-SMX for community-acquired methicillin-resistant *S. aureus*. On day 11 of treatment the patient developed fever, headache, and neck pain. He was taken to the emergency department (ED) on day 14 of treatment and diagnosed with viral meningitis. Three days later he returned to the ED with fever, vomiting, decreased energy and appetite, and abdominal pain. Elevated liver function tests were discovered upon hospitalization. Values returned to normal after discontinuation of the drug. While hepatotoxicity with TMP-SMX has been reported previously in both children and adults, it is uncommon. This case is a useful reminder to be aware of the potential for rare adverse effects with commonly used therapies. **Bell TL, Foster JN, Townsend ML. Trimethoprim-sulfamethoxazole-induced hepatotoxicity in a pediatric patient. Pharmacotherapy 2010;30:539.**

Valproate-induced Metabolic Effects

Long-term use of valproate has long been associated with the potential for weight gain and insulin resistance in children with epilepsy. A two part study was recently conducted to address the mechanism for these adverse effects. The first part, a cross-sectional study of children previously diagnosed with epilepsy was designed to evaluate insulin sensitivity and weight gain. Patients were divided into 3 groups: those who had not yet received valproate, patients currently receiving treatment, and those who had discontinued valproate at least 1 year previously. The second part of the study was a prospective longitudinal follow-up of the children in the first group after they began treatment with valproate. Sixty children were enrolled, with 20 continuing on to the longitudinal portion of the study.

When the children were divided into the 3 groups, there were no differences in age, or baseline glucose and insulin levels. There were, however, significant differences in body mass index (BMI) and measurements of insulin resistance. The group currently receiving valproate had a significantly higher BMI than the group who had not been treated (20.22 ± 4.11 compared to 15.97 ± 1.70, $p = 0.0002$). There was also higher insulin resistance in this group (1.67 ± 1.08 versus 1.04 ± 0.38, $p = 0.003$). No differences were found between the treatment group and those who had discontinued valproate. Significant correlations were found in the treatment group between the daily valproate dose and both insulin resistance ($r = 0.663$) and fasting insulin levels ($r = 0.765$). The longitudinal study revealed significant increases in fasting and post-glucose challenge insulin values at the one year follow-up, however the degree of insulin resistance eventually leveled off over time. The information gained from this study suggests a need for routine monitoring of weight and blood glucose values in children receiving long-term treatment. **Masuccio F, Verrotti A, Chiavaroli V, et al. Weight gain and insulin resistance in children treated with valproate: the influence of time. J Child Neurol 2010; 25:941-7.**

Summary

New reports of ADEs appear in the medical literature each month. These publications can provide pediatric health care providers with valuable information to guide drug selection, dosing, and monitoring to avoid or reduce the potential for adverse events in their patients.

The staff wishes to thank Dr. David Crowther for reviewing this manuscript prior to publication.