PEDIATRIC PHARMACOTHERAPY

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Pediatric Pharmacology Update

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Research in pediatric pharmacology has continued to make significant progress over the past decade. With the Food and Drug Administration's renewed interest in children as a special patient population and the benefits derived from the Best Pharmaceuticals for Children Act and the Pediatric Exclusivity Rule, the number of studies conducted in children has grown substantially. This issue of *Pediatric Pharmacotherapy* will review papers of interest to pediatric health care providers that were published in the pharmacy and pharmacology literature within the last six months.

Agalsidase alfa pharmacokinetics

This multicenter open-label study was designed to evaluate the pharmacokinetics and pharmacodynamics of agalsidase alfa, an enzyme replacement therapy for children and adolescents with Fabry disease. Twenty-four children participated in the study, ranging in age from 6 to 18 years. All patients received a 0.2 mg/kg agalsidase alfa dose infused over 40 minutes every other week. The drug had a biphasic elimination profile with a significantly longer elimination half-life in males than in females (70.8±12.7 min versus 50.2±10.2 min, p=0.003).

Clearance decreased with age, possibly reflecting more efficient binding of the drug to cell surface mannose-6-phosphate (M6P) receptors and transport into lysosomes. Despite the age-related difference in clearance, the reduction in plasma globotriaosylceramide (Gb3) levels produced was similar to values reported in studies of adults, leading the authors to conclude that further age-related dosage adjustments were not necessary. Ries M, Clarke JT, Whybra C, et al. Enzyme replacement in Fabry disease: pharmacokinetics and pharmacodynamics of agalsidase alfa in children and adolescents. **J Clin Pharmacol 2007;47:1222-30.**

Alpha-2 agonists in ADHD

Clonidine and guanfacine, alpha-2 adrenergic agonists, have been used for the treatment of attention-deficit/hyperactivity disorder (ADHD) for many years. This in-depth review explores the role of these agents in the treatment of ADHD, including a discussion of their mechanism of action and an overview of their safety and efficacy in clinical trials. Arnsten AF, Scahill L, Findling RL. Alpha-2 adrenergic receptor agonists for the treatment of attention-deficit/hyperactivity disorder: emerging concepts from new data**. J Child Adolesc Psychopharmacol 2007;17:393-406.**

Amphotericin nephrotoxicity

A retrospective study of risk factors associated with amphotericin nephrotoxicity has recently been published by investigators at Toronto's Hospital for Sick Children. The authors reviewed 151 amphotericin treatment courses in 130 children between January 1, 2000 and December 31, 2001. Nephrotoxicity was defined as a 20% reduction in creatinine clearance from baseline. In this study, the amphotericin dose, duration, and dosing schedule were not correlated with the development of nephrotoxicity. Of the 131 drugs administered concomitantly with amphotericin, only cyclosporine, nystatin, and ciprofloxacin were associated with a decrease in creatinine clearance. The relationship with concurrent cyclosporine use was striking: eight out of the 10 patients receiving the combination met the authors' definition of nephrotoxicity. The addition of tobramycin or vancomycin to amphotericin did not adversely affect creatinine clearance. Goldman RD, Ong M, Wolpin J, et al. Pharmacological risk factors for amphotericin B nephrotoxicity in children**. J Clin Pharmacol 2007;47:1049-54.**

Antipsychotic-induced tardive dyskinesia

One of the primary advantages of using the second-generation (atypical) antipsychotics is the reduced risk for serious adverse effects such as tardive dyskinesia. In this paper, the authors conducted a meta-analysis of 10 long-term studies of risperidone, quetiapine, or olanzapine in children to assess the risk of this adverse effect in the pediatric population. Three cases of tardive dyskinesia were identified in the 783 children and adolescents enrolled, giving an annualized rate of reaction of 0.42% (95% CI 0.087-1.24). In the two cases with descriptive information, symptoms resolved within weeks of discontinuing therapy. Although the results of this meta-analysis suggest a very low incidence of tardive dyskinesia in children treated with atypical antipsychotics, further studies are needed to confirm these results. Correll CU, Kane JM. One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review. **J Child Adolesc Psychopharmacol 2007;17:647-55.**

Community-acquired *Staphylococcus* infections

A sharp increase in community-acquired *Staphylococcus aureus* infections (CA-SAI), particularly those that are methicillin resistant, has been a cause for concern in many institutions. A number of researchers have attempted to provide an estimate of the true incidence of CA-SAI. Investigators at the University of Kentucky conducted a concurrent and retrospective study of CA-SAI in children seen at their institution between January 1, 2004 and December 31, 2005. Patients were included if they had a positive isolate collected within 48 hours of admission or clinic appointment. Patients with a history of methicillin-resistant *Staphylococcus aureus*, an in-dwelling catheter or device, recent surgery, or a chronic disease resulting in frequent hospitalization were excluded.

A total of 799 patients were screened, with 70 identified as meeting study criteria. The authors found an increase in the number of infections, with 9 in 2004 and 42 in 2005, but the difference was not statistically significant. There were no differences in age, race, or sex between the patients with methicillin-susceptible and methicillin-resistant infections. The patients with methicillin-resistant infections were more likely to have skin and soft tissue infections (p=0.002), while the group with methicillin-sensitive infections were more likely to have superficial skin infections (p=0.004). The methicillin-resistant group was treated primarily with vancomycin (in 60% of the cases), while the majority of the methicillin-susceptible patients (84.2%) received a beta-lactam antibiotic. Surgical incision and drainage was used in significantly more of the methicillin-resistant cases (68% versus 10.5%, p=0.04). The authors also present antibiotic sensitivity patterns for the isolates. Johnson PN, Rapp RP, Nelson CT, et al. Characterization of community-acquired *Staphylococcus aureus* infections in children. **Ann Pharmacother 2007;41:1361-7.**

Direct-to-consumer advertising

In October, *Clinical Pharmacology and Therapeutics* published an interesting point/counterpoint on the topic of direct-to-consumer (DTC) advertising. The authors presented a series of arguments both in favor of and in opposition to allowing pharmaceutical manufacturers to continue producing DTC ads. They site the potential benefits of DTC advertising in providing new information to consumers, improving patient compliance, potentially alleviating under-diagnosis and under-treatment, as well as motivating new product development. The authors also address the potential negative effects of DTC ads, such as inducing excess prescribing, interfering with the physician-patient relationship, and increasing drug costs. The authors offer several proposals to improve DTC advertising, including the development of tighter, enforceable industry guidelines for self-regulation and collaborative agreements with government and academia to provide non-proprietary medication education to consumers. Calfee JE. An assessment of direct-to-consumer advertising of prescription drugs. **Clin Pharmacol Ther 2007;82:357-60** and Kravitz RL, Bell RA. Direct-to-consumer advertising of prescription drugs: balancing benefits and risks, and a way forward. **Clin Pharmacol Ther 2007;82:360-2.**

Drug-induced skin, nail, and hair disorders

A great reference tool, this review article focuses on a unique set of adverse drug reactions. The authors include an extensive review of cutaneous reactions, from mild erythematous and urticarial reactions to Stevens-Johnson Syndrome and toxic epidermal necrolysis. The section on hair changes discusses drug-induced hair loss, as well as hirsutism, hypertrichosis, and changes in hair color and texture. Nail disorders include damage to the nail structure as well as discoloration. The authors conclude with their recommendations for a more consistent approach to the documentation and publication of drug-induced cutaneous reactions. Valeyrie-Allanore L, Sassolas B, Roujeau J. Drug-induced skin, nail, and hair disorders. **Drug Safety 2007;30:1011-30.**

Drug removal by plasmapheresis

This article provides a concise review of the case reports and studies published to date on drug removal during plasmapharesis. While not limited to the pediatric population, the article will be a valuable reference to pediatric intensive care practitioners using this therapeutic technique. The drugs are grouped by therapeutic class, and the results are summarized in a table for easy reference. An extensive reference list is also included. Ibrahim RB, Liu C, Cronin SM, et al. Drug removal by plasmapharesis: an evidence-based review. **Pharmacotherapy 2007;27:1529-49.**

Enoxaparin in neonates

It is well accepted that achieving optimal anticoagulation in neonates is a complex undertaking. This new retrospective review of 16 neonates provides additional data to suggest that young infants often require higher enoxaparin doses than currently recommended. The average starting dose was 1.41±0.15 mg/kg every 12 hours. Patients were then titrated to achieve an antifactor Xa level between 0.5 and 1.0 U/mL. In those neonates who achieved antifactor Xa levels in the desired range, the average effective dose was 1.92±0.43 mg/kg every 12 hours. The average time to achieve a therapeutic antifactor Xa level was 5.6 days, with a range of 1 to 15 days.

Preterm neonates required a larger dose than term neonates (1.94±0.39 versus 1.65±0.14 mg/kg every 12 hours, $p < 0.001$). Ten of the 14 thromboembolic events (71%) resolved, either partially or completely. Nine patients experienced minor local adverse effects. Systemic adverse effects possibly associated with enoxaparin included osteopenia and scleral hemorrhage (1 neonate each) and gastrointestinal tract bleeding (3 neonates). While this was a relatively small patient sample, the results of this study add further support for the need for higher enoxaparin doses in infants. Malowany JI, Knoppert DC, Chan AKC, et al. Enoxaparin use in the neonatal intensive care unit: experience over 8 years. **Pharmacotherapy 2007;27:1263-71.**

Insulin review

This extensive new review of insulin products will serve as a useful reference for students, residents, and health care providers caring for children or adults with diabetes mellitus. The author divides the currently available products into groups based on onset and duration of effect, reviews the characteristics of each product, and then addresses the utilization of these products in both type 1 and type 2 diabetes. A brief section on insulin pump therapy is also included. Bell DSH. Insulin therapy in diabetes mellitus: how can the currently available injectable insulins be most prudently and efficaciously utilized? **Drugs 2007;67:1813-27.**

Lamotrigine overdose

The case of a 17 year old girl who ingested an overdose of lamotrigine is presented in this brief report. Approximately two hours after the overdose, she vomited and lost consciousness. She required intubation and had uncontrolled limb movements, but her heart rate and blood pressure remained stable. There was no evidence of cardiac arrhythmias or cardiovascular depression. A serum lamotrigine concentration at the time of hospital admission was 161.3 micromol/L (therapeutic range 10-50 micromol/L). After 19 hours, it had declined to 77 micromol/L. The patient was extubated the morning after admission, but remained agitated. She experienced a full recovery and was discharged 2 days after admission. The authors note that this is the highest serum lamotrigine concentration reported after an overdose, yet it produced a relatively mild clinical course. Reimers A, Reinholt G. Acute lamotrigine overdose in an adolescent. **Ther Drug Monit 2007;29:669-70.**

Management of asthma in the ED

This retrospective study evaluated the compliance of asthma management in the emergency department (ED) of a large university hospital with the National Asthma Education and Prevention Program guidelines. A total of 141 cases were included from October 1, 2003 to October 31, 2004. Two thirds of the patients were classified as having mild asthma, with another 29% classified as moderate. Nearly all of the patients were being treated with beta-2 agonists prior to arrival, although 32% of the patients who should have been receiving corticosteroids were not. All of the patients were evaluated by pulse oximetry, as recommended. At discharge, only 20% of patients received a written action plan and 67% received no formal training in using inhaler devices. Only half of the patients ≥ 6 years of age were given a peak flow meter. The authors concluded that there were several areas for improvement at their institution and describe their action plan for change. Ly CD, Dennehy CE. Emergency department management of pediatric asthma at a university teaching hospital. **Ann Pharmacother 2007;41:1625-31.**

Naproxen versus acetaminophen

This randomized, double-blind trial compared naproxen to acetaminophen in the management

of musculoskeletal ankle injuries in 77 children between 8 and 14 years of age. Patients were seen in a pediatric ED and randomly assigned to either acetaminophen 15 mg/kg or naproxen 5 mg/kg given four times daily for 5 days. Patients rated their pain and disability on a 10 cm visual analog scale on days 0 and 7. Physician assessment of pain, tenderness, and swelling was also noted.

Both groups showed significant improvement by day 7. There were no statistically significant differences between the groups in patient evaluation of disability (a decline from 7.2±1.9 cm to 1.4±1.5 cm in the naproxen group versus a 7.4±2.0 cm to 1.0±1.2 cm decline in the acetaminophen group, p=0.21). Pain scores showed a similar improvement (a drop from 6.8±3.0 cm to 0.7±1.1 cm in the naproxen group compared to a drop from 6.4±2.7 cm to 0.5±0.9 cm in the acetaminophen group, p=0.78). There were also no differences in physician assessments or adverse effects. Based on these results, the authors concluded that the two agents were equally effective in the management of children with ankle injuries. Cukiernik VA, Lim R, Warren D, et al. Naproxen versus acetaminophen for therapy of soft tissue injuries to the ankle of children. **Ann Pharmacother 2007;41:1368-74.**

Ontogeny of hepatic UGT1A4

While most research on the development of metabolic function has focused on the cytochrome P450 enzyme system, investigators have recently begun to turn their attention to the development of the UDP-glucuronosyltransferase (UGT) family. The authors of this study evaluated enzymatic activity of UGT1A4, an enzyme involved in glucuronidation, in pediatric and adult liver microsome samples. Enzyme activity reached maximum (adult) levels by 20 months of age, with no identifiable differences between genders or ethnic groups. The authors note that this is in agreement with previous clinical studies of drug metabolism. Miyagi SJ, Collier AC. Pediatric development of glururonidation: the ontogeny of hepatic UGT1A4. **Drug Metab Dispos 2007;35:1587-92.**

Statistics in pharmacology

The British Journal of Pharmacology has commissioned a series of articles reviewing the use of statistics in pharmacology studies. Each article begins with a case example, followed by a series of questions designed to analyze the problems within the case. The first two cases address issues in developing conclusions based on difficult data and the use of analysis of variance testing. Lew M. Good statistical practice in pharmacology: problem 1. **Br J Pharmacol 2007;152:295-8** and Lew M. Good statistical practice in pharmacology: problem 2. **Br J Pharmacol 2007;152:299-303.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/26/07:

1. Cytomegalovirus (CMV) immune globulin, intravenous (CytoGam®), was added to the Inpatient Formulary for prophylaxis of CMV disease in solid organ transplant recipients. There is currently a nationwide shortage of this product, and the supply is limited.

2. Raltegravir (Isentress®), an HIV integrase strand transfer inhibitor (HIV1 INST), was added to both the Inpatient and Outpatient Formularies.

3. Insulin Regular Concentrate (Humulin® Regular U-500) was added to the Inpatient Formulary with restriction to the Endocrinology Service. This product is to be used only in adults who have been previously started on this therapy as an outpatient. Because of the potential for error, special prescribing restrictions will apply and this product will only be stocked in the pharmacy.

4. Due to increasing bacterial resistance in the adult patient care areas, meropenem and ertapenem have been reclassified as Category A (restricted) antimicrobials for adult patients.

5. Omege-3-acid ethyl esters (Lovaza®) was added to the Outpatient Formulary. This highly concentrated formulation of omega-3 fatty acids is the only FDA approved product of its type.

6. Trimethoprim was deleted from the Inpatient and Outpatient Formularies because of lack of use.

The staff at Pediatric Pharmacotherapy wish you a happy holiday season!

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