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Food and Drug Administration Update for Pediatric Health Care Professionals

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The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) has recently approved several new drugs which may be useful in the treatment of pediatric patients. In addition, a number of important safety alerts have been issued that affect medications used in children.[1] This issue of *Pediatric Pharmacotherapy* will review these changes and their potential impact on the care of infants and children in the United States.

New Drug Approvals

Alglucosidase alfa, rhGAA

The first treatment for patients with Pompe disease, alglucosidase alfa, rhGAA (Myozyme®), was approved by the FDA on April 28, 2006. Pompe disease, an inherited deficiency or lack of acid alpha-glucosidase, results in impaired muscle development and function. In two clinical trials of patients from 1 month to 3.5 years of age, alglucosidase alfa, rhGAA administration significantly increased the length of time until ventilatory support was necessary.[1]

Anidulafungin

On February 21, 2006, anidulafungin (Eraxis®) was approved by the FDA. This is the third echinocandin antifungal approved in the United States.[1] Like caspofungin and micafungin, anidulafungin is indicated for the treatment of *Candida* sp. infections. The usual adult dose is 200 mg as a loading dose on day one, followed by 100 mg/day thereafter. Duration of therapy is typically two weeks after the last positive culture. A dose of 100 mg on day one, followed by 50 mg/day is recommended for esophageal candidiasis. Although currently indicated for use only in adults, there are preliminary pharmacokinetic and dosing information in children between 2 and 17 years of age. In clinical trials, loading doses of 1.5 to 3.5 mg/kg followed by doses of 0.75 to 1.5 mg/kg/day have produced serum anidulafungin concentrations similar to those observed in adults given the recommended dose.[2-4]

Generic approvals

Generic brands of colestipol, fluticasone, pravastatin, and zonisamide were approved in the first four months of 2006.[1]

Ibuprofen lysine injection

An injectable form of ibuprofen (NeoProfen®) was approved on April 13th for the closure of clinically significant patent ductus arteriosus (PDA) in premature infants weighing between 500 and 1,500 grams who are less than 32 weeks gestational age.[1] The approval was based on the results of a placebo-controlled trial in 136 infants showing a reduction in the need for alternative methods of PDA closure after ibuprofen use. Additional information is available from a recent meta-analysis of studies comparing ibuprofen and indomethacin for PDA closure.[5] After reviewing data from nine trials, the authors concluded that ibuprofen and indomethacin provided similar efficacy in PDA closure. Preterm infants treated with ibuprofen, however, had lower serum creatinine values, higher urine output, and less vasoconstrictive adverse effects.

Ibuprofen lysine is administered intravenously in a three dose regimen, with a first dose of 10 mg/kg, followed by two doses of 5 mg/kg at 24 hour intervals. Each dose should be administered over 15 minutes. As with indomethacin, doses should not be given if the patient develops anuria or oliguria. A second treatment course may be given if the initial three dose series fails to close the PDA.[1]

Inhaled insulin

The FDA approved Exubera®, an inhaled insulin product, for the treatment of type 1 or type 2 diabetes on January 27, 2006. In clinical trials, peak insulin concentrations were achieved 49 minutes after inhalation of Exubera® (range 30 to 90 minutes) compared to 105 minutes after injection of regular insulin (range 60 to 240 minutes). While the product is currently approved only for use in adults, clinical trials are being conducted in the pediatric population.

Transdermal methylphenidate

A new methylphenidate patch (Daytrana®) was approved by the FDA on April 6, 2006.[1] This product is designed for children 6 to 12 years of age with attention deficit/hyperactivity disorder (ADHD) as an alternative for patients unable to swallow tablets or capsules. A new patch is applied each morning and removed after up to 9 hours. The patch will be available in 10, 15, 20, and 30 mg strengths.[6] Two studies using an earlier version of the transdermal system have been published, a dose-ranging study and an 8 week placebo-controlled trial which showed improved in ADHD symptom control.[7,8]

Safety Alerts and Labeling Modifications

Bosentan

On March 2, 2006 the FDA and Actelion notified health care professionals of changes in the labeling for bosentan (Tracleer®) to highlight potential drug-induced hepatotoxicity. Patients should have monthly liver function tests (AST/ALT). Values three to five times the upper limit of normal should result in holding or reducing the dose until pre-treatment levels are achieved. Patients with values greater than five times, but less than eight times, the upper limit of normal should have doses held, and patients with values greater than eight times the upper limit of normal should not continue to receive bosentan.[1]

Diazepam rectal gel

On March 30, 2006, the FDA issued a Public Health Advisory for Diastat AcuDial® after receiving reports of cracks in the applicator tips.[1] The advisory recommended that patients or family members inspect the prefilled applicators to look for damage or leaking of the gel. The manufacturer (Valeant Pharmaceuticals) has provided specific directions for inspecting the applicators on their website at www.diastat.com or patients/families may call 1-877-361-2719 for further assistance.

Isotretinoin

The new iPLEDGE program for patients using isotretinoin (Accutane® or generic brands) was implemented on March 1, 2006.[1] This program is designed to reinforce patient education about the risk for teratogenicity associated with the use of this medication. In addition to registering with iPLEDGE, patients must comply with requirements for providing informed consent, participating in counseling about the risks of therapy, and for women of childbearing age, completing the required pregnancy testing. For more information on the program, prescribers or patients may contact the iPLEDGE call center at 1-866-495-0654 or review the information available on-line at www.ipledgeprogram.com

Oral sodium phosphate products

In March, the FDA also released an alert to notify prescribers of the risk for acute phosphate nephropathy associated with the use of oral sodium phosphate solutions, such as Fleet Phospho-soda®, for bowel cleansing. Elderly patients, as well as those with existing kidney disease or decreased intravascular volume are at higher risk. Patients taking medications that reduce renal perfusion or function, such as diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers or nonsteroidal anti-inflammatory drugs are also at higher risk for acute phosphate nephropathy.[9]

Promethazine

On April 25, 2006, the FDA issued a Safety Alert for promethazine to call attention to the strengthened warnings in the prescribing information about the potential for fatal respiratory depression in children under 2 years of age.[1] Patient information sheets and the revised promethazine prescribing information is available on the CDER website at www.fda.gov/cder/drug/infopage/promethazine/default.htm.

Salmeterol

New labeling and Medication Guides were approved on March 2, 2006 for salmeterol xinafoate (Serevent Diskus®) and fluticasone propionate/ salmeteral xinafoate (Advair Diskus®). These changes were made to highlight the potential for bronchospasm in patients receiving salmeterol.[1]

Topical calcineurin inhibitors

On January 19, 2006, the FDA approved the addition of a black box warning label to topical pimecrolimus (Elidel®) and tacrolimus (Protopic®).[1] The warning highlights the potential risk for cancer after long-term use, based on several case reports and animal studies which suggest an association with these drugs. The FDA also approved Medication Guides to be distributed to patients and their families explaining this new information. The American Academy of Dermatology Association has recently published a review of this issue which includes tips for discussing the use of these products with patients and families.[10]

Other Actions

Modafinil

An FDA expert panel on March 24, 2006 voted against the approval of modafinil for the

treatment of children and adolescents with ADHD.[9] Modafinil is currently approved for the treatment of narcolepsy and is sold under the trade name Provigil®. The request from the manufacturer, Cephalon, was supported by recent studies demonstrating the efficacy of modafinil in patients with ADHD.[12,13] While the panel agreed on the efficacy of the treatment, the concern for severe dermatologic reactions, including Stevens Johnson syndrome (SJS), drove the 12-1 vote against approval. One case of SJS was reported during the ADHD clinical trials. The FDA's Adverse Event Reporting System has received another four reports. The panel recommended further clinical trials, enrolling at least 3,000 patients, to demonstrate the drug's safety.

Standardized Labeling Requirements

In addition to these changes, on January 18th, the FDA announced a new format for prescribing information. This format is designed to highlight important safety information, making it more useful to prescribers. More information about the Final Rule on the Content and Format of Prescription Drug Labeling, as well as the new drugs and safety alerts, may be found on the FDA CDER website.[1]

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Pharmacology Literature Review

Aminoglycoside/Vancomycin Nephrotoxicity

Both aminoglycosides and vancomycin have been associated with nephrotoxicity, but whether or not the use of these agents in combination could lead to a greater risk for renal damage is unclear. The author of this review summarizes both animal and human studies with the combination, highlighting six reports from the pediatric literature. Despite the relatively small number of available reports, the author concludes that the data do not appear to support an increased risk of nephrotoxicity when an aminoglycoside is used in combination with vancomycin. Timpe EM. Nephrotoxicity with combination vancomycin-aminoglycoside therapy. **J Pediatr Pharmacol Ther 2005;10:174-82.**

Aprotinin for Amniotic Fluid Embolus

The authors present the case of a 26-year old gravida 2, para 1 woman who developed amniotic fluid embolus and coagulopathy following rupture of the amniotic membranes. After emergency cesarean delivery of a 41 week neonate, the patient was treated with replacement blood products, routine supportive measures, and aprotinin to reduce the bleeding. A 1 mL test dose was given, followed by a bolus of 500,000 international units given over 20 minutes. An infusion of 150,000 international units/hr was then started to maintain hemostasis. The infusion was discontinued after 10 hours, when bleeding had been controlled. Forty-eight hours after delivery, the patient was transferred from the intensive care unit to the postpartum floor in stable condition. The authors concluded that aprotinin was a useful adjunct to standard supportive therapies in the management of amniotic fluid embolus. Stroup JS, Haraway GD, Beal JM. Aprotinin in the management of coagulopathy associated with amniotic fluid embolus. **Pharmacotherapy 2006;26:689-93.**

Daptomycin Pharmacokinetics

The authors of this case report describe the pharmacokinetic profile of daptomycin in a 13-year old boy with vancomycin-resistant *Enterococcus faecium* endocarditis. The patient received a daptomycin dose of 6 mg/kg for two days, followed by a dose of 8 mg/kg for six days. The half-life after the initial dose was 2.31 hrs, which lengthened to 4.58 hrs with repeated dosing. Clearance was 20.13 mL/hr/kg on day 1, but declined to 13.47 mL/hr/kg by day 6. The area under the concentration-time curve increased from 298.01 to 593.92 mcg·hr/mL during this period. Compared to previously published values in adults, the authors found a faster rate of elimination, shorter half-life, and an increased clearance in their adolescent patient, suggesting significant age-related pharmacokinetic differences and highlighting the need for further study of daptomycin in children. Akins RL, Haase MR, Levy EN. Pharmacokinetics of daptomycin in a critically ill adolescent with vancomycin-resistant enterococcal endocarditis. **Pharmacotherapy 2006;26:694-8.**

Nesiritide in Pediatrics

In the February 2006 issue of *Pharmacotherapy*, Moffett and colleagues present two case reports of nesiritide, recombinant B-type natriuretic peptide, in pediatric patients. In the first case, a 3 year old girl with dilated cardiomyopathy and acute decompensated heart failure was started on nesiritide after failing traditional vasoactive therapy. She was well controlled on a dose of 0.02 to 0.04 mcg/kg/min. On the 45th day of therapy she received an inadvertent 18-fold overdose with no adverse hemodynamic, cardiac, or renal effects. Therapy was discontinued when the patient received a transplant. Moffett BS, Jefferies JL, Price JF, et al. Administration of a large nesiritide bolus dose in a pediatric patient: case report and review of nesiritide use in pediatrics. **Pharmacotherapy 2006;26:277-80.**

In the second case, the authors treated a term neonate with pulmonary hypertension, polycystic kidney disease, and heart failure. Nesiritide was administered for a period of 6 days, at a dose of 0.01 to 0.03 mcg/kg/min. No adverse effects on hemodynamics or renal function were noted during treatment. Therapy was discontinued after improvement of cardiac indices. Moffett BS, Jefferies JF, Rossano J, et al. Nesiritide therapy in a term neonate with renal disease. **Pharmacotherapy 2006;26:281-4.**

Sevelamer for Pediatric Renal Disease

This case report describes the use of sevelamer in a 19-month old girl with end-stage renal disease. Sevelamer is a non-calcium, non-aluminum-containing phosphate binder used to treat hyperphosphatemia secondary to end-stage renal disease in adults. The patient had failed to respond to calcium carbonate doses of 1,250 mg given three times daily. The authors administered a sevelamer dose of 100 mg/kg/day divided and given every 8 hours, which was titrated to 130 mg/kg/day based on response. Her serum phosphorus concentration decreased from 8.6 mg/dL to 5.2 mg/dL within 5 days of starting therapy. No adverse effects were noted. While additional studies are needed, sevelamer may offer a useful alternative to standard therapies to manage hyperphosphatemia in children with renal disease. Storms LE, Chicella MF, Dice JE. Sevelamer therapy for pediatric end-stage renal disease. **Pharmacotherapy 2006;26:410-3.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/28/06:

1. Pregabalin (Lyrica™), a structural derivative of gamma-aminobutyric acid, was added to the Inpatient and Outpatient Formularies for the management of neuropathic pain associated with diabetic neuropathy or postherpetic neuralgia and as adjunctive therapy in adults with partial onset seizures. It is restricted to prescribers in Neurology and Pain Clinic.

2. Exenatide (Byetta®), an incretin mimetic that enhances insulin secretion from beta-cells, was added to the Inpatient and Outpatient Formularies for the management type 2 diabetes mellitus. It is indicated as adjunct therapy in patients taking metformin, a sulfonylurea, or a combination of those products, who have failed to achieve glycemic control. It is restricted to prescribers in Endocrinology.

3. The Non-Formulary Requests and the Adverse Drug Reaction Quarterly Reports were presented. For more information, please contact Drug Information Services at 4-8034.

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