PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

Volume 8 Number 1 January 2002

Food and Drug Administration Update for Pediatric Practitioners

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The Food and Drug Administration (FDA) has approved several new drugs and dosage formulations of interest to pediatric health care professionals. This issue of *Pediatric Pharmacotherapy* provides information on these releases as well as updates on other drugs used in children.

New Drug Releases

A second topical immunomodulator for eczema

On December 13, 2001, pimecrolimus 1% cream (Elidel®; Novartis) was approved by the FDA for the treatment of mild to moderate atopic dermatitis in patients two years of age and older. Like topical tacrolimus, this product selectively inhibits T-cell activation, blocking the production and release of cytokines. In clinical trials, reductions in itching and redness were seen within 8 days of starting treatment. The most frequently reported adverse effect in clinical trials was a transient feeling of warmth or burning. There is minimal systemic absorption after topical use. Pimecrolimus cream is available in 15, 30, and 100 gram tubes.[1]

Darbepoetin alfa approved

Darbepoetin alfa (Aranesp®; Amgen) was approved by the FDA on September 18, 2001 for the treatment of anemia associated with chronic renal failure. With its longer half-life, darbepoetin can be given less frequently than traditional epoetin. It can be given once weekly (0.45 mcg/kg intravenously or subcutaneously) in patients who were receiving epoetin three times per week or every other week in patients who were receiving epoetin on a weekly schedule.[2] Darbepoetin was added to the UVA Formulary last month. While initially approved by the FDA only for adults, it is anticipated that this drug will have application in pediatric patients as well.

Single isomer dexmethylphenidate approved

The FDA approved dexmethylphenidate (expected to go by the trade name Ritadex®) on November 13, 2001 for the management of attention deficit/hyperactivity disorder (ADHD). This product, a single isomer of methylphenidate, is a co-marketing venture from Novartis, the maker of Ritalin®, and the Celgene Corporation. Methylphenidate has previously only been available as a racemic mixture. It is hoped that the new product will allow better dose titration to minimize adverse effects. Dexmethylphenidate comes in 2.5, 5, and 10 mg tablet strengths.[3]

New Dosage Formulations

Adderall XR® approved

On October 12, 2001, Shire Pharmaceuticals received approval to market an extended release preparation of Adderall®, its widely-used amphetamine/dextroamphetamine product for the treatment of ADHD. A single morning dose is designed to provide effective symptom control throughout the entire school day. Adderall XR® is available as 10, 20, and 30 mg capsules.[4]

Extra strength amoxicillin/clavulanate

A new amoxicillin/clavulanate preparation, Augmentin ES-600® (GlaxoSmithKline), was approved by the FDA on November 6, 2001 for children 3 months of age or older with recurrent or persistent acute otitis media. The product, an oral suspension, contains 600 mg amoxicillin and 42.9 mg clavulanate per 5 ml. It has been designed to facilitate a high-dose amoxicillin regimen (90 mg/kg/day divided into two doses) without providing excessive clavulanic acid.[5]

Budesonide product for Crohn's disease

An orally administered formulation of budesonide (Entocort EC®; AstraZeneca) has been approved by the FDA for the treatment of mild to moderate active Crohn's disease. This formulation releases drug into the intestine, where it works locally to decrease inflammation. Entocort EC® has been shown to provide the same degree of improvement in symptoms as oral prednisone or prednisolone, but with fewer systemic adverse effects. It is currently approved only for adults, but will likely also be used in

younger patients in order to minimize steroid-associated growth impairment.[6]

Low-dose albuterol solution for nebulization

Dey Labs has received approval from the FDA to market their new albuterol product, AccuNeb®, for use in children between 2 and 12 years of age. The product is available in 1.25 mg/3 ml and 0.63 mg/3 ml concentrations for nebulization without further dilution. It is a sterile, preservative-free solution and does not contain benzalkonium chloride. This is the first albuterol product designed for younger patients.[7]

New Dosing Information

Azithromycin short-course approved

At the end of the year, the FDA approved a request by Pfizer to include information on one-day and three-day dosing regimens for acute otitis media in their product labeling for Zithromax®. Although the FDA's Anti-Infective Drugs Advisory Committee recommended approval for these shorter regimens during their November 7th meeting, committee members stated their concern over the lack of pharmacokinetic data in children supporting the one-day regimen. The manufacturer did supply data in adults, as well as data in children comparing three- and five-day regimens.[8]

Lamivudine for children with hepatitis

Lamivudine (Epivir-HBV®; GlaxoSmithKline) is known to be effective in reducing the symptoms of chronic hepatitis B infection. On August 16, 2001, the FDA approved the addition of dosing information for this use in children to the product labeling. The recommended dose for children 2 to 17 years of age is 3 mg/kg/day, given once daily, not to exceed 100 mg.[9]

Sufentanil kinetic information added

On August 28, 2001, pharmacokinetic information in pediatric patients was added to the labeling information for sufentanil (Sufenta®; Akorn). The elimination half-life of sufentanil in infants and children has been found to be significantly shorter than that of adolescents and adults (97±42 versus 434±160 minutes, respectively). Conversely, the clearance in neonates is approximately half that in older patients, making a reduction in dose necessary. Neonates with cardiovascular disease appear to have an even slower clearance, requiring further dosage adjustment.[10]

Adverse Effect Warnings

Benzyl alcohol warning highlighted

While the association between benzyl alcohol and gasping syndrome (cardiopulmonary collapse) in neonates is well known by most practitioners, the potential risk for using products containing this preservative can sometimes be overlooked. The product labeling for doxapram (Dopram®; Wyeth Ayerst) has recently been revised to highlight this risk in the neonatal population, where the drug is used for severe apnea. In addition, more detailed information on adverse effects in the neonatal population has been included.[11]

Droperidol potential for arrhythmias

On December 4, 2001, Akorn Pharmaceuticals sent a letter to health care professionals notifying them of changes in the labeling of droperidol (Inapsine®). In conjunction with the FDA, the manufacturer has added a "black box" warning calling attention to the risk of arrhythmias with droperidol use. The drug had previously carried a warning about the risk of sudden cardiac death with high-dose therapy, but will now have labeling to warn of arrhythmias, including QT interval prolongation resulting in torsades de pointes, following doses within, or even below, the standard dosing range. The manufacturer now recommends an electrocardiogram (ECG) prior to initiating therapy in all patients. If the QT interval is prolonged and therapy is still considered necessary, ECG monitoring should be continued for the first 2 to 3 hours of treatment. The maximum recommended dose in children is now listed as 0.1 mg/kg.[12]

Infliximab warnings

Centocor, Inc., the manufacturer of infliximab (Remicade®) has recently distributed "Dear Health Care Professional" letters regarding a worsening of symptoms in patients with congestive heart failure (CHF) who received infliximab for Crohn's disease.[13] The manufacturer, in conjunction with the FDA, recommends that the drug not be used in patients with CHF and that therapy be discontinued in patients receiving chronic therapy if their CHF worsens. This information follows another recent change in Remicade® labeling to highlight the risk of serious infection, including tuberculosis, during treatment.[14] Information on the use of infliximab in children can be found in *Pediatric Pharmacotherapy* 1999;5(11):1-4.

Topiramate ocular effects

Topiramate (Topamax®; Ortho-McNeil) has become one of the most frequently used newer anticonvulsants on the U.S. market. It is indicated as adjunctive therapy for partial onset and primary generalized tonic-clonic seizures in patients 2 years of age or greater (*Pediatric Pharmacotherapy* 2001;7(6):1-4). In September 2001, topiramate received an additional indication as add-on therapy for patients with

Lennox-Gastaut syndrome. With its increased use has come more information on its adverse effect profile. Based on post-marketing surveillance, product labeling for topiramate was revised on August 28, 2001 to highlight an association with an ocular syndrome characterized by acute myopia and secondary angle closure glaucoma. This can occur in pediatric patients as well as adults. Patients should seek immediate medical attention if they experience blurred vision or periorbital pain. The manufacturer recommends discontinuation of therapy as rapidly as possible.[15]

New Dispensing Regulations

Isotretinoin regulations implemented

Over the past year, new prescribing and dispensing regulations for isotretinoin (Accutane®) have been developed by the FDA and the drug's manufacturer, Roche Pharmaceuticals (*Pediatric Pharmacotherapy* 2001;7(7):1-4). On January 2, 2002, training materials on the SMART program (System to Manage Accutane Teratogenicity) were distributed to health care professionals. This program was developed to reduce the number of pregnancies occurring in women taking isotretinoin. Prescriptions for Accutane® must now have a yellow dated qualification sticker, provided by Roche to the prescriber, attached at the time the prescription is written. This sticker ensures that the patient has provided informed consent, is aware of the risks associated with therapy, and that female patients have had the appropriate negative pregnancy tests. The target date for full implementation of the SMART program is April 10, 2002. After that date, only a 30-day Accutane® supply may be dispensed. Prescriptions for female patients may only be filled within 7 days of the sticker qualification date. An FDA MedGuide must also be given to the patient with each prescription.[1,16]

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Pharmacology Literature Review

Adherence to asthma therapies

Adherence with standard therapies to manage asthma symptoms is frequently poor in pediatric patients. In this retrospective study, adherence to two common treatments, oral montelukast and inhaled fluticasone, was compared. In the population sampled, 54 patients were receiving montelukast, 48 were using fluticasone, and 69 children had prescriptions for both. Based on pharmacy refill histories, adherence rates were 59% for montelukast and 44% for fluticasone. No relationship was found between adherence and age, length of monitoring, or the use of combination therapy. Sherman J, Patel P, Hutson A, et al. Adherence to oral montelukast and inhaled fluticasone in children with persistent asthma. **Pharmacotherapy 2001;21:1464-7.**

Buspirone pharmacokinetics

Thirteen children and 12 adolescents participated in this three week, open-label buspirone dose escalation study. The results obtained from these patients, all being treated for anxiety, were compared to pharmacokinetic parameters and adverse effect profiles obtained from 14 healthy adult volunteers. The authors found that peak plasma buspirone concentrations were highest in the children and the lowest in the adults. This was offset, however, by a more rapid clearance in the children. The most frequent adverse effects were lightheadedness (68%), headache (48%),

and dyspepsia (20%), similar to the findings in adults. Salazar DE, Frackiewicz EJ, Dockens R, et al. Pharmacokinetics and tolerability of buspirone during oral administration to children and adolescents with anxiety disorder and normal healthy adults. **J Clin Pharmacol 2001;41:1351-8.**

Drug interactions with ADHD treatment

The authors of this review discuss known drug interactions with the most commonly prescribed therapies for ADHD. In addition to methylphenidate, amphetamines, and pemoline, the article also covers antidepressants, anticonvulsants, and clonidine. Markowitz JS, Patrick KS. Pharmacokinetic and pharmacodynamic drug interactions in the treatment of attention-deficit hyperactivity disorder. **Clin Pharmacokinet 2001;40:753-72.**

Gentamicin by IV bolus

Although typically administered over 30 to 60 minutes, gentamicin may also be given as an IV bolus. In this retrospective study from Children's Hospital in Columbus, Ohio, the safety and efficacy of bolus administration were evaluated in 123 patients ranging from newborns to adults. Mean peak and trough serum concentrations were within the therapeutic range for all age groups. Serum creatinine and BUN remained unchanged in all but two patients. Both were receiving other nephrotoxic drugs and had a return to normal parameters after stopping therapy. Auditory exams were normal in all neonatal patients. The authors suggest that bolus administration be considered as a means of decreasing personnel time and equipment needs as well as increasing flexibility with administration of other medications or fluids. Robinson RF, Nahata MC. Safety of intravenous bolus administration of gentamicin in pediatric patients. **Ann Pharmacother 2001;35:1327-31.**

Methadone for opioid withdrawal

In this open-label study, the authors evaluated the effectiveness of enteral methadone in preventing symptoms of withdrawal in children who had been receiving continuous infusions of fentanyl. Twenty-two children (mean age 6 years) were enrolled. The average length of previous fentanyl therapy was 17.8±8.4 days. Methadone was initiated at a dose of 0.5 mg/kg/day while the fentanyl dose was being tapered, and was then slowly weaned. The average length of methadone therapy was 18.2±11.9 days, reflecting a high degree of patient variability. Only one patient experienced withdrawal symptoms, and responded to reinstitution of fentanyl and an increase in methadone dose. This study, while small in size, supports previous work demonstrating the efficacy of methadone in preventing iatrogenic opioid withdrawal. Lugo RA, MacLaren R, Cash J, et al. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. **Pharmacotherapy 2001;21:1566-73.**

Midazolam pharmacokinetics

Single-dose midazolam pharmacokinetics were evaluated in 133 children after receiving either an oral or intravenous dose. While several other kinetic studies have been performed in children, this is the first large-scale study to evaluate the effects of the syrup formulation. Absorption of the syrup was rapid, with children less than 12 years having a faster absorption than older children. In addition, elimination half-life was shorter and production of the primary metabolite, alpha-hydroxymidazolam, was greater in the younger subjects. Overall, bioavailability of the syrup was 36% (range 9-71%). No relationship between bioavailability and age was detected. Based on their data, the authors suggest an oral midazolam dose of 0.2 to 0.3 mg/kg for procedural sedation. Reed MD, Rodarte A, Blumer JL, et al. The single-dose pharmacokinetics of midazolam and its primary metabolite in pediatric patients after oral and intravenous administration. **J Clin Pharmacol 2001;41:1359-69.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/14/01:

1. Darbepoetin alfa (Aranesp®) was added to the Formulary for the treatment of anemia associated with chronic renal failure, including both dialysis and non-dialysis patients.
2. Perflutren lipid microsphere injectable suspension (Definity®) was also added. This product in an injectable contrast agent used during echocardiography.
3. Drotrecogin alfa (Xigris®), also known as activated protein C, was added for the management of adults with severe sepsis. Its use requires prior approval by an intensive care attending physician. Specific guidelines for use are available on MIS.

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