PEDIATRIC PHARMACOTHERAPY

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

• *celebrating 10 years of publication* •

Children's Medical Center
UVA HEALTH SYSTEM

Volume 10 Number 3 March 2004

Recent Revisions in Drug Labeling for Children

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In February, the Food and Drug Administration (FDA) updated its listing of pediatric labeling changes resulting from the Pediatric Exclusivity Program.[1] The program, which allows the FDA to grant an additional six months of marketing exclusivity to manufacturers submitting pediatric data, was developed as part of the FDA Modernization Act of 1997.[2] Since 1999, when the program became active, pediatric data have been evaluated for 101 medications, with 86 granted first-time exclusivity and five granted a second period. Based on the data submitted, changes are made in the product labeling, including all product information inserts, advertisements, and promotional materials. This issue of *Pediatric Pharmacotherapy* will review the labeling changes approved during the period from January 2003 to January 2004.

Amlodipine

Based on the FDA approval granted in January 2004, product labeling for the calcium channel blocker amlodipine (Norvasc®; Pfizer) will now include information on dosing and pharmacokinetics in children ages 6 to 17 years. The recommended dosage range for children is 2.5 to 5 mg given once daily. In addition, labeling will indicate that the adverse effect profile observed in children is similar to that established in adults.

Atovaquone/Proguanil

The combination of atovaquone and proguanil (Malarone®; GlaxoSmithKline) will now include a statement that safety and efficacy for the treatment of malaria have been established down to patients weighing 5 kg. In pediatric patients, the most frequent adverse effect in clinical trials was diarrhea (6%). The apparent drug clearances (CL/F) of both atovaquone and proguanil were related to weight in the pediatric studies. As a result, dosing recommendations are weight-based for patients weighing less than 40 kg. New labeling, as of December 2003, will also include instructions to crush the tablets and mix with condensed milk for children unable to swallow whole tablets.

Budesonide

Budesonide (Pulmicort® Respules; AstraZeneca) is now labeled with safety information in pediatric patients with asthma as young as 6 months of age. In addition, adverse effect information will include results from a 12-week trial in infants 6 to 12 months of age which suggested that budesonide produces a dose-dependent effect on growth similar to that observed in studies of other inhaled corticosteroids. Pneumonia has also been observed more frequently in pediatric patients treated with budesonide than placebo.

Busulfan

Pharmacokinetic data from an open-label study in 24 infants and children has been incorporated into the product labeling for busulfan (Busulfex®; Orphan Medical). The children, ranging in age from 5 months and 16 years, were given busulfan as part of a conditioning regimen administered prior to stem cell transplantation. Based on the results of this study, a suggested dosing regimen has been developed.

Fentanyl

Transdermal fentanyl (Duragesic®; Alza) labeling will now indicate that it may be used in children ages 2 years and older with chronic pain who are opioid-tolerant. The safety of the transdermal system was evaluated in three open-label trials which enrolled a total of 291 children with chronic pain who were between 2 and 18 years of

age. Adverse effects in these trials included fever (35%), vomiting (33%), and nausea (24%). There were no pediatric-specific adverse effects. New pharmacokinetic, dosing, and administration information has also been added to the labeling, as well as patient information and a precaution to guard against accidental ingestion of the patches by children.

This labeling change represents a considerable advancement in the tools available for the management of chronic pain in young children. While many pediatric institutions have already been using the transdermal fentanyl preparation, the availability of standardized dosing recommendations should reduce the likelihood of medication errors. The new product information should be reviewed carefully to ensure appropriate conversion from intravenous or oral opioids to the transdermal system.

Fexofenadine

Labeling for fexofenadine (Allegra®; Aventis) was amended in May 2003 to include the results of three new pediatric studies. The trials provided safety and efficacy data from a total of 845 infants and children up to 5 years of age with allergic rhinitis.

Fludarabine

Pediatric studies were conducted by the manufacturer of fludarabine (Fludara®; Berlex); unfortunately, data from the 62 children evaluated were insufficient to establish efficacy in childhood malignancies.

Fluoxetine

In January 2003, the labeling for fluoxetine (Prozac®; Lilly) was amended to state that effectiveness had been established in children 7 to 17 years of age with obsessive-compulsive disorder and in children 8 to 17 years of age with major depressive disorder. In addition, pediatric pharmacokinetic and adverse effect information was incorporated, as well as dosing recommendations. Additional adverse effect information includes data from a 19-week placebo-controlled trial of fluoxetine in pediatric patients in which treated patients gained an average of 1.1 cm less height and 1.1 kg less weight than controls. It is recommended that height and weight be monitored periodically in pediatric patients throughout treatment.

The approval of fluoxetine for children has been one of the more controversial labeling changes. While welcomed by health care providers caring for children who would benefit from the use of a selective serotonin reuptake inhibitor (SSRI), there has been concern over a possible link between other SSRIs and suicide in adolescents. This association is still being evaluated by the FDA, and further information is expected this year.

Fluticasone

Data from a new 1-year, placebo-controlled trial in children (3 to 9 years of age) with allergic rhinitis receiving fluticasone nasal spray (Flonase®; GlaxoSmithKline) has been added to the product information. In this trial, no statistically significant adverse effect on growth was found with treatment. No evidence of clinically significant effects on HPA axis function or bone mineral density were observed.

Pediatric approval, however, was not granted for fluticasone ointment (Cutivate Ointment®; GlaxoSmithKline). This product is indicated in the management of corticosteroid-responsive dermatoses. In a study of 35 children with atopic dermatitis, subnormal adrenal function was observed with cosyntropin stimulation testing. Labeling will continue to state that Cutivate Ointment® is indicated for use only in adult patients.

Fosinopril

Data from a double-blind study of fosinopril (Monopril®; Bristol-Myers Squibb), an angiotensin converting enzyme inhibitor used in the treatment of hypertension, have now been incorporated into the product labeling. The study was conducted in 252 children between 6 and 16 years. At this time, only dosing recommendations for children weighing greater than 50 kg will be included, as there is no lower dosage strength available for smaller patients.

Lisinopril

Lisinopril (Prinivil®; Merck and Zestril®; AstraZeneca), another angiotensin converting enzyme inhibitor, will now be labeled for patients 6 to 16 years of age. Information on efficacy, pharmacokinetics, and dosing will be included for pediatrics. It is recommended that lisinopril not be used in children with a glomerular filtration rate < 30 ml/min/1.73m^2. New product labeling will also include an extemporaneous formulation for preparing the drug as an oral liquid.

Moxifloxacin

In April 2003, the labeling for the ophthalmic preparation of moxifloxacin (Vigamox®; Alcon) was changed to incorporate a statement that safety and effectiveness has been established in patients as young as 1 year of age. The ophthalmic moxifloxacin product is indicated for the treatment of bacterial conjunctivitis.

Orlistat

Orlistat (Xenical®; Roche), which is used to promote weight loss by blocking fat absorption, will now carry a statement that use in 12 to 16 year olds is supported by studies in adults and additional data from a 54-week safety and efficacy study conducted in obese adolescents. The adverse effects observed during this study were similar to those occurring in adults. Product labeling will also carry a recommendation that all patients taking orlistat take a daily multivitamin that contains fat-soluble vitamins.

Oxybutynin

Oxybutynin (Ditropan®; Johnson & Johnson) is currently approved by the FDA for use in children and adults with overactivity of the bladder detrusor muscle. In April 2003, product labeling was amended to include additional pediatric pharmacokinetic and dosing information. In addition, the extended-release product (Ditropan XL®) now includes a statement that safety and effectiveness has been established in children as young as 6 years of age.

Temozolomide

Temozolomide (Temodar®; Schering) is currently approved by the FDA for the treatment of adults with refractory anaplastic astrocytoma. The results of two pediatric studies, one with 63 glioma and astrocytoma patients and a second with 122 patients who had a variety of CNS and non-CNS tumors, were submitted to the FDA in 2002. Based on these data, however, it was determined that effectiveness in children had **not** been demonstrated. The adverse effect profile of the drug does appear to be similar in children and adults.

Summary

Largely as a result of the Pediatric Exclusivity Program, a total of 15 drug products underwent labeling changes during the last year to incorporate pediatric information. As hoped, the program has become a useful catalyst for manufacturers to conduct pediatric safety and efficacy studies. For more information, the FDA Center for Drug Evaluation and Research website[1] contains a summary of the labeling changes with direct links to the newly revised product labeling.

References

1. Pediatric Exclusivity Labeling Changes. Available at: www.fda.gov/cder/pediatric/labelchange.htm (accessed 2/13/04)

2. Buck ML. The FDA Modernization Act of 1997: impact on pediatric medicine. Pediatr Pharmacother 2000;6;12:1-4.

Pharmacology Literature Review

Acetaminophen and ibuprofen as antipyretics

This brief paper reviews the available literature comparing the antipyretic effects of acetaminophen and ibuprofen in children. The author included 22 papers published during the period 1966 to 2000. Based on this review, he concluded that acetaminophen and ibuprofen appear to have equal tolerability. Acetaminophen produced a greater reduction in temperature within the first 30 minutes after ingestion, but ibuprofen had a longer antipyretic effect. Wahba H. The antipyretic effect of ibuprofen and acetaminophen in children. **Pharmacotherapy 2004;24:280-4.**

Atomoxetine drug interactions

Atomoxetine, a selective norepinephrine reuptake inhibitor, is a new option for the treatment of attention deficit/hyperactivity disorder. In this report, the manufacturer of atomoxetine provides the results of several studies designed to identify atomoxetine drug interactions. Using isolated human hepatic microsomes, the authors found significant inhibition of cytochrome P450 (CYP) 2D6 and CYP3A by atomoxetine only at concentrations representing high-dose therapy. During studies performed in healthy volunteers using known metabolic probes (desipramine to assess CYP2D6 activity and midazolam to evaluate CYP3A activity), the administration of atomoxetine did not produce significant changes in the pharmacokinetics of the probe drugs. As a result, the authors concluded that atomoxetine administration with substrates for either CYP2D6 or 3A did not produce significant drug interactions. Sauer J, Long AJ, Ring B, et al. Atomoxetine hydrochloride: clinical drug-drug interaction prediction and outcome. **J Pharmacol Exp Ther 2004;308:410-8.**

Ibuprofen in patients with cystic fibrosis

Ibuprofen is currently being investigated as a tool to decrease inflammation in the lungs of patients with cystic fibrosis (CF). As has been shown with many other drugs, the pharmacokinetics of ibuprofen are altered in patients with CF, resulting in a reduced bioavailability, increased volume of distribution, and more rapid clearance. In this new review, the authors summarize the studies conducted to date in this area and suggest directions for future research. Han EE, Beringer PM, Louie SG, et al. Pharmacokinetics of ibuprofen in children with cystic fibrosis. **Clin Pharmacokinet 2004;43:145-56.**

Nicotine transfer into breastmilk

Nicotine patches are often used by women attempting to stop smoking during pregnancy or while breastfeeding. The authors of this study measured the concentrations of nicotine and cotinine in the breastmilk of 15 women using nicotine patches to determine the relative risk of patch use. Serial milk samples were collected from each woman when she was smoking, as well as when she was stable on the 21 mg/day, 14 mg/day, and 7 mg/day patches. The 21 mg/day patch produced nicotine and cotinine concentrations in the milk similar to that during smoking, but the two lower patch strengths produced significantly lower concentrations of both compounds. Overall, there was a 70% reduction in nicotine and cotinine between the time during which the mothers were smoking and when they were using the 7 mg/day patch. Milk intake by the infants did not appear to be affected by the use of the patches. Ilet KF, Hale TW, Page-Sharp M, et al. Use of nicotine patches in breast-feeding mothers: transfer of nicotine and cotinine into human milk. **Clin Pharmacol Ther 2003;74:516-24.**

Pamidronate pretreatment

A retrospective chart review was conducted to evaluate the effectiveness of pretreatment with ibuprofen or acetaminophen in 27 children given pamidronate. The patients ranged in age from 3 to 21 years. Nineteen (70%) were being treated for osteogenesis imperfecta, and the remainder for juvenile osteoporosis. The patients were divided into three groups: those who received acetaminophen 10 mg/kg, those given ibuprofen 10 mg/kg, or those who did not receive pretreatment. Both treatment groups had significantly less pyrexia and bone pain than the group given no pretreatment. Fewer pamidronate-associated adverse effects were reported with ibuprofen (17%) than with acetaminophen (83%). The incidence of nausea, dizziness, and leukopenia did not differ among the groups. The authors concluded that pretreatment with either ibuprofen or acetaminophen appears to reduce pamidronate-associated adverse effects, with ibuprofen use associated with the least adverse effects. Robinson RF, Nahata MC, Hayes JR, et al. Effectiveness of pretreatment in decreasing adverse effects associated with pamidronate in children and adolescents. **Pharmacotherapy 2004;24:195-7.**

Surfactant comparison

At Shands Jacksonville Medical Center, both beractant and calfactant have been available on Formulary. In order to determine the preferred agent, the institution conducted a comparative retrospective chart review of data from 107 neonatal patients. Fifty patients received beractant, either as prophylaxis or rescue therapy, and fifty-seven were given calfactant. There was no significant difference between the groups in fraction of inspired oxygen (FiO2) at 72 hours, time to an FiO2 of 30%, total doses required, or adverse effects. One patient in each group developed a pneumothorax. Cost did not differ between the groups; however, the amount of drug wasted was greater with beractant because of the limitation of a single vial size. The authors concluded that the two surfactant products were similar in terms of safety and efficacy. The only significant difference was less waste with calfactant; however since publication of this article, beractant has become available in a smaller vial size which would likely minimize the cost difference. Hastings LK, Renfro WH, Sharma R. Comparison of beractant and calfactant in a neonatal intensive care unit. **Am J Health-Syst Pharm 2004;61:257-60.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 2/27/04:

1. Perflexane lipid microspheres (Imagent®) was added to the Inpatient Formulary. This product is used to opacify the left ventricular chamber and improve the improve the delineation of the left ventricular endocardial border during echocardiograms.

2. A sterile talc product is now available for the prevention of recurrent malignant pleural effusion.

3. The quarterly and yearly reports for the Adverse Drug Reaction (ADR) Reporting Program were presented. The drugs most frequently responsible for ADRs were analgesic/antipyretic agents (21.2%) and anti-infectives (15.8%). For more information about the report or documenting ADRs, please contact the Drug Information Service at 4-8034.

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