PEDIATRIC PHARMACOTHERAPY

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Recent Actions by the Food and Drug Administration

Marcia L. Buck, Pharm.D., FCCP

In the past year, the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) has made a number of significant changes in the labeling of prescription drugs for children as part of the Pediatric Exclusivity Program.[1] A number of agents received pediatric indications. In several other cases, preliminary studies failed to demonstrate safety and efficacy in children, but provided useful information on dosing, pharmacokinetics, or adverse effects that might aid prescribers in determining the appropriateness of these agents in children. In addition to these changes, there have been several important FDA Safety Alerts involving medications commonly used in children.[2-4]

Labeling Changes Under the Pediatric Exclusivity Act

Anagrelide

The product labeling for anagrelide (Agrylin®; Shire) was changed in December 2004 to include information on the pharmacokinetics, dosing, and adverse effects in children 6 to 17 years of age. Anagrelide is used in the treatment of thrombocytopenia due to myeloproliferative disorders.

Benazepril

Labeling for benazepril (Lotensin®; Novartis), an angiotensin converting enzyme inhibitor, was changed in March 2004 to include an indication for children 6 to 16 years of age. Benazepril is not recommended for children under 6 years of age (because of lack of sufficient data) or in patients with renal dysfunction. Pharmacokinetic studies have shown a significantly higher clearance rate in children than in adults, with an elimination half-life 1/3 of adult values. Instructions for the preparation of an oral suspension have also been included.

Ciprofloxacin

Ciprofloxacin (Cipro®; Bayer), a quinolone antibiotic, has been approved for use in children 1 to 17 years of age for the treatment of complicated urinary tract infections and pyelonephritis. The drug is not recommended as first-line therapy in this age range. In clinical trials, there was an increased risk of adverse effects in the patients receiving ciprofloxacin compared to those given placebo, including adverse effects related to joints and surrounding tissues. The most frequent adverse effects in children were gastrointestinal (15% compared to 9% of controls) and musculoskeletal (9.3% compared to 6% of controls).

Clofarabine

During the past year, only one agent received simultaneous pediatric and adult approval with an original New Drug Application. Clofarabine (Clolar®; Genzyme) is indicated for the treatment of relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This agent is currently approved for use in patients 1 to 21 years of age.

Desloratadine

The product information for desloratadine (Clarinex®; Schering) was amended in September 2004 to include an indication for patients 2 years of age and greater with perennial allergic rhinitis and chronic idiopathic urticaria. Information on dosing, pharmacokinetics, and adverse effects has been included in the product labeling.

Dorzolamide

The labeling of dorzolamide (Trusopt®; Merck) was modified in April 2004 to include efficacy and safety data in children. Dorzolamide reduces intraocular pressure by decreasing production of aqueous humor in patients with glaucoma or ocular hypertension.

Fenoldopam

The use of fenoldopam (Corlopam®; Hospira) was approved for the short-term reduction of elevated blood pressure in hospitalized pediatric patients greater than one month of age or weighing greater than 2 kg. Dosing, pharmacokinetic, and adverse effect information is now available in the product labeling.

Glyburide/metformin

In a clinical trial, the combination of glyburide and metformin (Glucovance®; BMS) was not found to be statistically superior to either agent given alone for pediatric patients with type 2 diabetes mellitus.

Irinotecan

New information has been added to the product labeling for irinotecan. Clinical trials did not establish the effectiveness of irinotecan (Camptosar®; Pfizer) in children. A phase 2 trial which enrolled 21 children with previously untreated rhabdomyosarcoma was halted because of a 23.6% incidence of progressive disease and 14% incidence of early deaths. Adverse effect data from a phase 2 trial of irinotecan in 170 children with refractory solid tumors was similar to that previously reported in adults, with neutropenia in 31.8% of patients and diarrhea in 20.6% of patients. In another study, dehydration occurred in 28.6% of the patients. Several experienced severe hypokalemia and hyponatremia. Serious infections were reported in 23.8% of patients.

Lansoprazole

In June 2004, lansoprazole (Prevacid®; Tap) labeling was amended to include an indication for patients 12 to 17 years of age. This drug, a proton pump inhibitor used to decrease gastric acid production, was previously approved for patients 1 to 11 years of age and adults.

Leflunomide

The safety and efficacy of leflunomide (Arava®; Aventis) has not been fully evaluated in children with juvenile rheumatoid arthritis (JRA), but preliminary information was added to the product labeling in March 2004. In a double-blind study of 94 children with JRA, 68% of those given leflunomide demonstrated clinical improvement, compared to 89% of patients on standard therapies. In a study of 74 children with JRA, adverse effects were similar to those reported in adults. Fourteen patients experienced elevated liver function tests, with 5 patients having values greater than three-fold the upper limit of normal.

Losartan

The angiotensin receptor blocker losartan (Cozaar®; Merck) now has labeling for use in hypertensive patients between 6 and 16 years of age. Information on dosing, pharmacokinetics, and adverse effects has been included, as well as information on the preparation of an extemporaneous oral suspension. Lorsartan is currently not recommended for patients less than 6 years of age or in patients with renal dysfunction.

Methylphenidate

The labeling of once-daily methylphenidate (Concerta®; Alza) has been expanded to include a new strength and information on the dosing, pharmacokinetics, and adverse effects in children 13 to 17 years of age. A higher maximum dose for adolescents has also been incorporated.

Because the data submitted to the FDA were deemed inadequate to determine whether chronic use of stimulants suppresses growth, the labeling of this product has been amended to highlight the need for monitoring growth during treatment. Patients who are not growing or gaining weight should have their treatment interrupted. In addition, caution should be used when prescribing methylphenidate for patients with hypothyroidism, hypertension, or cardiovascular conditions that might be worsened by drug-related elevations in blood pressure or heart rate.

Nelfinavir

A protease inhibitor for the treatment of patients with HIV-1 infection, nelfinavir (Viracept®; Pfizer), has been approved for use in children 2 to 13 years of age. New dosing information has been added to the labeling for this population. In addition, the results of pharmacokinetic studies in patients from birth to 13 years of age have been added, with attention to the problem of highly variable drug exposure in children.

Nizatidine

The labeling of nizatidine (Axid®; Reliant Pharma), a histamine (H_2) blocker, was changed in May 2004 to include an indication for patients 12 years of age and older. Dosing, pharmacokinetic, and safety data were added.

Paricalcitol

The safety and efficacy of paricalcitol (Zemplar®; Abbott) was studied in a 12-week trial in 29 children with end-stage renal disease. Nine of the 15 patients (60%) given paricalcitol had significant decreases from baseline parathyroid hormone levels compared to 3 of 14 patients (21%) in the placebo group.

Remifentanil

Remifentanil (Ultiva®; Abbott) labeling was amended in March 2004 to include information on its use for maintenance of anesthesia in infants. Because of the highly variable clearance rate observed during clinical trials in neonates, a recommendation for careful dose titration has been included.

Sodium ferric gluconate complex

Labeling for sodium ferric gluconate complex (Ferrlecit®; Watson) was amended in August

2004 to include patients 6 to 15 years of age. Information on dosing, pharmacokinetics, and adverse effects in this age group has been added.

Sumatriptan
Five clinical trials of sumatriptan (Imitrex Nasal Spray®; Glaxo) have failed to show significant benefit when compared to placebo in pediatric patients with migraines. Information from these trials, including the adverse effects observed in children, was added to the product labeling. At this time, the use of sumatriptan in patients less than 18 years of age is not recommended.

Tolterodine
Pharmacokinetic data in patients 11 to 15 years of age was added to the product information for tolterodine (Detrol LA®; Pfizer). This drug is an anticholinergic used for patients with an overactive bladder.

Venlafaxine
The antidepressant venlafaxine (Effexor® and Effexor XR®; Wyeth) was studied in adolescents with depression, but did not show significant benefit compared to placebo. During placebo-controlled trials, decreased appetite and a reduced growth velocity were observed. Elevations in blood pressure and serum cholesterol were reported in children at rates similar to those observed in adults.

Zolmitriptan
As with sumatriptan, studies with zolmitripan (Zomig®; AstraZeneca) in adolescents with migraines have not established safety and efficacy when compared to placebo. The adverse effects observed were similar to those in adults.

Safety Alerts for Pediatric Patients

Anagrelide
The labeling of anagrelide (Agrylin®; Shire) was revised in December 2004 to include a contraindication for use in patients with severe hepatic impairment and the need to reduce the dose in patients with moderate hepatic impairment. These patients should be carefully monitored for adverse cardiovascular effects.

Antidepressants
On May 5, 2004, after more than a year of review, the FDA requested a warning be added to the labeling of bupropion (Wellbutrin®), citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluvoxamine (Luvox®), paroxetine (Paxil®), mirtazapine (Remeron®), nefazodone (Serzone®), and venlafaxine (Effexor® and Effexor XR®) to encourage close observation of patients for worsening depression or the emergence of suicidality. On October 15th, the warning was expanded to all antidepressants and a request was made to add a boxed warning to alert health care professionals of the increased risk in children and adolescents. A proposed FDA Medication Guide on this topic is available at www.fda.gov/cder/drug/antidepressants /SSRI/MedicationGuide.htm

Atomoxetine
On December 17, 2004, the FDA notified health care professionals of a new warning for atomoxetine (Strattera®; Lilly). The labeling for this agent was amended to include information on potential hepatic injury following two recent case reports.

Atypical antipsychotics
In March 2004, the FDA requested that all manufacturers of atypical antipsychotics revise their product labeling to address the risk of hyperglycemia and diabetes with these agents. The following agents have undergone label revision: aripiprazole (Abilify®; BMS), clozapine (Clozaril®; Novartis), olanzapine (Zyprexa®; Lilly), risperidone (Risperdal®; Janssen), quetiapine (Seroqel®; AstraZeneca), and ziprasidone (Geodon®; Pfizer).

Controlled release amphetamine (Adderall XR®)
On February 9, 2005, the FDA issued a public health advisory to notify health care professionals that Health Canada had suspended the sale of Adderall XR®. This action was based on post-marketing reports of sudden death in pediatric patients. The FDA is currently evaluating these reports. A patient information sheet describing this alert, as well as additional information for prescribers, is available at www.fda.gov/cder/drug/infopage/adderall/default.htm

Infliximab
The FDA alerted health care professionals in August 2004 of a revision in the warnings for infliximab (Remicade®; Centocor), a monoclonal antibody to tumor necrosis factor. The warning calls attention to the risk for leukopenia, neutropenia, and pancytopenia with this drug, as well as reports of systemic vasculitis with central nervous system manifestations. In October, an additional alert was distributed regarding the increased risk of lymphoma in treated patients; and in December, further revisions in the product labeling were made to incorporate reports of hepatotoxicity with infliximab use.

Non-steroidal anti-inflammatory drugs
Beginning with the voluntary withdrawal of rofecoxib (Vioxx®; Merck) on September 30,

2004, there has been considerable attention to the risk of adverse cardiovascular events with non-steroidal anti-inflammatory drugs (NSAIDS). The FDA is currently analyzing data from a large number of NSAID trials. The Public Health Advisory issued on December 23rd is available from the FDA CDER website at www.fda.gov/cder/drug/advisory/nsaids.htm

Oseltamivir

On June 24, 2004, oseltamivir (Tamiflu®; Roche) labeling was revised to address the lack of safety and efficacy data in infants. The manufacturer does not recommend this agent in infants because of the potential for penetration across an immature blood-brain barrier.

Promethazine

In January 2005, a black box warning with a contraindication to use in patients less than 2 years of age was added to the labeling for promethazine (Phenergan®; Wyeth and generic). The new labeling will call attention to the risk for respiratory depression in this age range, even with standard dosing. It replaces earlier labeling which stated that the use of promethazine in these patients was not recommended.

Saquinavir

Last month, health care professionals were alerted to a potential drug interaction between saquinavir (Invirase® and Fortovase®; Roche) and rifampin. Use of this combination has resulted in hepatotoxicity.

Somatropin

The use of somatropin (Nutropin Depot®; Genentech) is now contraindicated in patients with Prader-Willi syndrome, according to labeling changes made in October 2004. Fatalities have been reported with the use of this agent in Prader-Willi patients with the following risk factors: severe obesity, upper airway obstruction or sleep apnea, or respiratory infection. Males also appear to be at greater risk.

Topical Macrolide Immunosuppressants

On February 14, 2005, the FDA issued alerts for pimecrolimus cream (Elidel®; Novartis) and tacrolimus ointment (Protopic®; Fujisawa). In post-marketing reports, these agents have been linked to lymphoma and skin cancer in children and adults. Although a causal relationship has not been established, the FDA urges clinicians to carefully weigh the risks and benefits of treatment. Prescribers are reminded that these agents are not first-line therapies for atopic dermatitis and should not be used in children less than 2 years of age. FDA alerts and patient information sheets are available at www.fda.gov/cder/drug/infopage/elidel/default.htm and www.fda.gov/cder/drug/infopage/protopic/default.htm

Summary

Over two dozen drugs have undergone labeling changes to incorporate pediatric information since January 2004. While many of these changes have been to include pediatric dosing information, there have also been some important new safety warnings. For additional information, the FDA CDER and MedWatch websites contain information on these changes and links to new product labeling.[1]

References

1. Pediatric Exclusivity Labeling Changes. Available at: www.fda.gov/cder/pediatric/labelchange.htm (accessed 2/19/05)
2. Baker DE. Current FDA-related drug information. Hosp Pharm 2005;40:170-83.
3. 2004 Safety Alerts for Drugs, Biologics, Medical Devices, and Dietary Supplements. Available at www.fda.gov/medwatch/SAFETY/2004/safety04.htm. (accessed 2/17/05)
4. 2005 Safety Alerts for Drugs, Biologics, Medical Devices, and Dietary Supplements. Available at www.fda.gov/medwatch/SAFETY/2005/safety05.htm. (accessed 2/17/05)

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/25/05:

1. Ziconotide (Prialt®) was added both to the Inpatient and Outpatient Formularies for intrathecal administration to patients with severe chronic pain (restricted to the Pain Service).
2. Paclitaxel protein-bound particle injectable suspension (Abraxane®) was added both Formularies for patients with refractory metastatic breast cancer and documented hypersensitivity to paclitaxel.
3. The restriction on modafinil (Provigil®) was amended to include use by the Neurology and Palliative Care Service for specific indications.
4. Cortisone tablets and triamcinolone acetonide spray were removed from the Formulary.
5. A protocol for the use of intravenous enoxaparin for patients undergoing percutaneous coronary intervention was approved.

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