

Pediatric Pharmacotherapy

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Recent Actions by the Food and Drug Administration (FDA)

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There have been several recent actions by the Food and Drug Administration (FDA) that affect pediatric patients. As anticipated, the final ruling on the FDA Modernization Act, which requires pediatric labeling information on commonly used medications, has spurred manufacturer interest in pursuing pediatric indications. This brief review will highlight several new drug releases and new labeling for some drugs already on the market in the United States.

Caffeine citrate

An injectable form of caffeine citrate has long been desired by neonatal health care providers. That need has now been filled with the recent FDA approval of Cafcit[®], produced by Roxane Laboratories, for short-term use in neonates with apnea of prematurity. This product is available in 3 ml vials with a concentration of 20 mg/ml.¹ Although aminophylline has traditionally been used for apnea when an injectable product was necessary, caffeine citrate offers the advantages of a wider therapeutic range and once daily dosing. The injectable forms of caffeine previously available contained benzyl alcohol as a preservative, making them unacceptable for use in neonates because of the risk of neonatal gasping syndrome.

Epoetin alfa

Epoetin alfa (Epogen[®]; Amgen) has been approved by the FDA for use in the treatment of anemia in children with chronic renal failure who are undergoing dialysis.² As in adults, epoetin administration has been shown to decrease the need for transfusions in patients receiving dialysis.

Mometasone

An intranasal dosage formulation of mometasone (Nasonex[®]; Schering-Plough) has received FDA approval for use in children 3 years of age and older. Intranasal mometasone is indicated for the treatment of seasonal and allergic rhinitis. The use of inhaled mometasone has not been associated with significant growth inhibition in pediatric patients. Studies of children between 3 to 9 years of age receiving inhaled mometasone documented no effect on growth velocity when compared to placebo.

Pneumococcus vaccine

Last month, Wyeth-Lederle's 7-valent conjugate pneumococcus vaccine received a recommendation for approval from the Vaccines and Related Biological Products Advisory Committee of the FDA.³ This recommendation echoes the unanimous support of the vaccine by the Advisory Committee on Immunization Practices of the Centers for Disease Control.⁴ The vaccine, to be marketed as Prevenar[®], is recommended for immunization of all children < 5 years of age. Initially, children less than 2 years of age or those at higher risk for infection will be targeted for vaccination, with eventual

inclusion of the vaccine into the standard childhood immunization series given at 2, 4, 6, and 12-15 months of age.⁵

The FDA advisory committee also recommended long-term follow-up of vaccinees to document continued protection. The duration of antibody response is currently unknown.⁶

Poractant alfa

Another surfactant has recently been approved by the FDA. Poractant alfa (Curosurf[®]; Dey) is a porcine product approved for the treatment of respiratory distress syndrome (RDS) in premature infants.⁷ This product has been tested extensively in Europe and is already on the market in several foreign countries. The approval of poractant alfa in the United States was delayed because of FDA concerns about the European prophylaxis trials. As a result, poractant alfa is only approved for treatment of RDS, rather than both prophylaxis and treatment. This distinction separates the product from the other currently available surfactant products, all of which carry approval for both indications. Poractant alfa is administered as an initial dose of 2.5 ml/kg. If needed, up to 2 additional doses of 1.25 ml/kg may be given at 12 hour intervals. The product is available in both 1.5 and 3 ml vial sizes.

Topiramate

Topiramate (Topamax[®]; Ortho-McNeil) has received an additional indication from the FDA as adjunctive therapy for primary generalized seizures in children ages 2 to 16 years. This product has been used under protocol at the University of Virginia for several years in children with refractory mixed seizure disorders.

Zafirlukast

The leukotriene receptor antagonists have made a significant contribution to the management of asthma in children and adults. Zafirlukast (Accolate[®]; AstraZeneca) is now available in a 10 mg unflavored mini-tablet for use in children ≥ 7 years of age.¹ The recommended dose of zafirlukast in children is 10 mg twice daily. The usual adult dose is 20 mg twice daily. Studies of the drug in younger children are currently underway.

References

1. Fax Stat on Drugs. 1999;8(42):1.
2. Fax Stat on Drugs. 1999;8(48):1.
3. Fax Stat on Drugs. 1999;8(47):1.
4. Fax Stat on Drugs. 1999;8(49):1.
5. FDC Reports. 1999;61(45):16.
6. FDC Reports. 1999;61(44):13.

Literature Review

Acetaminophen by rectal administration

Acetaminophen is commonly given to neonates using a suppository dosage formulation. In this study from The Netherlands, the authors studied the pharmacokinetics of acetaminophen in 10 neonates who received four 20 mg/kg doses given at 6 hour intervals. The mean peak serum acetaminophen concentration for the group was 10.79 ± 6.39 mg/L. Of interest, male neonates had significantly higher serum concentrations than females (15.34 ± 5.21 vs. 6.24 ± 3.64 mg/L), although the small sample sizes limit the conclusions which can be drawn from this difference. The average time to peak serum concentrations after the initial rectal dose was 1.5 hours. The authors found no correlation between serum concentrations and pain relief scores, using a validated neonatal pain scale. While this study supports the efficacy of the rectal route for acetaminophen in newborns, readers should be cautious in applying the conclusions to their patient population. The study used specially compounded suppositories to ensure accurate dosing, while commercially available suppositories that have been cut to size for neonates do not provide reliable, consistent doses. van Lingen RA, Deinum HT, Quak CME, et al. Multiple-dose pharmacokinetics of rectally administered acetaminophen in term infants. **Clin Pharmacol Ther** 1999;66:509-15.

Chromium and zinc in parenteral nutrition

There has long been concern over the potential adverse effects of long-term parenteral nutrition use in children. This study was designed to evaluate the potential accumulation of chromium and zinc in children who had received parenteral nutrition for at least 2 months. A total of 11 children were evaluated: 4 infants and 7 children between 1 and 12 years of age. Baseline serum and urine concentrations were evaluated at the time of enrollment and again after an additional 4 to 6 months of therapy. In all cases, serum and urine concentrations of both minerals were much higher than recommended. Although some accumulation was noted during the follow-up period, serum and urine mineral concentrations were not significantly different than those documented at enrollment. The authors concluded that parenteral nutrition solutions for children frequently provide excessive amounts of chromium and zinc. They suggest that chromium be eliminated as a routine supplement for parenteral nutrition solutions and that zinc supplementation be further studied. Mouser JF, Hak EB, Helms RA, et al. Chromium and zinc concentrations in pediatric patients receiving long-term parenteral nutrition. **Am J Health-Syst Pharm** 1999;56:1950-6.

Consumer drug information on the Internet

Many families now turn to the Internet for information on their children's medications. The quality of information provided on these sites has become a concern for health care providers. The authors of this paper reviewed four Internet sites to evaluate the quality of their information on 30 commonly prescribed drugs. The sites, MedicineNet, RxList, Drug InfoNet, and thriveonline, were evaluated according to sponsorships, references cited, frequency of updates, ease of use, and organization of the webpage, as well as the quality and quantity of information provided. A standard evaluation sheet was prepared with 22 variables. Of the areas assessed, the percentage of variables met by the sites was 60%, 84%, 87%, and 72%, respectively. One consistent weakness of all the sites was a lack of regular updates. The authors concluded that these four sites provided useful consumer drug information, but failed to meet the standards set for an ideal website. Hatfield CL, May SK, Markoff JS. Quality of consumer drug information provided by four Web sites. *Am J Health-Syst Pharm* 1999;56:2308-11.

Empiric vancomycin use

With the advent of resistant bacterial strains, there has been considerable interest in methods to decrease the empiric use of vancomycin. The authors of this paper conducted a retrospective review of children admitted with fever and neutropenia who received vancomycin. The study was designed to identify those characteristics which would most likely indicate a serious gram positive bacterial infection warranting treatment with vancomycin. Thirty-three pediatric oncology patients were evaluated over a total of eighty-eight admissions. Nearly all patients (92%) had central intravenous catheters in place. During 17 admissions, blood cultures documented an infection with gram positive organisms, most frequently coagulase negative staphylococci. The most common characteristics separating these patients were the previous use of high-dose cytarabine (ARA-C), inflammation at the central line site, hypotension, and other early signs of septic shock. The authors used this information to create a treatment pathway detailing when the use of vancomycin would be appropriate. While the study design and limited sample size limit the conclusions which can be drawn from this work, the paper does provide an excellent framework for initiating further discussions about the role of vancomycin in children with cancer. Adcock KG, Akins RL, Farrington EA. Evaluation of empiric vancomycin therapy in children with fever and neutropenia. *Pharmacotherapy* 199;19:1315-20.

HMG-CoA reductase inhibitors

Until recently, there have been few treatment options for children with hypercholesterolemia. The hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, such as lovastatin, pravastatin, or simvastatin, provide a new alternative to

reduce serum low-density lipoproteins. While this therapeutic class has been well studied in adults, there are only a few papers describing their use in children and adolescents. The author of this brief review describes the experience published in children to date, summarizing their effectiveness and the literature describing adverse effects. This four page review would be a nice addition to any general pediatric practitioner's literature files. Duplaga BA. Treatment of childhood hypercholesterolemia with HMG-CoA reductase inhibitors. **Ann Pharmacother** 1999;33:1224-7.

Itraconazole-clarithromycin interaction

Both itraconazole, an azole antifungal, and clarithromycin, a macrolide antibiotic, are metabolized through the cytochrome P450 enzyme system, specifically through the CYP3A4 isozyme. In addition, both agents are known to be inhibitors of this enzyme. The interaction between these agents when given in combination is the focus of this article. The authors studied 3 immunocompromised adults receiving both drugs. All 3 had an elevated serum concentration of clarithromycin as well as an elevated ratio of unchanged clarithromycin to metabolite (14-OH-clarithromycin), reflecting reduced metabolism. Despite these increased serum concentrations, there were no clinical adverse effects. The authors suggest that this combination can be given together safely, but recommend further studies in a larger series of patients. Auclair B, Berning SE, Huitt GA, et al. Potential interaction between itraconazole and clarithromycin. **Pharmacotherapy** 1999;19:1439-44.

Kawasaki disease- therapy review

This brief review covers the standard approach to the management of children with Kawasaki disease. The authors, one of whom is credited with first describing the disease which bears his name, begin their paper with a discussion of the use of aspirin. The efficacy and safety of high dose (≥ 80 mg/kg/day) aspirin therapy is reviewed and compared to the results achieved with more moderate doses (30-50 mg/kg/day). The use of intravenous immune globulin is then covered in considerable detail. The authors highlight the success of these therapies in minimizing the development of coronary artery aneurysms. They conclude with a discussion of potential therapies for patients who prove resistant to standard approaches. Onouchi Z, Kawasaki T. Overview of pharmacological treatment of Kawasaki disease. **Drugs** 1999;58:813-22.

Management of juvenile rheumatoid arthritis

A thorough review of therapies for juvenile rheumatoid arthritis (JRA) is long overdue. The author of this review has compiled information on a variety of

treatments for JRA, ranging from the standard therapies such as non-steroidal anti-inflammatory drugs, to newer agents such as methotrexate and cyclosporine. He also discusses controversial and experimental therapies. Brief sections on the role of nutritional therapy and psychosocial issues related to medication compliance are also included. Cassidy JT. Medical management of children with juvenile rheumatoid arthritis. **Drugs 1999;58:831-50.**

Permeability of hospital gloves to antineoplastics

Eighteen antineoplastics were tested for their ability to penetrate four common glove materials- nitrile rubber, latex, polyurethane, and neoprene in this trial. Fingertips of the sample gloves were placed in direct contact with the drugs to simulate a potential exposure. Samples of the glove materials were then assessed after 30, 60, 90, and 120 minutes. Significant permeation was observed in only one sample, with > 5% of a thiotepa dose penetrating one of the nitrile rubber gloves, presumably through a pinhole defect. All of the gloves tested were considered by the investigators to be impermeable to the 18 drugs tested and safe for clinical use. Connor TH. Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs. **Am J Health-Syst Pharm 1999;56:2450-3.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/3/99:

1. Eptifibatide (Integrilin[®]; COR Therapeutics) was added to the Formulary. This agent is a glycoprotein IIb/IIIa inhibitor used for its antiplatelet effect in patients with acute coronary syndrome.
2. Quinupristin/dalfopristin (Synercid[®]; Rhone-Poulenc Rorer) was added to the Formulary for the treatment of infections caused by bacteria known to be resistant to vancomycin. Limited pediatric information is available, but a dose of 7.5 mg/kg IV every 8 or 12 hours has been used in children.
3. Oseltamivir (Tamiflu[®]; Roche) and zanamavir (Relenza[®]; GlaxoWellcome) were added for a trial period. These agents are both neuraminidase inhibitors used for the treatment of uncomplicated infections with the influenza virus in patients ≥ 12 years of age.
4. Meprobamate and oral pentobarbital were removed from the Formulary because of lack of use.
5. A proposal for standardization of pediatric oral liquid doses was approved by the committee. This process will restrict 40 commonly used pediatric oral liquid drugs to a preselected group of doses, requiring prescribers to round to the nearest available dose. Exceptions can be made for children previously stabilized on a different dose or in situations where precise dose titration is needed. Some

examples of drugs affected by this process are: acetaminophen, ibuprofen, baclofen, prednisone, theophylline, vitamins, laxatives, and most antibiotics.

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