# PEDIATRIC PHARMACOTHERAPY

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## 2001 Pediatric Vaccine Update

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There have been a number of changes in the routine childhood immunization schedule within the past several years. Some of these changes, for example the addition of the pneumococcal conjugate vaccine, provide the opportunity to reduce or eliminate a significant cause of morbidity and mortality in the pediatric population. Other changes, such as the transition to inactivated poliovirus vaccine and the use of acellular pertussis, have reduced the risks associated with vaccine administration. This issue of *Pediatric Pharmacotherapy* will review several new case reports, surveillance studies, and announcements from the Food and Drug Administration (FDA) related to vaccines.

Tetanus toxoid shortage to continue

Most healthcare providers are now aware of a shortage of tetanus toxoid in the United States. This shortage is primarily a result of the decision by Wyeth-Lederle to discontinue production of tetanus toxoid (TT), tetanus and diphtheria toxoid (Td), and their diphtheria-tetanus-acellular pertussis (DTaP) vaccine, ACEL-IMMUNE®. This leaves Aventis Pasteur as the sole manufacturer of TT and Td in the United States. Aventis Pasteur, who also produces the Tripedia® brand of DTaP, and GlaxoSmithKline, maker of the Infanrix® brand of DTaP, are attempting to increase production to offset this change. Despite their increased production schedule, it is anticipated that the shortage may last as long as 12 to 18 months.[1]

Thimerosal elimination nearing completion

In related news, the FDA recently announced the approval of a new formulation of Aventis Pasteur's DTaP vaccine, Tripedia®. The new product contains no preservatives and only trace amounts of thimerosal. This represents a greater than 95% reduction in the amount of thimerosal compared to the original formulation.

The removal of thimerosal from vaccines has been the result of a call from the American Academy of Pediatrics and the United States Public Health Service to eliminate this preservative as a source of mercury exposure in infants.[2] While there have been no case reports of mercury toxicity associated with the use of thimerosal, there was a perceived need to reduce the potential for mercury accumulation during childhood. Since the initial recommendation on July 8, 1999, vaccine manufacturers have voluntarily responded by reformulating their products. At this time, all vaccines in the recommended childhood immunization schedule are available in at least one thimerosal-free or reduced-thimerosal formulation.

No link found between autism and MMR

An association between autism and administration of the combined measles, mumps, rubella (MMR) vaccine was first suggested in 1996. Fudenberg and colleagues had studied a new therapy in 40 children with autism; and as an aside, reported that 15 of the children developed their symptoms of autism within one week of receiving the MMR vaccine. While this first paper garnered little attention in the medical literature[3], a second paper by Wakefield and colleagues[4] generated much more interest. In this paper, the authors described 12 children with chronic enterocolitis and regressive developmental disorders. The onset of symptoms was temporally related to the administration of an MMR dose in eight of the children. In both papers, the authors suggested a potential relationship between autism and MMR, but could not establish causality.

An accompanying editorial to the Wakefield paper and several letters to the editor immediately called to attention the implausibility of the link. Since that time, a number of small surveillance studies have found no relationship between autism and MMR immunization. Recently, two large-scale database analyses have also refuted the link.[5,6] In the February 24th issue of the *British Medical Journal*, Kaye and colleagues published their evaluation of data contained in the United Kingdom General Practice Research Database.[5] The authors evaluated two groups, one included all children with autism diagnosed between the years 1988 and 1999, and a cohort of boys aged 2 to 5 years born between 1988 and 1993. The authors theorized that, if the MMR were linked to autism, a parallel would be found between number of patients vaccinated and the frequency of autism. While the prevalence of MMR vaccination remained relatively unchanged during that period (over 95% in the cohort group), the incidence of autism increased sevenfold. The greatest percentage of the increase occurred in boys, with a peak at 3 to 4 years of age. The authors concluded from their analysis that no correlation existed between the prevalence of MMR vaccination and the rapid rise in the diagnosis of autism.

A similar time trend analysis, published earlier this month in *JAMA*, was carried out by Dales and coworkers using kindergarten enrollment records in California.[6] The authors compared immunization rates with the number of children diagnosed with autism who were enrolled in the state's Department of Developmental Services system over the period 1980 through 1994. As with the British paper, MMR immunization rates remained relatively unchanged throughout the study period (with an increase of 14%), while the rate of autism increased by 373%. Based on their assessment, the authors made a similar conclusion to the Kaye study, that the data do not suggest an association between MMR immunization and the current increase in cases of autism.

Pneumococcal vaccine reduces otitis media

In addition to demonstrating a reduction in invasive disease, premarketing trials of the conjugate pneumococcal vaccine (PCV7) also showed a 7% reduction in otitis media among treated children.[7] This effect has now been reproduced in a study conducted in Finland and published in the February 8th issue of the *New England Journal of Medicine*.[8] The Finnish Otitis Media Study Group enrolled 1,662 infants in a randomized, double-blind study comparing PCV7 to a control (hepatitis B vaccine given at the same 2, 4, 6, and 12 month visits). PCV7 administration reduced the overall occurrence of otitis media by 6%. Subset analysis revealed a 34% reduction in otitis caused by *Streptococcus pneumoniae* and a 57% reduction in cases caused by the seven serotypes contained in the vaccine. While this reduction may seem small at first, the impact is expected to be sizable. In the United States, a reduction of this magnitude could result in a healthcare cost savings of 300 to 500 million dollars annually.

New combination under investigation

With the inclusion of the conjugate pneumococcal vaccine in the routine childhood immunization schedule and the conversion to inactivated poliovirus vaccine, the average child will receive more than 20 injections by 6 years of age. Healthcare providers and parents have become sensitive to this issue. In an attempt to reduce the number of injections, several new combination vaccine products are under development.

GlaxoSmithKline has produced a combination vaccine which incorporates their DTaP vaccine, Infanrix®, with hepatitis B and inactivated poliovirus vaccines. While preliminary studies appear favorable, release of this product is likely to be delayed for another year. On March 7th, the FDA Vaccines and Related Biological Products Advisory Committee voted six to five to recommend that the combination not be approved at this time.[9] While the committee members acknowledged the benefit of the 5-vaccine product, they requested additional efficacy data to better establish the antigenicity of the individual components. In particular, members expressed concern about the immunologic response to the combination when given at the same time as the conjugate pneumococcal vaccine and about the rate of fever in recipients. In Phase III trials, fever occurred in 43% of infants vaccinated with the combination product versus 26% of those receiving standard immunizations.

Progress made towards eradication of polio

While the goal of global eradication of poliomyelitis by the year 2000 was not achieved, the end does appear to be in sight. On October 29, 2000, the Western Pacific region of the World Health Organization (WHO) was certified as free of indigenous wild poliovirus transmission.[10,11] The Western Pacific region incorporates 37 countries and approximately 27% of the world's population. This is the second of the six WHO regions to be declared

polio-free; the first was the Americas in 1994. The European region is expected to be the next area to achieve eradication. No new indigenous cases have been reported in this region since November 1998.

Additional information

The 2001 Immunization Schedule is available from the American Academy of Pediatrics at www.aap.org/family/parents/immunize.htm or in the journal *Pediatrics*.[12] The schedule is also published on the Centers for Disease Control (CDC) website for the National Immunization Program at www.cdc.gov/nip. This site contains a number of other educational tools for both healthcare providers and the lay public. The CDC vaccine information sheets for parents are also available in the publications section of this website.

Summary

The reduction of infectious diseases resulting from the use of vaccines has been one of the past century's greatest public health successes. The achievement of eradication or near-eradication of many pediatric infections has been the result of continued research, active governmental involvement, and the work of countless healthcare providers. The United States childhood immunization program continues to evolve, incorporating new vaccines and modifications of older products in an effort to continue to improve safety and efficacy.

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## Pharmacology Literature Review

Antihistamine safety review

For anyone using antihistamines in their clinical practice, this extensive review is an excellent resource. The authors divide antihistamines into three generations. With each generation, they cover both common and rare adverse effects in children, including cardiac toxicity, as well as symptoms of overdose. The authors pay special attention to the long-term effects of some antihistamines on learning and school performance, an often unrecognized problem. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. **Drug Safety 2001;24:119-47.**

Budesonide review

This article focuses on the newest formulation of budesonide, a liquid suspension for nebulization. The author gives a brief overview of the drug itself, then devotes the remainder of the review to efficacy and safety trials performed in the United States and abroad. Particular attention is paid to those studies evaluating the effects of inhaled budesonide on hypothalamic-pituitary-adrenal axis function and growth. Szefler SJ. A review of budesonide inhalation suspension in the treatment of pediatric asthma. **Pharmacotherapy 2001;21:195-206.**

Protease inhibitors in children

The authors of this observational study evaluated the safety and efficacy of protease inhibitors (ritonavir, nelfinavir, indinavir, and saquinavir) in 21 children over a period of 3 years. Viral load was reduced in the ritonavir, nelfinavir, and indinavir groups, while CD4+ counts increased with all protease inhibitors. Overall, compliance was 70%, relatively high for a complex chronic regimen. The most frequently reported adverse effects were diarrhea and vomiting. Ritonavir was associated with the greatest number of adverse effects (28 reported in 19 children). The most frequent alterations in laboratory values were increases in cholesterol, serum creatinine, and triglycerides. Temple ME, Koranyi KI, Nahata MC. The safety and antiviral efficacy of

protease inhibitors in children. **Pharmacotherapy 2001;21:287-94.**

Sotalol pharmacokinetics

The pharmacokinetics of sotalol, a beta-adrenergic blocker used in patients with tachycardia, were evaluated in 26 children and adults to evaluate age-related differences. The study involved 4 newborns (13-26 days), 11 infants and toddlers (1 month to 3 years), 5 children (6-9 years), and 5 adolescents and adults (13-35 years). All patients enrolled were previously receiving sotalol, with daily oral doses between 1.90 and 6.86 mg/kg. The infant/toddler group showed significantly faster clearance than the adolescent/adult group (3.93±1.25 versus 2.00±0.29 ml/min/kg), resulting in a shorter elimination half-life (5.0±1.4 versus 7.7±1.3 hrs). The group of 6-9 year olds fell between the values for infants/toddlers and adolescents/adults. Newborns had a longer elimination half-life than the infant/toddler group. In contrast, volume of distribution, when normalized for weight, did not vary significantly among the groups. The authors suggest that infants and young children may require dosing three times daily to achieve maximal response. Laer S, Wauer I, Behn F, et al. Pharmacokinetics of sotalol in different age groups of children with tachycardia. **J Pediatr Pharmacol Ther 2001;6:50-9.**

Tacrolimus clearance in children

Serum tacrolimus concentrations from 18 children, aged 4 months to 16 years, were used to evaluate the influence of several covariates on drug elimination. The authors built a nonlinear mixed-effects model (NONMEM) for tacrolimus clearance using 287 serum concentrations. The covariates having the greatest degree of influence on clearance with this model were total body weight, time since the onset of therapy, serum bilirubin, and ALT values. The authors suggest that despite the apparent value of these covariates in determining clearance, there remains considerable interpatient variability in response. As a result, they suggest that their mathematical calculation not be used for initial dosing, but may be of use during routine dosage adjustment. For clinicians not routinely using NONMEM, the study still has value. It highlights some of the routine laboratory values, other than serum concentration, that may be of use in predicting changes in tacrolimus clearance. Garcia Sanchez MJ, Manzanares C, Santos-Buelga D, et al. Covariate effects on the apparent clearance of tacrolimus in paediatric liver transplant patients undergoing conversion therapy**. Clin Pharmacother 2001;40:63-71.**

Therapies for otitis media

This review of antibiotics for the prevention and treatment of otitis media focuses on the recent recommendations of the Centers for Disease Control. The authors discuss the expert panel's guidelines and the ensuing controversy over their antibiotic selection. Erramousepe J, Heyneman CA. Treatment and prevention of otitis media. **Ann Pharmacother 2000;34:1452-68.**

## Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/23/01:

1. Polyethylene glycol 3350, NF (Miralax®) was added to the Formulary for the management of refractory constipation in children. Its use is restricted to the Pediatric Gastroenterology Division. The usual dose of Miralax® is 1 tablespoonful in 8 ounces of water daily.

2. Intravenous chlorothiazide sodium (Sodium Diuril®) was also added. It is restricted to use in the Neonatal Intensive Care Unit for infants requiring long-term diuretic therapy who might be at risk from developing renal calcifications or metabolic bone loss with loop diuretics. The usual intravenous dose of chlorothiazide in infants is 2-8 mg/kg/day in two divided doses.

3. Remifentanil (Ultiva®), a short-acting opioid analgesic, was also added to the Formulary. During surgery, dosing is dependent on the concomitant anesthetics used. In the postoperative period, an infusion of 0.025-0.2 mcg/kg/min is recommended for adults and children ≥ 2 years of age.

4. Iohexol (Omnipaque®), a nonionic imaging agent, was added for intrathecal or intravascular administration in children and adults.

5. A product line extension was approved for budesonide respules (Pulmicort Respules®). This product is indicated for the treatment of asthma in children 1 to 8 years of age. The recommended dose is 0.5 to 1 mg per day, in one or two doses.

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