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Routine Hepatitis A Vaccination in the United States

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It has been estimated that 100,000 to 300,000 hepatitis A infections occur in the United States each year, resulting in 11,000 cases of symptomatic disease and 50-100 cases of liver failure or death.¹ These infections occur despite the availability of hepatitis A vaccines and the implementation of several policies from the Centers for Disease Control and Prevention (CDC) designed to encourage their use in high-risk populations. This issue of *Pediatric Pharmacotherapy* will describe the available vaccines for hepatitis A and review the new recommendation for routine immunization during childhood.

Immunization Policies

Beginning in 1996, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination of children living in communities with a high rate of hepatitis A infection. In 1999, the implementation of a routine immunization program was recommended for 11 states where the annual disease rate was at least 20 cases/100,000 people. This policy also suggested that implementation of a hepatitis A immunization program be considered by another six states with disease rates between 10 and 20 cases/100,000 people.¹⁻³

A recent survey conducted by the CDC revealed that only 51% of children living in the 11 states with routine hepatitis A immunization programs had received the vaccine. Twenty-five percent of children were immunized in the six states where immunization programs were suggested, and only 1.4% of children in the remaining 33 states.⁴ While infected children are often asymptomatic or have mild disease, they play a major role in the transmission of the virus to adults.

In October, 2005, the ACIP recommended expansion of hepatitis A vaccination to include all children, beginning at 1 year of age (during the 12 to 18 month period). The move toward routine immunization is considered an important step in eliminating hepatitis A in the United States. The new policy was finalized by the

CDC and is now part of the 2006 Recommended Childhood and Adolescent Immunization Schedule.^{5,6}

Hepatitis A Vaccines

There are currently two hepatitis A vaccines available in the United States, Havrix[®], manufactured by GlaxoSmithKline, and Vaqta[®], produced by Merck. Both products are inactivated whole virus vaccines derived from a virus strain propagated in MRC-5 human diploid cells. They are approved by the Food and Drug Administration (FDA) for use in patients 1 to 18 years of age.⁵⁻⁷

Vaccine Efficacy

The efficacy of both hepatitis A vaccines has been established in several studies conducted by their manufacturers. In clinical trials involving over 600 children between 11 and 25 months of age who were vaccinated with Havrix[®], seroconversion was reported in 99-100% of subjects after the second dose. Geometric mean antibody titers (GMT) ranged from 1,461 to 1,911 mIU/mL. Studies in children 12 to 23 months of age receiving Vaqta[®] produced similar results, with seroconversion in 100% of children after the second dose, with an average GMT of 6,920 mIU/mL.⁷⁻⁹

Clinical efficacy may also be assessed by the effectiveness of previous immunization programs.^{1,10-11} In a longitudinal analysis conducted by the CDC, the incidence of hepatitis A disease in 2003 was compared to rates from a period prior to the initiation of targeted immunization programs (1990-1997) as a baseline.¹ Between the baseline and 2003, the overall incidence of hepatitis A cases reported to the National Notifiable Diseases Surveillance System declined 76% (from 10.7 cases/100,000 people at baseline to 2.6 cases/100,000 in 2003). The rate of disease in the 17 states with active immunization programs decreased by 88% (from 21.2 cases/100,000 at baseline to 2.5 cases/100,000 in 2003).

Additional evidence of vaccine efficacy can be obtained from the results of immunization programs in high-risk communities. In a paper published in the November 2005 issue of *The Pediatric Infectious Disease Journal*, Duggirala and colleagues evaluated the efficacy of a hepatitis A vaccination program in Maricopa County, Arizona.¹⁰ The authors conducted a case-control study, involving patients seen between August 1, 1999 and April 30, 2000. The results of the study suggested that the risk of developing hepatitis A in children attending a child-care center was significantly reduced.

Universal immunization of toddlers has also resulted in a significant decrease in hepatitis A in Israel.¹¹ After implementation of routine immunization in 1999, the annual incidence of hepatitis A disease decreased from 50.4 cases per 100,000 people to 2.2-2.5 cases per 100,000 people, representing a 95% decline. The reduction in disease was observed not only in children, but in all age groups. Of the 433 cases of hepatitis A reported in Israel during the period from 2002 to 2004, 97.9% occurred in people who had not been fully vaccinated.

Contraindications and Precautions

The use of hepatitis A vaccine is contraindicated in patients with a known hypersensitivity to any component of the vaccine. Havrix[®] is also contraindicated in patients with known hypersensitivity to neomycin.⁷⁻⁹

The tip cap and plunger of the pre-filled Havrix[®] syringes, as well as the vial stopper and syringe plunger of Vaqta[®] contain latex, and may produce an allergic reaction in latex-sensitive patients. Because of the potential for hypersensitivity reactions to the vaccine or latex, the manufacturers of both hepatitis A vaccines recommend that epinephrine and equipment for the management of anaphylaxis be available at the time of use.⁷⁻⁹

Adverse Reactions

Information on adverse reactions has been collected from both vaccine manufacturers. In older children and adults, the most frequently reported adverse reactions include mild injection site soreness (16-56%), headache (2-16%), swelling or redness at the injection site, fatigue, fever, anorexia, nausea, vomiting, or diarrhea (1-10%), pharyngitis and upper respiratory infection (1-3%).^{8,9}

When the results of studies of infants between 11 and 25 months of age with Havrix[®] and Vaqta[®] were combined, the most common adverse effects were pain or soreness at the injection site

(3-21%), erythema (1-21%), and swelling (1-8%), drowsiness (15-17%), irritability (10-36%), loss of appetite (1-19%), fever (1-9%), upper respiratory tract infection or congestion (1-13%), and rash (3-6%). For more specific adverse reaction information, refer to each product's prescribing information.^{8,9}

Availability and Dosing

Havrix[®] and Vaqta[®] are available in 0.5 ml single-dose vials and pre-filled syringes for use in children and adolescents. Both products require refrigeration, but should not be frozen. The vaccine is a suspension and should be shaken prior to use. For each product, the 0.5 ml dose should be administered intramuscularly. The deltoid muscle is the preferred site of administration for older children and adults. In toddlers, the dose may be injected into the anterolateral aspect of the thigh.⁷⁻⁹

The primary immunization schedule consists of two doses, given at least 6 months apart. The CDC considers the two hepatitis A vaccine products interchangeable, so the second dose does not have to be the same brand as the first.⁷⁻⁹ The concurrent administration of hepatitis A vaccine with measles-mumps-rubella, diphtheria-tetanus-acellular pertussis-inactivated polio, and *Haemophilus influenzae* type b conjugate vaccine has shown no reduction in immunogenic response.^{7-9,12}

The Havrix[®] vaccine is also available in combination with Hepatitis B vaccine as Twinrix[®] (GlaxoSmithKline). While most pediatric patients receiving routine hepatitis A immunization in the United States will have already completed their hepatitis B immunization series, the combination may be useful for children who have not been fully immunized.¹³

Cost

The average wholesale price of Havrix[®] is approximately \$35.00 per dose, while Vaqta[®] costs approximately \$40.00 per dose.¹⁴ Prices vary considerably with contract purchasing.

Parent Education

Knowledge about hepatitis A in the lay population is limited, particularly in those regions with low rates of infection. In 2002, the American Liver Foundation conducted a survey of 865 parents (including 365 from states with active immunization programs) to assess hepatitis A awareness.¹⁵ Nearly half (43%) of parents surveyed did not know that hepatitis A was a highly contagious disease that can result in serious complications. Twenty-seven percent did not know how it was transmitted, and 40% did

not know the disease could be fatal. When asked what diseases their children should be vaccinated against, only 3% of parents included hepatitis A. With the addition of hepatitis A vaccine to the recommended childhood immunization schedule, it is likely that many parents will have questions about the benefits and risks of this vaccine. The CDC has recently revised the hepatitis A vaccine information sheet for parents and caregivers. The new sheet is available on the National Immunization Program website at www.cdc.gov/nip/publications/VIS/vis-hep-a.pdf

The Immunization Action Coalition also provides a wide variety of resources for families on their website at www.vaccineinformation.org/hepa/links.asp

Summary

While the incidence of hepatitis A infections in the United States has declined with the immunization of children in endemic areas, there is still an unacceptably high level of disease. The ACIP has recently recommended the expansion of immunization to all children, beginning at 1 year of age, in an effort to eliminate hepatitis A disease. Clinical studies support the efficacy and safety of the currently available vaccines in the pediatric population, but additional data following the implementation of routine immunization will be needed to assess the outcomes of this new program.

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Pharmacology Literature Review

Acetaminophen Overdose

Analgesics remain a leading cause of accidental drug ingestions in the United States. This retrospective review was conducted to describe the common characteristics of pediatric acetaminophen overdoses reported to a regional poison center. During the period from October 31, 2000 to October 31, 2003, there were 473 ingestions reported. Among those reports, 76% occurred in children < 6 years of age, 3% in children 6-12 years of age, and 21% in children 13-17 years of age. The majority of calls to the poison center for the children < 6 years (62%) were made by parents, while the majority of calls regarding adolescent patients (61%) were made by health care professionals. All of the ingestions in the children < 6 years were deemed accidental, while 91% of the ingestions in the 13-17 year old group were intentional. In the latter group, 87% of the patients were female. While the information gathered from this study may not be unique, it provides useful background data for developing programs to educate the community about acetaminophen toxicity. Angalakuditi MV, Coley KC, Krenzelok EP. Children's acetaminophen exposures reported to a regional poison control center. ***Am J Health-Syst Pharm* 2006;63:323-6.**

Antiviral Therapy for Influenza

Despite the recommendation for universal influenza immunization in young children, there continues to be a need for effective antiviral therapy in patients with influenza. The authors of this concise review discuss the currently available therapies and compare the results of clinical trials in the pediatric population. They also address the potential for development of resistant viral strains. Townsend KA, Eiland LS. Combating influenza with antiviral therapy in the pediatric population. ***Pharmacotherapy* 2006;26:95-103.**

Complementary and Alternative Medicine

The authors of this review address complementary and alternative medicine (CAM) in the treatment of upper respiratory tract infections. After conducting an extensive literature search, they present the available studies describing the use of herbal medicine, including Chinese herbal preparations, ascorbic acid, cod liver oil, zinc, homeopathic remedies, physical manipulation, and psychological therapies. Based on limitations such as sample size and study design, the authors concluded that currently available data do not support the use of CAM in the prevention or treatment of upper respiratory tract infections. Carr RR, Nahata MC. Complementary and alternative medicine for upper-respiratory-tract infection in children. **Am J Health-Syst Pharm 2006;63:33-9.**

Cyclosporine Kinetics in Stem Cell Transplants

The authors of this study compared the pharmacokinetic profiles of cyclosporine using both the original (Sandimmune[®]) and the modified oral (Neoral[®]) formulations. Twenty-four children (0.5-17 years) participated in the prospective, cross-over study. Patients were given either oral liquid or capsules. Mean maximum concentrations were significantly higher with the modified formulation (594.9 \pm 349.7 mcg/L versus 483.0 \pm 363.0 mcg/L with the original formulation, $p = 0.003$). Area under the concentration-time curve (AUC) from 0 to 12 hours was also significantly higher with the modified formulation (3432 \pm 1563 versus 3244 \pm 1780 mcg/L-hr, $p = 0.022$). Unlike the original formulation, cyclosporine concentrations with the modified formulation had only a weak relationship with the AUC, suggesting that dosage adjustment with trough concentrations may not be appropriate. Dupuis LL, Taylor T, Saunders EF. Disposition of two oral formulations of cyclosporine in pediatric patients receiving hematopoietic stem cell transplants. **Pharmacotherapy 2006;26:15-22.**

Sildenafil Suspension Formulation

Sildenafil has been found to be useful therapy in the management of children with pulmonary hypertension. The commercially-available tablets are not appropriate for the treatment of younger patients, resulting in the need for a compounded oral liquid formulation. The stability of two 2.5 mg/mL extemporaneous sildenafil oral suspensions was assessed at both room temperature and under refrigeration in this study. Both preparations, including one prepared with Ora-Sweet[®] and Ora-Plus[®] and another prepared with 1% methylcellulose and simple syrup, retained their potency over a 91-day evaluation period at room temperature or when

refrigerated. Nahata MC, Morosco RS, Brady MT. Extemporaneous sildenafil citrate oral suspensions for the treatment of pulmonary hypertension in children. **Am J Health-Syst Pharm 2006;68:254-7.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/24/06:

1. Measles, mumps, rubella and varicella vaccine (ProQuad[®]) was added to the Inpatient Formulary.
2. Aprepitant (Emend[®]), a selective high-affinity antagonist of human substance P/neurokinin (NK₁) receptors, was added to the Inpatient and Outpatient Formularies for use in combination with oral serotonin antagonists and dexamethasone for the prevention of nausea and vomiting in adult patients receiving highly emetogenic cancer chemotherapy.
3. SAME (S-adenosylmethionine), a dietary supplement used in the treatment of alcoholic steatohepatitis patients, was added to the Inpatient Formulary. Patients must sign a waiver prior to receiving SAME.
4. In a therapeutic class review of the serotonin 5-HT₁ receptor agonists, almotriptan, eletriptan, frovatriptan, and rizatriptan were rejected. Naratriptan was deleted from the Formulary. Sumatriptan and zolmitriptan were retained on the Formulary.
5. Cefotetan was removed from the Inpatient Formulary.
6. Levothyroxine sodium (generic) was added to the Outpatient Formulary as an alternative to Synthroid[®].

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