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Tetanus, Diphtheria, Acellular Pertussis Booster Vaccination for Adolescents

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The number of cases of pertussis continues to increase in the United States. In 2004, there were 18,957 cases reported to the Centers for Disease Control and Prevention, including over 5,000 cases in adults.[1] It is likely this number substantially underestimates the true incidence, as many cases, particularly those in older patients, go undiagnosed. As immunity from the primary childhood immunization series wanes, adolescents and adults are left susceptible to infection.[2-5] While typically a mild disease in this population, 1.4 to 7.5% of adolescents and 3.5 to 5.7% of adults with pertussis require hospitalization.[6] The spread of infection by adolescents and adults may also place more vulnerable patients, including newborns, at greater risk.[7] In a 2004 study, Bisgard and colleagues found that 75% of pertussis cases in infants were attributable to an adult source, usually parents or grandparents.[8]

In the past two months, the Food and Drug Administration (FDA) has approved two new combination tetanus, diphtheria, and acellular pertussis (Tdap) vaccines for booster immunization beyond the primary childhood immunization series. These products are intended to replace the current tetanus-diphtheria (Td) booster given at 11 to 12 years of age. Boostrix™, manufactured by GlaxoSmithKine, was approved on May 3, 2005 for immunization of individuals between 10 and 18 years of age.[9] Adacel™, manufactured by Sanofi Pasteur, was licensed on June 10, 2005 for use in patients between 11 and 64 years of age.[10] This issue of *Pediatric Pharmacotherapy* will describe these new vaccines and review the studies documenting their efficacy and safety in children.

Vaccine Components

The two currently available Tdap products differ slightly in antigen composition. The following table provides the doses for the pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbrae 2+3 (FIM), diphtheria toxoid (D), and tetanus toxoid (T) components of the vaccines.[2-5,9,10]

Antigen	*Boostrix*™	*Adacel*™
PT (mcg)	8	2.5
FHA (mcg)	8	5
PRN (mcg)	2.5	3
FIM (mcg)	0	5
D (Lf)	2.5	2
T (Lf)	5	5

These values are lower than those of the diphtheria, tetanus, acellular pertussis (DTaP) vaccines used in the primary childhood immunization series. Both Tdap products contain aluminum as an adjuvant.[9,10]

Vaccine Efficacy in Adolescents and Adults

The efficacy of Tdap (Boostrix™) was evaluated by the manufacturer in a multicenter, randomized trial comparing it with the traditional tetanus-diphtheria vaccine (Td) in 2,516 adolescents between 10 and 18 years of age.[9] Compared to antibody titers at baseline, Tdap produced a significant booster response to PT in 94.5% of patients, to FHA in 95.1%, and to PRN in 95.4%. Antibody response to tetanus and diphtheria toxoids was not significantly different in the Tdap and Td groups. There was a measurable increase in tetanus antibody titers in 89.7% of the Tdap subjects versus 92.5% of the Td subjects. For diphtheria antibodies, the number of Tdap patients responding was 90.6%, compared to 95.9% of the subjects receiving Td.

In 2004, Van Damme and Burgess published the combined results of two clinical trials with Tdap in adults.[11] The studies were conducted in Belgium and Australia. At the time of study enrollment, approximately one-third of the 824 subjects had no detectable levels of antibody to PT or PRN. Subjects were randomized to receive either Tdap (Boostrix™) or Td. On repeat assessment one month following immunization, 98.7% of the subjects in the Tdap group were seropositive for antibodies to PT, FHA, and PRN. The increase in tetanus and diphtheria antibodies was similar in both groups. In the subjects given Tdap, 93% were seropositive for diphtheria and 99.8% for tetanus. In the Td

group, 93.2% were seropositive for diphtheria and 99.5% for tetanus.

The efficacy of Adacel™ was evaluated by the manufacturer in 749 adolescents and adults (12 to 54 years of age) in three clinical trials.[10] As in the other studies, patients were randomized to receive immunization with either Tdap or Td. Antibody titers were evaluated one month after immunization. Of the 446 Tdap subjects in whom serum antibody titers were evaluated, all had tetanus antibody titers > 0.1 IU/ml, 84% had diphtheria titers > 0.1 IU/ml, and pertussis antibody levels were similar to those reported with the 3-dose primary immunization series in infants.

In the June 22, 2005 issue of *JAMA*, Pichichero and colleagues reported the results of a prospective, randomized, double-blind trial comparing Tdap (Adacel™) to Td.[12] The study enrolled 4,480 adolescents and adults (11 to 64 years of age) at 39 sites within the United States. For both vaccines, seroconversion (the presence of antibody concentrations > 0.1 IU/ml) was demonstrated in 94.1 to 99.8% of patients for diphtheria and 99.8 to 100% of patients for tetanus. In the group given Tdap, serum antibody titers to the five pertussis components exceeded levels known to result from the primary immunization series in infants, suggesting adequate protection against infection. The frequency of adverse reactions was similar in the two groups. The authors concluded that Tdap provided an effective immune response to tetanus, diphtheria, and pertussis.[12]

Southern and colleagues compared both Tdap products, as well as Td and an investigational Tdap-inactivated poliovirus vaccine (Tdap-IPV) in 323 adolescents in the United Kingdom.[13] All four groups demonstrated similar increases in diphtheria and tetanus antibody titers. There were significant increases in the geometric mean titer (GMT) and geometric mean fold rises (GMFRs) to the pertussis antigens in both Tdap groups as well as the Tdap-IPV group ($p<0.001$). The incidence of adverse reactions was similar in all four groups. While there were differences in GMFRs between the two Tdap products, the clinical significance of these differences is not known. The authors concluded that the addition of acellular pertussis vaccine did not alter the response to tetanus and diphtheria booster vaccines.

Contraindications and Precautions

The use of a Tdap vaccine is contraindicated in patients with a known hypersensitivity to any component of the vaccine, including diphtheria toxoid, tetanus toxoid, or any pertussis-containing vaccine, and in patients with a history of a severe reaction to any other vaccine containing similar components. Patients with a history of encephalopathy, a progressive neurologic disorder, epilepsy, or progressive encephalopathy after the administration of any pertussis vaccine should not receive Tdap or any other pertussis vaccine product.[9,10]

The stopper of the Tdap vaccine vials (both Boostrix™ and Adacel™ brands) 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 Tdap vaccines recommend that epinephrine and equipment for the management of anaphylaxis be available at the time of use.[9,10]

Patients at risk for hemorrhage should not receive Tdap, including those with hemophilia, thrombocytopenia, or receiving anticoagulants, unless the benefit clearly outweighs the risk for bleeding after vaccination. Immunosuppressed patients may not achieve the expected level of immune response from Tdap vaccination. Vaccination with Tdap during pregnancy is not recommended because the potential for teratogenic effects is not known. In addition, it is not known whether Tdap is excreted into breastmilk.[9,10]

Adverse Reactions

Information on adverse reactions has been collected from a study of Boostrix™ in 3,080 adolescents in the United States.[9] In this trial, patients were randomized to receive either Boostrix™ or Td. No patient in either vaccine group had a serious adverse event. The most commonly reported reactions were mild pain (in 75.3% of the Tdap group), redness (22.5%), and swelling at the injection site (21.1%). Other reactions included fever (13.5%), headache (43.1%), fatigue (37%), and gastrointestinal symptoms (26%). Only pain at the injection site was more frequent in the Tdap group than the Td patients. The incidence of the other adverse events was similar in both groups.

The adverse event profile of Adacel™ was compared to Td in a trial of 749 adolescents and adults.[10] The most frequently reported events were mild pain (88.6%), redness (11.8%), and swelling at the injection site (16.7%). The most common systemic reactions included headache (38.8%), fatigue (20-30%), nausea (14.7%), chills (12.5%), diarrhea (10%), fever (9.4%), swollen joints (9.1%), and vomiting (2.4%).

These adverse events were observed in comparable rates in the Td group.

In the adolescents enrolled in the trial conducted by Pichichero and colleagues, the incidence of adverse events was similar in the Tdap and Td groups.[12] The only adverse reactions which occurred more frequently with Tdap than with Td were pain (rate ratio 1.10, 95% CI 1.04-1.16) and fever (rate ratio 1.85, 95% CI 1.13-3.02).

Serious reactions have been reported with Tdap in less than 2% of subjects enrolled in clinical trials. In the Pichichero trial, two adults given Tdap experienced transient nerve compression.[12] Previous experience with diphtheria, tetanus, acellular pertussis vaccines, however, would suggest that there is the potential for development of hypersensitivity reactions or neurologic illness after Tdap administration.[9,10]

Availability and Dosing

The Tdap vaccine is available as Boostrix™ or Adacel.™ Boostrix™ is available in 0.5 ml single-dose vials and syringes. Adacel™ is available in 0.5 ml single-dose vials. Both products require refrigeration, but should not be frozen. For each product, the 0.5 ml dose should be administered intramuscularly. The preferred site of administration is the deltoid.[9,10]

The Tdap booster vaccine is indicated for administration beginning with the 11 to 12 year physician visit, in place of the traditional Td vaccine. It may be given at the same time as meningococcal vaccine, but the two vaccines should be administered in separate sites. Subsequent doses of Tdap or Td should be administered at 10 year intervals. The Tdap booster is not indicated for administration to infants or young children as part of the primary childhood immunization series.[9,10,14]

Cost

The average wholesale price of Boostrix™ is $43.50 per dose for the pre-filled syringes or single-dose vials. The AWP of Adacel™ is $44.13 per dose.

Several economic assessments of the impact of Tdap immunization have been published in the past two years.[15] In 2004, Purdy and colleagues performed a cost effectiveness analysis to estimate the effect of booster immunization with Tdap in the United States.[16] The results of their analysis, which compared a variety of strategies for pertussis immunization, demonstrated that immunization of adolescents, between 10 and 19 years of age, with a single Tdap dose replacing a Td booster, could prevent between 0.4 and 1.8 million cases of pertussis and save approximately $0.3 to 1.6 billion over a decade.

Iskedjian and colleagues published a similar economic analysis for Tdap immunization of adolescents in Canada.[17] The authors estimated a yearly additional expected cost of $0.52 (Canadian dollars) for the vaccine, with an anticipated savings of $168 per pertussis case avoided. For a model cohort of 144,000 12-year-old adolescents in Ontario, a total cost savings of $858,106 would be realized over a 10-year period. Based on their model, the authors suggest that over 4,400 cases of pertussis would be avoided, and 50 hospital admissions prevented. They concluded that the administration of Tdap rather than Td at 12 years of age provided a reduction in the economic burden of pertussis at a reasonable cost.

In the May 2005 issue of the *Pediatric Infectious Disease Journal*, Caro and colleagues, working as part of the Global Pertussis Initiative, reported their evaluation of the cost effectiveness of Tdap administration to a cohort of adolescents in the United States.[18] The authors suggested that 80% vaccination coverage of patients between 11 and 18 years of age would result in a reduction in pertussis cases of more than 68,000 and the prevention of 41 pertussis-related deaths within the first 10 years after immunization. In their model, the cost of this strategy would range from $6,000 to $22,000 per life saved.

An additional analysis conducted by the Lee and colleagues and funded through the CDC was published in *Pediatrics* last month.[19] Based on an estimated Tdap cost of $15 (compared to $10 for Td) and assuming a 76% vaccination rate of 11 year-olds, the authors calculated that the addition of a pertussis booster would prevent 30,800 cases of disease. The estimated cost of immunization would be $1,100 per case of pertussis prevented.

Summary

On June 30th, the Advisory Committee on Immunization Practices voted to recommend the use of Tdap instead of Td for immunization of adolescents. This vaccine has the potential to provide considerable benefit, both in reducing the frequency of disease in adolescents and adults and in minimizing the spread of infection to more high-risk patient populations. The two Tdap products currently available provide significant increases in pertussis antibody titers and appear to be well tolerated. While initial cost-benefit analyses for Tdap look favorable, the impact of routine immunization during adolescence remains to be determined.

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Pharmacology Literature Review

Atomoxetine pharmacokinetics

This extensive review describes the pharmacokinetic studies of atomoxetine published to date. The authors include a description of pharmacokinetic drug interactions with atomoxetine resulting from its metabolism through the cytochrome P450 2D6 and 3A pathways, as well as dosing recommendations for patients with renal or hepatic dysfunction. Sauer J, Ring BJ, Witcher JW. Clinical pharmacokinetics of atomoxetine. **Clin Pharmacokinet 2005;44:571-90.**

Treatment of type 2 diabetes in children

The authors of this paper conducted a 5-year retrospective review of the therapies used in 42 children with type 2 diabetes mellitus. The most common therapies used were insulin (in 31% of patients), metformin (14.3%), and sulfonylureas (14.3%). Combination therapy was used in 14.3%. The average hemoglobin A_{1c} decreased from 10.6±2.7% at baseline to 8.0%±2.0% after approximately 3 months of treatment. Adverse reactions occurred in 15 patients, including gastrointestinal distress and hypoglycemia. The gastrointestinal symptoms were most common with metformin, while hypoglycemia was more frequent in the patients receiving insulin. The authors concluded that these agents appeared to be effective in reducing hemoglobin A_{1c} values, but recommended further prospective studies. Benavides S, Striet J, Germak J, et al. Efficacy and safety of hypoglycemic drugs in children with type 2 diabetes mellitus. **Pharmacotherapy 2005;25:803-9.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/24/05:

1. Testosterone gel 1% (Androgel®) was added to the Inpatient and Outpatient Formularies for the treatment of men with primary hypogonadism or hypogonadotropic hypogonadism
2. Entecavir (Baraclude™), a deoxyguanoside nucleoside analog that inhibits hepatitis B, was added to the Inpatient and Outpatient Formularies, with restriction to patients intolerant or unresponsive to lamivudine.
3. Morphine sulfate extended-release liposomal injection (DepoDur™) was added for the treatment of pain following surgery. It is administered epidurally or into the lumbar region prior to surgery. Use is restricted to Anesthesiology.
4. Requests for the addition of telithromycin (Ketek®) and ursodiol tablets (Urso 250® and Urso Forte™) were rejected.

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