Vaccine 30 (2012) 4644–4647

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The immunogenicity and safety of DTaP interchangeable immunization among Korean children

Ga Young Kwak[a], Hyo Jin Kwon[b], Jong Hyun Kim[a], Hwang Min Kim[c], Joon Soo Park[d], Sang Hyuk Ma[e], Jun Gyou Kim[f], Jin Han Kang[a,*]

[a] Department of Pediatrics, College of Medicine, The Catholic University, Seoul, Republic of Korea
[b] Department of Pediatrics, College of Medicine, Korea University, Seoul, Republic of Korea
[c] Department of Pediatrics, College of Medicine, Yonsei University, Wonju, Republic of Korea
[d] Department of Pediatrics, College of Medicine, Soonchunhyang University, Cheonan, Republic of Korea
[e] Department of Pediatrics, Fatima Hospital, Changwon, Republic of Korea
[f] The Korea Food and Drug Administration, Osong Heath Technology Administration Complex, Osong, Republic of Korea

ARTICLE INFO

Article history:
Received 25 February 2012
Received in revised form 23 April 2012
Accepted 27 April 2012
Available online 10 May 2012

Keywords:
DTaP vaccine
Interchangeability
Immunogenicity
Safety

ABSTRACT

Since the production of various vaccine formulations by different pharmaceutical companies and interruptions in vaccine supply cannot be fully regulated, problems caused by DTaP interchangeability may occur. However, the interchangeability data on the first primary series of DTaP vaccination have not been well described. In this study we investigated immunogenicity and overall safety of diphtheria, tetanus, pertussis in children who had adventitiously received an interchangeable DTaP vaccination. A total 97 of participants were enrolled (mean age, 11 months). High immunogenicity (1.8 ± 0.4 IU/mL, 100%) was noted against diphtheria toxoid, and similar high immunogenicity (3.2 ± 2.1 IU/mL, 100%) was noted against tetanus toxoid. Immunogenicity against pertussis antigen was significantly greater in the interchangeable vaccinated group compared to the control group, and 57% of the interchangeable vaccinated subjects achieved high levels of protective immunity (45.2 ± 21.5 EU/mL). No serious adverse effects were noted, and most adverse effects resolved without treatment. The immunogenicity against each antigen was high in patients who were interchangeably vaccinated for DTaP. Our results provide clinical evidence affirming the non-inferiority of interchangeable vaccination when it cannot be avoided such as in limited vaccine supply situations or different prices.

1. Introduction

Diphtheria and tetanus can be prevented by vaccination, and immunity to pertussis can be maintained for 10–14 years by natural infection and vaccination [1–3]. DTaP is an important vaccine since a low rate of vaccination coverage can lead to the collapse of herd immunity (except tetanus) and a subsequent increase in disease prevalence because the associated pathogens are widely distributed in nature. Evaluating the immunogenicity, efficacy and safety of this vaccine is of paramount importance in developed countries and these evaluations serve as the basis of systemic immunization policy [4,5].

The two components DTaP vaccine containing anti-pertussis toxin (PT) and filamentous hemagglutinin (FHA) produced in Japan has been widely used in Korea since its introduction in 1982. In 1999, the three components DTaP vaccine with pertactin (PRN) was introduced from Europe and both vaccines continue to be used in Korea. Manufacturing methods for DTaP vaccine preparation can vary by manufacturer in terms of the seed bacteria used, antigen purification and separation techniques, antigen inactivation methods and the amount of antigen used in the manufacturing process. Because no studies have evaluated the interchangeability of DTaP vaccine, it is strictly recommended that primary immunizations at 2, 4, and 6 months of age be performed using products from the same manufacturer [6,7]. However, interchangeable DTaP vaccination is unavoidable if the manufacturer of the previously administered vaccine is unknown or the supply of vaccine from a particular manufacturer is disrupted. Although some countries limit the variety of vaccines available on the market due to concerns regarding vaccine interchangeability, it is critical to assess DTaP vaccine interchangeability to address situations in which the manufacturers of similar vaccine cannot be prohibited or new combination vaccines are introduced. In fact, accidental or unavoidable interchangeable DTaP vaccinations may occur due

* Corresponding author at: Department of Pediatrics, Seoul St. Mary's Hospital, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 137-701, Republic of Korea. Tel.: +82 2 2258 2828; fax: +82 2 537 4544.
E-mail address: kjhan@catholic.ac.kr (J.H. Kang).

0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2012.04.094

to price differences between the two components (free in public health center) and three components (high cost in private clinics) DTaP vaccines, parents' or guardians' ignorance of primary DTaP vaccination rules, and shortage of DTaP vaccines in our country.

In this aspect, evaluation of DTaP interchangeability is necessary. Unfortunately, a prospective study of DTaP vaccine interchangeability cannot be conducted because of ethical issues. Hence, we evaluated the status of immunogenicity and safety in interchangeable DTaP vaccination cases among children who were adventitiously immunized with different vaccine products. In addition, this data was compared to the previously reported results for the three components DTaP vaccination [8].

2. Methods

2.1. Study design and procedures

This study was conducted as a multicenter, open clinical trial and the protocol was approved by the institutional review boards at each participating center. Among children who visited the pediatric department at five hospitals (Seoul St. Mary's Hospital of Catholic University, Suwon St. Vincent's Hospital of Catholic University, Cheonan Hospital of Soonchunhyang University, Changwon Fatima Hospital and Wonju Hospital of Yonsei University) between July 2009 and December 2010, those aged less than one year who were administered different DTaP vaccines at public health centers and private clinics were enrolled. Infants who received the third primary DTaP vaccine at least 4 weeks to 12 weeks prior were included in this study. Parents or guardians provided informed consent. Subjects eligible based on inclusion criteria after eligibility examinations were assigned an identification number.

Blood samples were collected from each patient in order to assess levels of antibody to diphtheria, tetanus and pertussis antigens. We evaluated the antibody levels against each antigen after the primary vaccinations, and then compared the results with the immunogenicity data for the three components DTaP vaccine that was obtained previously at the same investigational site as the KFDA project (2008–2009) [8]. Safety was evaluated by administering questionnaires to subjects' parents to determine the occurrence of severe systemic and local adverse events after administration of DTaP vaccines.

2.2. Study population

Among infants aged less than 1 year who had received the primary DTaP vaccinations at public health centers, private clinics or hospitals, we enrolled those who were objectively documented as being interchangeably administered with two components and three components DTaP vaccine in their vaccination records or by health care providers who administered the vaccine. Informed consent was obtained from parents or guardians. Infants for whom interchangeable immunization status could not be determined by vaccination records or reports from health care providers, those with an acute illness or congenital disease, and those with immunodeficiency or who were currently receiving an immunosuppressant were excluded from the study.

2.3. Study vaccines

Two components DTaP vaccine (Biken DTaP®, Biken, Osaka, Japan) and three components DTaP vaccine (Infanrix®, GSK, Rixensas, Belgium), both distributed in Korea, were used in this study. Two components DTaP vaccine and three components DTaP vaccine have different diphtheria toxoid antigens, tetanus toxoid antigens and pertussis antigens as follows: each 0.5 mL dose two components DTaP vaccine contained 15 Lf of diphtheria, 2.5 Lf tetanus toxoid, 23.4 g PT and 23.4 g FHA. And each 0.5 mL dose three components DTaP vaccine contained 30 IU of diphtheria, 40 IU tetanus toxoid, 25 g PT, 25 g FHA and 8 g PRN.

Table 1
Demographic characteristics of the control [8] and the study groups (interchangeably immunized group).

Characteristics	Parameters/Categories	Control group	Study group
Gender	Male, *n* (%)	34 (47.2)	45 (46.4)
	Female, *n* (%)	38 (52.8)	52 (53.6)
Age (month)	Mean ± SD	16.6 ± 1.1	11.5 ± 0.2

SD: standard deviation.

2.4. Immunogenicity

Five milliliters of blood was collected from each subject to obtain 1 mL of serum, which was stored at −70 °C until analysis. Serum levels of specific antibodies to diphtheria, tetanus and pertussis toxin (PT) were measured by enzyme-linked immunosorbent assay (ELISA) (IBL, Hamburg, Germany). Antibody titers for diphtheria and tetanus ≥0.1 IU/mL each were defined as protective immunity, and an antibody titer for PT ≥ 24 EU/mL was defined as protective immunity for pertussis, as defined by the ELISA kit manufacturer. In addition, we assessed the geometric mean titer (GMT) for each antibody and evaluated the immunogenicity after primary vaccination.

2.5. Data analysis and statistical considerations

For statistical analysis, Student's *t*-test was used to compare the mean antibody titers between the DTaP vaccine interchangeable immunization group and the control group (three component DTaP vaccination group in primary series) [8]. The GMT with a 95% confidence interval was estimated for each antibody. Data were analyzed using SPSS statistical software, version 13.0 for Windows (Chicago, IL, USA). Statistical significance was defined as a *P*-value < 0.05.

3. Results

3.1. Demographic data

A total of 97 subjects (45 boys (46.4%) and 52 girls (53.6%)) with a mean age of 11 months who were interchangeably administered two and three components DTaP vaccine at local public health centers, private clinics and hospitals during the study period were enrolled. The control group included 34 boys (47.2%) and 38 girls (52.8%) and their mean age was approximately 16 months (Table 1).

3.2. Immunogenicity

The mean antibody titer against diphtheria toxoid antigen in the interchangeably immunized group was 1.8 ± 0.4 IU/mL, which was significantly higher than that in the control group that had completed the primary vaccination series with three components DTaP vaccine. In addition, the GMT in the interchangeably immunized group was significantly higher than the control group. The antibody titers of all subjects in the interchangeably immunized group were over 0.1 IU/mL, indicating protective immunity. In fact, the antibody titers of all subjects were much greater than 1.0 IU/mL (Table 2).

The mean antibody titer for tetanus toxoid in the interchangeably immunized group was 3.2 ± 2.1 IU/mL, which was significantly higher than that in the control group. The GMT of tetanus toxoid antibody was also higher in the interchangeably immunized group compared to the control group. The antibody titers of all