

Hypotonic-hyporesponsive Episodes After Diphtheria, Tetanus and Acellular Pertussis Vaccination

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Background: Hypotonic-hyporesponsive episode (HHE) after whole cell pertussis vaccination is a known adverse event. Less is known about the risk of HHE after administration of acellular pertussis vaccines.

Methods: Using parental interviews, this study actively surveyed for HHE among infants after doses 1 and 2 of acellular pertussis vaccine.

Results: We interviewed the parents of 52,531 infants. HHE was reported at a rate of 22.8 per 100,000 doses (95% CI: 11.8–39.9) of acellular pertussis vaccine, approximately 45 episodes per 100,000 children.

Conclusions: These rates are lower than HHE rates reported after whole cell pertussis vaccines and within the range of HHE rates reported in other studies of acellular pertussis vaccines.

Key Words: hypotonic-hyporesponsive episode, diphtheria, tetanus and acellular pertussis, vaccine, adverse events following immunization

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Hypotonic-hyporesponsive episodes (HHEs) are characterized by sudden onset of reduced muscle tone (limpness, floppiness), hyporesponsiveness (decreased responsiveness to verbal or other stimuli) and change in skin color (pallor or cyanosis) that occur within a brief period after vaccination. HHE was first described in 1961 in association with whole cell pertussis vaccines, either as single antigen or combined as diphtheria, tetanus and whole cell pertussis vaccine (DTwP).¹ HHE has also been associated with *Haemophilus influenzae* type b (Hib) and hepatitis B vaccines (HBVs).²

HHE has been reported most commonly after DTwP vaccines, particularly after the first dose. However, data on the rates of HHE after receipt of pertussis-containing vaccines vary, mainly related to differences in case definitions,^{2,3} with rates reported as high as 145 per 100,000 doses after DTwP and 81 per 100,000

doses after the primary series of diphtheria, tetanus and acellular pertussis (DTaP) vaccines.⁴ Reported rates after the toddler booster dose are much lower, at 29 and 10 per 100,000 doses after DTwP and DTaP, respectively.⁴

After licensure of a 5-component DTaP vaccine (DTaP₅, DAPTACEL; Sanofi Pasteur Inc, Swiftwater, PA), we assessed rates of HHE in infants after DTaP vaccination. We assessed HHE rates after DTaP₅, 3-component DTaP vaccine (DTaP₃, Infanrix; GlaxoSmithKline, Research Triangle Park, NC) and after DTaP₃-HBV-inactivated polio vaccine (IPV) (DTaP-HBV-IPV, Pediarix; GlaxoSmithKline, Research Triangle Park, NC). During the study period, 4 doses of DTaP were recommended for the first 2 years of life at 2, 4, 6 and 15–18 months of age. Also recommended were 3 doses of HBV, 4 doses of Hib vaccine, 3 doses of IPV and 4 doses of pneumococcal conjugate vaccine, a measles, mumps and rubella vaccine and a varicella vaccine.⁵ The schedule allowed for some variation, such as an additional dose of HBV if given as part of a combination vaccine.⁶ Per the recommended schedule, DTaP would be administered with several concomitant vaccines.

MATERIALS AND METHODS

Study Setting and Population

Kaiser Permanente Northern California (KPNC) is an integrated healthcare organization that provides comprehensive medical care to more than 4 million members. KPNC maintains clinical databases that contain information on all inpatient, emergency department and outpatient encounters, as well as, but not limited to, data on all immunizations, prescriptions, radiology and laboratory reports. During the period of the study, 2002–2005, KPNC's annual birth cohort was approximately 30,000.

The KPNC Institutional Review Board approved the study.

The study was not registered on clinicaltrials.gov (not required for an observational study).

Study Design

This was an open-label, nonrandomized, observational, postmarketing safety study of DTaP₅ to describe the rates of HHE, selected injection site and systemic reactions, seizures and other serious adverse events after DTaP administered to infants as part of routine clinical care. This current report focuses only on HHE.

At the time the study began (September 2002), KPNC mainly used DTaP₃ vaccines. To assess rates of HHE after DTaP vaccination, we manually allocated clinics to either administer DTaP₅ or to continue DTaP₃ vaccines to allocate roughly equal aggregate birth cohorts. We attempted to balance socioeconomic and other key characteristics across the groups, based on available information on the racial and ethnic distribution and newborn enrollment of each clinic. The goal was for the DTaP₅ and DTaP₃ groups to have approximately equal numbers of infants and balanced socioeconomic and other demographic characteristics between the 2 groups.

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The original primary aim of the HHE analysis was to first test for noninferiority and then superiority, of DTaP₅ versus DTaP₃ with regard to rate of HHE. To meet this aim, the study prespecified accumulation of 56,250 infants in each group who received the first dose of DTaP₅ or DTaP₃ and 53,750 infants in each group who received a second dose of DTaP₅ or DTaP₃. We focused on the first and second doses as HHE is most likely to occur in this age range.⁷ Several months after the study began (December 2002), the combination vaccine DTaP-HBV-IPV was licensed. Soon thereafter, many KPNC clinics switched to the combination DTaP-HBV-IPV vaccine. Although many KPNC clinics continued to administer DTaP₅ to infants who had started their DTaP series with it, most 2-month-old infants received DTaP-HBV-IPV.

This change resulted in minimal DTaP₃ use and markedly slowed accrual of infants administered DTaP₅. The study was therefore unable to reach the number of DTaP₅- and DTaP₃-vaccinated infants originally planned for the HHE objective. The sponsor and the Food and Drug Administration agreed that the study would continue to achieve its other objectives, but the HHE objective would not include analyses for noninferiority or superiority of HHE after DTaP₅.

HHE Case Definition

Consistent with the US Public Health Service Working Group definition, we defined HHE as a sudden-onset event occurring within 48 hours of immunization, with duration ranging from 1 minute to 48 hours in children younger than 10 years of age.³ We further specified that all the following must have been present to be considered an HHE case: (1) limpness or hypotonia, (2) reduced responsiveness or hyporesponsiveness and (3) pallor or cyanosis or failure to observe or to recall skin coloration. We did not confirm cases as HHE if (1) there was a known or identified cause of these symptoms (eg, postictal), (2) urticaria was present during the event, (3) there was normal skin coloration throughout the episode or (4) the child was sleeping.

At the time the study design and the protocol were developed (2002), the Brighton Collaboration HHE case definition did not yet exist.⁸

Database Surveillance for HHE

We used KPNC's electronic medical record to identify HHE events in the inpatient, emergency department and outpatient setting (database surveillance). As a specific diagnosis code was not available, we manually examined free-form diagnostic text for terms such as "reaction," "limp," "spell," "lethargy," or "syncope." Potential cases identified by database surveillance were compared with the list of cases identified by active surveillance so as not to duplicate cases.

Active HHE Surveillance

We also identified cases of HHE using active surveillance to collect information regarding postvaccination HHE reactions for which healthcare may not have been sought. To do so, we created daily lists of infants within KPNC who had recently received their first or second doses of DTaP and telephoned parents within 2–4 days of vaccination to inquire about possible HHE symptoms (detailed below). The sampling for the daily lists changed over the course of the study to best ensure we would have sufficient interviews for each vaccine type at each dose. We made multiple attempts to reach parents after both doses of DTaP vaccines. All interviews contained a brief verbal consent and were conducted in English or Spanish as appropriate.

Parents who reported that their child had potential HHE symptoms received a follow-up telephone call by the principal investigator, appropriate study staff or in some cases, the child's pediatrician. The purpose of this call was to collect more detailed information using scripted, open-ended questions (eg, "Can you tell me more about this?").

HHE Screening Questions

To screen for HHE after doses 1 or 2, we asked the parent whether the child became "unresponsive, less active, less alert or lethargic." If the answer was "yes," we asked the following additional questions:

- How long did the episode last?
- Would you say the symptoms were mild, moderate or severe?
- Was it more difficult to get him/her to pay attention or respond to you or to wake up?
- Did he/she seem limp or floppy or lacking in muscle tone?
- Was there a change in their skin tone or color during the episode? If yes, we asked for the duration and a description (ie, gray/ashen, blue, pale, red/flushed, other).
- Were they wheezing while having these symptoms or immediately beforehand?
- Did they have sudden puffy or blotchy swelling of the face, lips or arms or legs during, or immediately before, this episode?
- During this episode, did they have a rash?
- Were they taken to a clinic, emergency room or hospital? If so, where?

HHE Adjudication

All potential HHE identified via database surveillance or active HHE surveillance underwent review by a panel of 3 non-KPNC vaccine safety medical experts who were unaffiliated with the study or sponsor and blinded to the brand of vaccines received. Each expert independently adjudicated the potential case using the HHE case definition, followed by secret vote, with final HHE case status determined by expert majority.

Analyses

To calculate rates and risk, we only included HHE cases that were identified via active surveillance and confirmed as described above. We used the number of conducted interviews as the denominator for these calculations. We calculated rates of HHE per 100,000 doses of DTaP and risk per 100,000 children receiving 2 doses of DTaP among interviewees. CIs were estimated by the exact Clopper–Pearson method.

RESULTS

We included 73,702 dose 1 vaccinations, 69,460 dose 2 vaccinations, 65,597 dose 3 vaccinations and 53,819 dose 4 vaccinations in database surveillance (only data from doses 1 and 2 were used for the HHE endpoint). We conducted 27,391 active surveillance interviews after dose 1 and 25,140 after dose 2, with a demographic survey included as part of the dose 1 interview (Table 1). The proportion of male and female subjects and the mean age at first vaccination were similar for each of the vaccine groups. The highest percentage of subjects were White [29.8% (2823/9474) in the DTaP₅ group, 33.9% (2115/6240) in the DTaP₃ group, and 33.1% (3863/11,677) in the DTaP-HBV-IPV group], followed by Hispanic. There were more Black subjects in the DTaP₅ group than in the DTaP₃ and DTaP-HBV-IPV groups. The majority of subjects (>93%) did not attend day care. Almost all subjects received one or more concomitant vaccines with the first and second doses of DTaP (~99%). Demographic information captured at first dose interviews shows that the interviewed population was similar to the overall database population of vaccinees from which they were sampled (data

TABLE 1. Summary of Demographic and Socioeconomic Factors (Sex, Age, Race, Day-care Status) From Interviews After First Dose, KPNC 2002–2005

Subjects	All Subjects	DTaP ₅	DTaP ₃	DTaP-HBV-IPV
	n (%)	n (%)	n (%)	n (%)
Subjects interviewed at first dose, N	27,391	9474	6240	11,677
Sex				
Male	13,979 (51.0)	4772 (50.4)	3222 (51.6)	5985 (51.3)
Female	13,408 (49.0)	4702 (49.6)	3016 (48.3)	5690 (48.7)
Not answered	4 (0.01)	0 (0.00)	2 (0.03)	2 (0.02)
Mean age at first dose, mo	2.18	2.21	2.19	2.15
Race				
Asian	4858 (17.7)	1467 (15.5)	1143 (18.3)	2248 (19.3)
Black	2078 (7.6)	1304 (13.8)	278 (4.5)	496 (4.3)
Hispanic	6113 (22.3)	2026 (21.4)	1512 (24.2)	2575 (22.1)
White	8801 (32.1)	2823 (29.8)	2115 (33.9)	3863 (33.1)
Multiethnic	5045 (18.4)	1674 (17.7)	1115 (17.9)	2256 (19.3)
Other	92 (0.3)	40 (0.4)	16 (0.3)	36 (0.3)
Not answered	404 (1.5)	140 (1.5)	61 (1.0)	203 (1.7)
In day care?				
Yes	1365 (5.0)	533 (5.6)	336 (5.4)	496 (4.3)
No	25,816 (94.3)	8871 (93.6)	5882 (94.3)	11,063 (94.7)
Not answered	210 (0.8)	70 (0.7)	22 (0.4)	118 (1.0)

not shown), with 51.0% of those interviewed being male versus 51.1% in the database surveillance population, 37.2% White versus 32.1% in the database population, 22.3% Hispanic versus 22.5% in the database population, 17.7% Asian versus 16.8% in the database population and 6.7% Black versus 7.6% in the database population.

HHE Cases

There were 21 potential HHE cases within 48 hours of the first dose: 5 after DTaP₅, 2 after DTaP₃ and 14 after DTaP-HBV-IPV. There were 15 potential cases within 48 hours of the second dose: 4 after DTaP₅, 2 after DTaP₃ and 9 after DTaP-HBV-IPV, with a potential 10th case identified through passive database surveillance after a second dose of DTaP-HBV-IPV. Of the total 37 identified potential HHE cases, 36 were found via active surveillance (Table 2). We observed no subjects with potential HHE after both the first and second doses.

After adjudication, 13 (35.1%) of 37 potential HHE were confirmed (6/13 via unanimous vote). Nine HHE cases occurred after the first dose (2 DTaP₅, 7 DTaP-HBV-IPV), and 4 occurred after the second dose (all DTaP-HBV-IPV). Not all subjects received

the same product at each of their doses; there were no HHE cases in subjects who received more than one type of DTaP product.

Twelve of the 13 confirmed cases were identified using active surveillance. The 13th case sought care in the emergency room after a DTaP-HBV-IPV dose and was described as “floppy,” “nonresponsive,” “possible dusky appearance”; the infant left against medical advice when the episode resolved.

Rates of HHE

Based on confirmed HHE cases, the overall estimated rate of HHE within 48 hours after either dose 1 or dose 2 was 22.8 per 100,000 doses (95% CI: 11.8–39.9; Table 2). The rate of HHE was 32.9 per 100,000 doses (95% CI: 15.0–62.4) after any first dose and 11.9 per 100,000 doses (95% CI: 2.5–34.9) after any second dose. After the 1st dose, the HHE rate was highest in the DTaP-HBV-IPV group at 60.0 per 100,000 doses (95% CI: 24.1–123.5) and lowest in the DTaP₃ group at 0.0 (95% CI: 0.0–59.1). Across combined first and second doses (ie, after either dose 1 or dose 2 or after both), the HHE rate was highest in the DTaP-HBV-IPV group

TABLE 2. Rates of Confirmed HHEs Within 48 Hours of a First or Second Dose of Any DTaP Vaccine, KPNC 2002–2005

Group	Dose	Doses Under Active Surveillance	Potential HHE Cases Adjudicated	Confirmed HHE	Rate (95% CI) per 100,000 Doses	Risk (95% CI) per 100,000 Children With 2 Doses
DTaP ₅	Dose 1	9474	5	2	21.1 (2.6–76.2)	21.1 (0.0–50.4)
	Dose 2	7235	4	0	0.0 (0.0–51.0)	
	Doses 1 and 2 combined	16,709	9	2	12.0 (1.5–43.2)	
DTaP ₃	Dose 1	6240	2	0	0.0 (0.0–59.1)	0.00 (NA)
	Dose 2	3834	2	0	0.0 (0.0–96.2)	
	Doses 1 and 2 combined	10,074	4	0	0.0 (0.0–36.6)	
DTaP-HBV-IPV	Dose 1	11,677	14	7	60.0 (24.1–123.5)	81.5 (30.9–132.2)
	Dose 2	13,902	9*	3	21.6 (4.5–63.1)	
	Doses 1 and 2 combined	25,579	23	10	39.1 (18.7–71.9)	
Cross-over	Dose 2	169	0	0	0.0 (0.0–2159.1)	NA
Total	Dose 1	27,391	21	9	32.9 (15.0–62.4)	44.9 (19.5–70.3)
	Dose 2	25,140	15	3	11.9 (2.5–34.9)	
	Doses 1 and 2 combined	52,531	36	12	22.8 (11.8–39.9)	

*An additional potential HHE case after a second dose DTaP-HBV-IPV was detected by database surveillance, referred to the panel and confirmed as HHE by 2 of the 3 panelists. The case is not included in the counts or rates in this table, which is based on active surveillance.

NA indicates not applicable.

Cross-over means any subject receiving a different DTaP at dose 2 than at dose 1.

at 39.1 per 100,000 doses (95% CI: 18.7–71.9) and lowest in the DTaP₃ group at 0.0 (95% CI: 0.0–36.6).

Among children who received 2 doses, the estimated overall risk of HHE within 48 hours after either of the first 2 doses was 44.9 per 100,000 children (95% CI: 19.5–70.3; Table 2).

DISCUSSION

In this study, we actively surveilled for HHE and conducted more than 52,000 parental interviews within KPNC, followed by adjudication of all potential cases by a panel of experts. Although we were unable to make statistical comparisons between rates of HHE by vaccine type or risk of HHE for children, we estimated these figures and compared them with other rates and risk in the literature. We estimated that the overall rate of confirmed HHE after 2 doses of infant pertussis-containing vaccine was approximately 23 cases per 100,000 doses. More confirmed cases occurred after the first dose. When considering the first 2 doses of DTaP administered to infants, the overall estimated risk was approximately 45 cases of HHE per 100,000 children.

Our estimated rate of HHE after DTaP was comparable with those reported in previous studies, with published rates ranging from 7 to 36 episodes of HHE per 100,000 doses of DTaP⁹ or risk of approximately 4–140 cases per 100,000 children vaccinated with DTaP.^{10,11} Notably, our rate was substantially lower than the 81 cases per 100,000 doses of DTaP reported in the meta-analysis by Zhang et al.⁴

Gustafson et al¹² studied DTaP₅ in comparison with a 2-component acellular pertussis vaccine and a DTwP vaccine and observed a rate of 13 episodes per 100,000 doses in the DTaP₅ group, 81 episodes per 100,000 doses in the DTwP group and no cases in the 2-component acellular pertussis group. Olin et al¹³ compared 2-component DTaP vaccine, DTaP₃ and DTaP₅ (although not the same formulation as the DTaP₅ studied here) and a DTwP vaccine in a randomized clinical trial and observed a rate of 36 episodes of HHE per 100,000 doses of DTaP and 55 episodes per 100,000 doses of DTwP. The trial by Gustafsson et al¹² did not have a prospectively well-defined HHE case definition, and it observed cases retrospectively for the HHE outcome, whereas the study by Olin et al¹³ had a prospectively well-defined HHE case definition to which staff were trained and parents were queried at study visits, which likely accounts for its higher rate. Most of the data in meta-analysis by Zhang et al⁴ (~95%) were from the study by Olin et al.¹³

DuVernoy and Braun⁷ looked for HHE in Vaccine Adverse Event Reporting System data over the period 1996–1998, and they were able to characterize 215 HHE cases, most of which were after DTwP (144/215) and DTaP (56/215), with some HHE after other vaccines. They were unable to estimate a rate per dose or risk for each child. They characterized HHE as generally benign, not usually recurring with subsequent doses of DTwP or DTaP, with a median onset of approximately 4 months of age.

This study had several important strengths, including its large size and the active surveillance via detailed parental interview to identify cases of HHE. To our knowledge, this study is the largest active surveillance investigation to estimate the rate of HHE after DTaP-containing vaccines, which are the standard for vaccination of infants in the United States and many other countries. Further, all cases of HHE were adjudicated by a panel of 3 blinded outside experts.

This study had several limitations. Although study personnel tried to call as many parents as possible, we were unable to contact all households. We did not conduct an analysis of households that we could not reach or that chose not to participate at the time of the trial, and we are unable to do so now. As most episodes of HHE resolve

without medical intervention, it is likely that we missed HHE cases among parents we were unable to contact or interview. In addition, cases of HHE often are not brought to medical attention. We were therefore unable to estimate HHE rates accurately using database surveillance, further highlighting the importance of our active surveillance. All but one case of HHE was observed in the study using active surveillance, which suggests that database surveillance alone is not sufficient for evaluation of HHE incidence. Our study was also conducted before development of the Brighton Collaboration HHE case definition; however, our case definition was similar to the subsequently published Brighton Collaboration HHE case definition.⁸ We did not conduct interviews at doses 3 and 4, so we do not have rates or risk of HHE at those doses. Finally, we were unable to compare HHE rates after DTaP₅ versus DTaP₃ vaccines (per the original primary aim) because of limited DTaP₃ use and reduced accrual of DTaP₅-vaccinated infants during the study period.

Since the time this study was conducted (2002–2005), DTaP as a standalone product has been largely replaced with DTaP combination products (eg, DTaP-HBV-IPV, DTaP-Hib-IPV or DTaP-Hib-IPV-HBV). Nonetheless, the information about HHE presented here will add to the consideration of benefits versus risks of DTaP products.

In conclusion, this study surveilled and interviewed parents of more than 52,000 infants and estimated that confirmed HHE occurred at a rate of approximately 23 per 100,000 doses after the first 2 doses of any DTaP vaccine, for a risk of approximately 45 cases of HHE per 100,000 children. The results of this study are consistent with rates reported in earlier studies.

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