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A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations

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ABSTRACT

Objective: Prophylactic antipyretic use during pediatric vaccination is common. This study assessed whether paracetamol or ibuprofen prophylaxis interfere with immune responses to the 13-valent pneumococcal conjugate vaccine (PCV13) given concomitantly with the combined DTaP/HBV/IPV/Hib vaccine.
Methods: Subjects received prophylactic paracetamol or ibuprofen at 0, 6–8, and 12–16 h after vaccination, or 6–8 and 12–16 h after vaccination at 2, 3, 4, and 12 months of age. At 5 and 13 months, immune responses were evaluated versus responses in controls who received no prophylaxis.
Results: After the infant series, paracetamol recipients had lower levels of circulating serotype-specific pneumococcal anticapsular immunoglobulin G than controls, reaching significance ($P < 0.0125$) for 5 serotypes (serotypes 3, 4, 5, 6B, and 23F) when paracetamol was started at vaccination. Opsonophagocytic activity assay (OPA) results were similar between groups. Ibuprofen did not affect pneumococcal responses, but significantly ($P < 0.0125$) reduced antibody responses to pertussis filamentous hemagglutinin and tetanus antigens after the infant series when started at vaccination. No differences were observed for any group after the toddler dose.
Conclusions: Prophylactic antipyretics affect immune responses to vaccines; these effects vary depending on the vaccine, antipyretic agent, and time of administration. In infants, paracetamol may interfere with

Abbreviations: AE, adverse event; DTaP/HBV/IPV/Hib, diphtheria-tetanus-acellular pertussis, hepatitis B, inactivated poliovirus, and *H influenzae* type b (INFANRIX® hexa); FHA, filamentous hemagglutinin; GMC, geometric mean concentration; GMR, geometric mean ratio; GMT, geometric mean titer; IgG, immunoglobulin G; LLOQ, lower limit of quantitation; mITT, modified intent to treat; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious adverse event.

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immune responses to pneumococcal antigens, and ibuprofen may reduce responses to pertussis and tetanus antigens. The use of antipyretics for fever prophylaxis during infant vaccination merits careful consideration.

Conclusions: ClinicalTrials.gov identifier: NCT01392378 https://clinicaltrials.gov/ct2/show/NCT01392378?term=NCT01392378&rank=1

1. Introduction

Immunization against *Streptococcus pneumoniae* with a pneumococcal conjugate vaccine (PCV) is routinely recommended for children in many countries. Fever is frequently associated with pediatric vaccination, and over-the-counter antipyretics are often administered prophylactically at vaccination or shortly thereafter. While paracetamol may reduce fever [1,2] and other common adverse effects [3,4] after vaccination, limited data suggest that it may also have deleterious effects on immune response. A 2009 study [5] reported decreased antibody production against all 10 pneumococcal serotypes in infants given paracetamol concomitantly with 10-valent PCV vaccination. Moreover, immune responses to a coadministered multicomponent vaccine were also reduced; some of these effects persisted 1 month after a booster dose for both vaccines [5]. Limitations of that study included evaluation of only one antipyretic agent (paracetamol) given in a single dosing regimen; other agents and the impact of dose timing on vaccine immune responses were not explored. Ibuprofen is also available over-the-counter and is widely used in this setting [6–9], but no information exists regarding its effect, if any, on the immunogenicity of routinely administered vaccines.

This paper reports results of a large, randomized, controlled, open-label trial examining effects of coadministration or delayed administration (ie, dose timing) of paracetamol or ibuprofen on immune responses to PCV13 and coadministered antigens after an infant vaccination series and a toddler dose.

2. Methods

This research protocol (ClinicalTrials.gov identifier: NCT01392378) sponsored by Pfizer Inc was reviewed and approved by institutional review boards and/or independent ethics committees for each participating center. This study was conducted according to principles derived from the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Both parents of all participants gave written, informed consent before enrollment and before performance of study-related procedures. Data analysis was performed by the sponsor.

2.1. Objectives

The primary objective was to assess the effect of prophylactic paracetamol or ibuprofen on the immunogenicity of PCV13 (Prevnar 13/Prevenar 13®, Pfizer Inc, Sandwich, United Kingdom) relative to controls, as measured by serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) after completion of an infant vaccination series. Secondary objectives included assessment of prophylactic antipyretic effects on PCV13 serotype-specific IgG GMCs after a toddler dose, PCV13 immunogenicity measured by serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) in a subset of subjects after the infant series, and immunogenicity of diphtheria-tetanus-acellular pertussis, hepatitis B, inactivated poliovirus, and *H influenzae* type b (DTaP/HBV/IPV/Hib; INFANRIX® hexa, GlaxoSmithKline, Rixensart, Belgium) antigens measured by GMCs and GMTs after the infant series and toddler dose. The PCV13 safety profile was evaluated by measuring fever incidence and adverse events (AEs).

2.2. Study design

In this study conducted from August 2011–January 2013, subjects from 14 sites in Poland were enrolled and randomized by an interactive voice response system into 5 groups (10:10:10:10:12) to receive prophylactic antipyretics with PCV13 and DTaP/HBV/IPV/Hib at approximately 2, 3, 4 (infant series), and 12 months (toddler dose) of age. At each vaccine visit, Groups 1 and 2 received paracetamol (15 mg/kg/dose) or ibuprofen (10 mg/kg/dose), respectively, starting 6–8 h after vaccination and again 6–8 h after the initial antipyretic dose. Groups 3 and 4 received the same respective doses as Groups 1 and 2, but began paracetamol (Group 3) or ibuprofen (Group 4) with vaccination. Controls (Group 5) did not receive prophylactic antipyretics. For all groups, antipyretics were permitted for treatment of fever or other symptoms at the treating investigator's discretion. All antipyretic doses, including missed or additional doses, were recorded in an electronic diary (e-diary).

At approximately 5 and 13 months of age, blood samples (~5 mL) were collected for assessing serum concentrations of anticapsular IgG for all 13 pneumococcal serotypes in the vaccine by standardized ELISA, which used a C polysaccharide-containing cell wall extract and serotype 22F capsular polysaccharide [10–12]. The same blood samples were used to assess DTaP/HBV/IPV/Hib antibody responses for all subjects and serum OPA for the 13 serotypes (described in [13]) in a randomly selected subset of 75 subjects per group. Antibody responses to DTaP/HBV/IPV/Hib were measured as previously described [14–16].

Rectal temperature, recorded in the e-diary, was measured 6–8 h postvaccination, 6–8 h later, and during the next 3 days at bedtime and when fever was suspected. Fever was defined as a rectal temperature of 38.0–39.0 °C (mild), 39.1–40.0 °C (moderate), and >40.0 °C (severe). AEs and serious AEs (SAEs) were collected throughout the study in a case report form, and were analyzed as percentages of each group reporting a specific MedDRA preferred term.

2.3. Vaccines administered

PCV13 (lot number 10-088269) and DTaP/HBV/IPV/Hib (lot numbers 11-001342, 11-002167, 11-008164, or 11-008296) were given intramuscularly in the anterolateral thigh muscle in opposing legs. PCV13 contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM_{197}. Each 0.5-mL dose contains 4.4 μg of serotype 6B, 2.2 μg each of the remaining 12 saccharides, 5 mM succinate buffer, 0.02% polysorbate 80, and 0.125 mg aluminium phosphate. Each 0.5-mL dose of DTaP/HBV/IPV/Hib contains 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 μg pertussis toxin, 25 μg filamentous haemagglutinin (FHA), 8 μg pertactin, 10 μg hepatitis

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