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The effect of antipyretics on immune response and fever following receipt of inactivated influenza vaccine in young children

Emmanuel B. Walter [a,b,*], Christoph P. Hornik [b], Lisa Grohskopf [c], Charles E. McGee [a], Christopher A. Todd [a], Oidda I. Museru [d], Lynn Harrington [a], Karen R. Broder [d]

[a] Duke Human Vaccine Institute, Duke University School of Medicine, Durham, NC, USA
[b] Duke Clinical Research Institute, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA
[c] Epidemiology and Prevention Branch, Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA
[d] Immunization Safety Office, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA

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ABSTRACT

Background: Antipyretics reduce fever following childhood vaccinations; after inactivated influenza vaccine (IIV) they might ameliorate fever and thereby decrease febrile seizure risk, but also possibly blunt the immune response. We assessed the effect of antipyretics on immune responses and fever following IIV in children ages 6 through 47 months.

Methods: Over the course of three seasons, one hundred forty-two children, receiving either a single or the first of 2 recommended doses of IIV, were randomized to receive either oral acetaminophen suspension (n = 59) or placebo (n = 59) (double-blinded) or ibuprofen (n = 24) (open-label) immediately following IIV and every 4–8 h thereafter for 24 h. Blood samples were obtained at enrollment and 4 weeks following the last recommended IIV dose. Responses to IIV were assessed by hemagglutination inhibition assay (HAI). Seroprotection was defined as an HAI titer ≥1:40 and seroconversion as a titer ≥1:40 if baseline titer <1:10 or four-fold rise if baseline titer ≥1:10. Participants were monitored for fever and other solicited symptoms on the day of and day following IIV.

Results: Significant differences in seroconversion and post-vaccination seroprotection were not observed between children included in the different antipyretic groups and the placebo group for the vaccine antigens included in IIV over the course of the studies. Frequencies of solicited symptoms, including fever, were similar between treatment groups and the placebo group.

Conclusions: Significant blunting of the immune response was not observed when antipyretics were administered to young children receiving IIV. Studies with larger sample sizes are needed to definitively establish the effect of antipyretics on IIV immunogenicity.

1. Introduction

In young children, fever is the mostly commonly reported adverse event following immunization [1], and is occasionally associated with a febrile seizure (FS). FSs have been reported to occur in children following receipt of measles, mumps and rubella vaccine (MMR), measles, mumps, rubella and varicella vaccine (MMRV), pneumococcal conjugate vaccine (PCV), and inactivated influenza vaccine (IIV) [2,3]. During the 2010–2011 influenza vaccination season in the United States, the first year the 2009 pandemic H1N1 strain (2009pdmH1N1) was included in the seasonal influenza vaccine, an elevated risk of FS was observed in young children on the day of or day following (day 0–1) receipt of trivalent IIV (IIV3) [4]. The risk was noted to be highest in those receiving IIV3 and 13-valent PCV (PCV13) concomitantly [4]. An observational study performed during the subsequent 2011–2012 season, demonstrated that fever was more common on days 0–1 following vaccination among children receiving IIV and PCV13 simultaneously when compared to children receiving either vaccine alone [5]. A separate study, conducted over multiple seasons leading up to 2010–2011, further established that administration of IIV3 on the same day as PCV and/or diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) is associated with an increased risk of FS [6].

Although generally considered to be medically benign, FSs are frightening and anxiety provoking for parents [7]. Therefore, in

* Corresponding author at: Duke Vaccine and Trials Unit, Duke Human Vaccine Institute, 2608 Erwin Road, Suite 210, Durham, NC 27705, USA.
E-mail address: walte002@mc.duke.edu (E.B. Walter).

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attempts to reduce fever and potentially FS following immunization, it is thought that administering antipyretics in conjunction with some vaccines might be considered as a potential preventive strategy. Although antipyretics have not been shown to reduce the risk of recurrent FS, their use has not specifically been assessed for prevention of FS after immunization [8].

While antipyretics reduce fever following infant vaccines [9,10], there is concern that they might reduce the immune response to some vaccine antigens [11]. This raises concern about their potential routine use in children receiving childhood vaccines as a FS prevention strategy, which is not currently supported by available evidence [12]. It remains unknown, however, if antipyretics reduce the immune response to IIV in young children. Previous data from controlled studies of seasonal influenza vaccines in adults and one observational study of monovalent 2009pdmH1N1 influenza vaccine in children have shown this not to be the case [13–16]. Therefore, over the course of three seasons we undertook a series of investigations designed to begin assessing the effect of acetaminophen and ibuprofen on immunogenicity and safety outcomes. Our primary objective was to compare the immune response following IIV in children receiving acetaminophen or ibuprofen versus placebo in order to ascertain whether there was evidence that antipyretics blunted the immune response to IIV in children. We also compared the proportions of children with fever and other solicited symptoms following IIV in each antipyretic group versus placebo.

2. Methods

Two consecutive randomized, controlled trials were conducted from October 2013 to March 2014 (pilot study) and from September 2014 to April 2015 and September 2015 to March 2016 (expanded study); data were combined for this report. Studies were registered under ClinicalTrials.gov identifiers NCT01946594 and NCT02212990, respectively. The pilot was a randomized (1:1) controlled double-blind comparison of acetaminophen and placebo following IIV. The expanded study was similar in design but the randomization also included an open label ibuprofen arm (3:3:2). The ibuprofen arm was smaller, as it was added to obtain preliminary data on immunogenicity effects, and was open-label as the recommended dosing frequency differs from acetaminophen and because it was rescue therapy for children randomized to receive either acetaminophen or placebo and who developed fever. Protocols were approved by the Duke Institutional Review Board (IRB); the Centers for Disease Control and Prevention (CDC) relied on the determination of the Duke IRB.

2.1. Participants

At the time of enrollment, children were required to be between 12 and 35 months and 6 and 47 months of age for the pilot and expanded study, respectively, and could not have previously received the current season's influenza vaccine. During the pilot, only children needing a single dose of IIV per Advisory Committee on Immunization Practices (ACIP) recommendations were eligible, but during the expanded study, children needing either 1 or 2 doses were enrolled [17–19]. Three children enrolled in the pilot were also enrolled in the expanded study. Children were excluded if they were febrile ($\geq$37.8 °C), had a moderate to severe illness, or had already received an antipyretic medication within the prior 72 h; had a history of a severe allergic reaction to influenza vaccine or any of its components; had a history of Guillain-Barré syndrome within 6 weeks of receipt of a previous influenza vaccine dose; or had a history of immunosuppression. Children could not have received long term high dose oral steroids, any parenteral steroids or high-dose inhaled steroids within the previous 6 months. Children were required to be up-to-date on recommended immunizations and study participation could not cause immunization delay. Participants could not receive concomitant immunizations, or have received an inactivated vaccine within 14 days or a live vaccine within 28 days of a dose of IIV. Children could not be allergic to either acetaminophen or ibuprofen, have underlying conditions precluding their use, and parents could not be planning to routinely administer antipyretics prophylactically. Parents were required to provide written informed consent. The study was conducted at 3 primary care practices in or nearby Durham, NC. We preferentially worked to recruit children with a personal history of FS by performing a search of the patient database for an ICD-9 or ICD-10 coded diagnosis of FS and sending targeted recruitment letters.

2.2. Study drug and administration

Acetaminophen suspension was compounded to provide 160 mg per 5 mL and to match liquid placebo in appearance and taste. Commercially available ibuprofen suspension containing 100 mg per 5 mL was used. Antipyretic dosing is described in Table 1. Parents were directed to dose placebo similarly as would be recommended for acetaminophen. The first dose of study drug was administered during the clinic visit immediately following IIV receipt. For those children receiving 2 doses of IIV per ACIP recommendation, antipyretics or placebo were only prescribed at the time of the initial IIV dose [17–19]. Parents were instructed to record the time of administration of each dose of study drug on a paper memory aid/diary card.

2.3. Influenza vaccination

IIV was supplied by the clinic, given according to recommended dosing instructions, and administration was not considered a study procedure. During the pilot (2013–2014 influenza season) and first year (2014–2015) of the expanded study, influenza vaccine strains were: A/California/07/2009 X-179A (H1N1), A/Texas/50/2012 X-223A (H3N2) (an A/Victoria/361/2011-like virus), and B/Massachusetts/02/2012 (B Yamagata lineage) for the IIV3 formulation with the addition of the B/Brisbane/60/2008 (B Victoria lineage) strain for the quadrivalent formulation (IIV4) [20,21]. During the second year of the expanded study (2015–2016), the A/Texas/50/2012 X-223A (H3N2) and B/Massachusetts/02/2012 strains were replaced by an A/Switzerland/9715293/2013 (H3N2)-like virus and the B/Phuket/3073/2013-like virus (B Yamagata lineage) [22]. During the pilot study only IIV3 was used, while during the expanded study both IIV3 and IIV4 were used.

2.4. Study procedures

After obtaining written informed consent from the parent or legal guardian, study eligibility criteria were reviewed and the child's demographic information and medical history including personal history or family history of FSs and influenza vaccination history were obtained. The child's weight and axillary temperature were measured and the child was randomized to receive either acetaminophen or placebo (both studies) or open-label therapy with ibuprofen (expanded study only). Randomization was done in blocks of 4 (pilot study) or blocks of 8 (expanded study) for each of the practice sites. Randomization schemes were generated by the project statistician and shared with the research pharmacists. The remaining study staff was blinded to the randomization for acetaminophen or placebo.

Parents were provided a thermometer and were instructed to document the child's temperatures and solicited symptoms on

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