Prophylactic Use of Antipyretic Agents With Childhood Immunizations and Antibody Response: Reason for Concern?

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ABSTRACT

Introduction: In the pediatric primary care setting, well-child visits constitute over 50% of all encounters, treating over 24 million children annually. Anticipatory guidance topics vary based on different ages, but immunizations are a focal point of all well-child visits. This article addresses the prophylactic use of antipyretic agents with the administration of immunizations as a potential reason of concern.

Methods: A literature review of the use of antipyretic agents in conjunction with immunizations and the effectiveness of treatment was performed.

Results: Based on several studies, the standard recommendation of administering antipyretic agents with immunization administration was a routine. Twenty years later, the scientific evidence was questioned. A pivotal study questioned these standards, noting no benefit and potential decreased immune response.

Discussion: Although the prophylactic use of antipyretics has been a standard in pediatrics, the lack of scientific support in the reduction of adverse effects of the vaccinations and the possibility of decreased immune response warrants further research. J Pediatr Health Care. (2012) 26, 200-203.
well known for his work with Johns Hopkins Hospital and for establishing medical residency as a part of training, declared that, of fever, famine, and war, fever was the worst curse (Blumenthal, 1997). The fear of fever has continued throughout time, and with respect to children, the clarification of the common misconception that all fever is harmful is one of the greatest challenges of pediatric primary care.

LITERATURE REVIEW

The use of acetaminophen prophylaxis to prevent adverse effects after immunizations was the subject of a study by Ipp and colleagues (1987). The use of acetaminophen led to a noted decrease in the severity of reactions, including fever, although no mention was made of any compromise of the antibody response. A double-blinded randomized study by Uhari, Hietala, and Viljanen (1988) examined the effectiveness of acetaminophen in preventing fever after vaccination in 5-month-old infants. The results indicated no significant differences in the occurrence of fever and also noted no significant differences in antibody titers. However, the sample size was small and the study was based on a single dose of acetaminophen. Lewis and colleagues (1989) used a double-blinded, randomized method to determine the effectiveness of prophylactic acetaminophen; their study, which had a sample size of 282, included the use of six multiple doses administered every 4 hours, beginning 1 hour before the vaccine was administered. The results indicated that the administration of acetaminophen had a moderate effect on fever, pain, and fussiness. Although the adverse effects were better controlled, no mention was made of measuring a change in antibody response. Because of these and other studies, the recommendation to administer acetaminophen prophylactically was formulated, and pediatric health care providers routinely began to administer acetaminophen before vaccines, instructing parents to continue administering the medication every 4 hours for the next 48 to 72 hours to reduce the chance of any adverse effects (Centers for Disease Control and Prevention, 1987).

Approximately 20 years later, Manley and Taddio (2007) completed an extensive literature review regarding whether scientific evidence existed to support the administration of antipyretic agents prophylactically with childhood immunizations. Their conclusions indicated that the reviewed research was dated and based on vaccine formulations no longer in existence and that no evidence existed to support the use of ibuprofen or acetaminophen to reduce vaccine-associated adverse effects.

To further support this theory, Yalcın, Gümüş, and Yurdakök (2008) conducted a randomized, non-blinded study with a sample size of 270 to expound on the effects of antipyretic agents and fever related to vaccines. Groups were used that differentiated when and if acetaminophen was given. No significant differences were noted between the groups with respect to fever or comfort, and the investigators reiterated that medication should not be administered if it was not necessary.

A pivotal study questioning the standard use of prophylactic antipyretic agents was conducted by Prymula and colleagues (2009) in the Czech Republic as a series of two consecutive (primary and booster vaccination) phase 3, randomized, controlled, open-label studies in 10 different centers. The patients were divided randomly into two groups; one group was given three doses of paracetamol (known as acetaminophen in the United States), and the control group was not given any medication or placebo. When the time came for the booster vaccine, the children stayed in the same groups, but once the primary vaccination immunogenicity report was received by the researchers, use of prophylactic paracetamol was discontinued for the booster vaccine. Thus the study included three groups (Figure): a group that received primary and booster vaccines with prophylactic paracetamol, a group that received prophylactic paracetamol only during the primary vaccine series, and a group that did not receive any prophylactic paracetamol. Blood samples were collected a total of four times: before the first dose, 1 month after the primary vaccination, before the second dose, and 1 month after the booster dose. Using a 95% confidence interval, results indicated that initial antibody response levels were similar in all groups but that a significant decrease in the primary antibody response to the antigens in the vaccines occurred in the group that received paracetamol. It is unclear why this response occurred, and several theories were hypothesized. One theory suggested that the cell-mediated antibody responses depend greatly on temperature and that when antipyretic agents are used, temperatures do not reach optimal levels for attenuation, thus reducing the efficacy of the vaccines. When the antibody response in children with and without fever was reviewed, similarities were noted, thus making this theory unlikely. The most promising theory, supported by post-hoc analyses, hypothesized that the highest level of antibody response interference occurs when paracetamol is given early, as a prophylactic, but when the drug is given only after fever occurs, a smaller or negligible change in vaccine response occurs (Prymula et al., 2009).

Critiques in response to this study have been plentiful and overwhelmingly supportive in nature. Chen, Clark, and Halperin (2009) recognized the integrity of the randomization, doubted any system bias, and noted the need for further research, especially the scope of reduced population protection from vaccine-preventable diseases resulting from paracetamol administration. Acknowledging this point opens the door for further research in the field of vaccine development. Homme
and Fischer (2010) expressed their comfort level with the interpretations of the data presented and noted that, although on the basis of this report it appears that paracetamol reduces postvaccine antibody levels, individual practitioners must decide for themselves how these results will affect their present method of practice. The American Academy of Pediatrics (AAP) is not convinced that their guidelines should be changed and still recommend the use of antipyretic agents until further research is completed (Brady and Swanson, 2010). Suggestions for further testing by Homme and Fischer (2010) include assessing the timing, dosing, and method of administration of paracetamol in relation to vaccines and to begin studying the effects of other antipyretic agents such as ibuprofen on antibody response.

Yalçın (2010) suggested that one way of strengthening this study would be to follow patients from the initial vaccine and each booster, monitoring antibody response levels in the same fashion as previously described. Cuestas (2010) recognized the plausibility of Prymula’s findings but was not convinced that the results of one study are sufficient to change the methods of practice. Recommendations include confirming the results in other independent, randomized, blinded, placebo-controlled trials before eliminating prophylactic use of antipyretic agents with immunization administration.

**Relevance to Pediatric Primary Care Health Care Providers**

The pediatric HCP administers health advice at well-child visits to more than 24 million children annually (Belamarich, Gandica, Stein, & Racine, 2006). At each of these visits, numerous anticipatory guidelines need to be discussed with the child and parents, including immunizations. Vaccine administration and education are paramount to the well-being of the child and encompass a significant portion of the well-child visit. In today’s highly mobile and technology-savvy society, it is imperative that pediatric HCPs stay current with studies pertaining to their patients so that an informed decision may be formulated by the parent with the HCP’s assistance.

Parents who are concerned about providing the best care for their child often seek advice from their HCP. With respect to immunizations, essential topics for discussion are the reason for the vaccine, potential adverse effects, and preventive measures to reduce these adverse effects. Historically parents have been advised to give prophylactic antipyretic agents to prevent or
alleviate fever, discomfort, or fussiness. Given the results of the study by Prymula and colleagues, along with the intent to increase evidence-based practice, parental advice should include careful observation and administration of antipyretic agents as needed.

**CONCLUSION**

Because of the increase of accessibility of health care information to consumers, the daunting task of knowing and interpreting the most current data is imperative for HCPs. Determination and diligence are required to practice evidence-based medicine through the use of appropriate up-to-date practice guidelines. Immunizations are a daily topic of discussion for pediatric HCPs. In light of the study by Prymula and colleagues, the practice of providing prophylactic medication to children who are receiving vaccines has been disputed; questionable benefits and a potential decrease in antibody response has been noted, potentially decreasing the effectiveness of the vaccine. Careful monitoring, administration of antipyretic agents on a per-diem basis, and support and meticulous review of new research are imperative elements to ensure the best care for the child.

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