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Practical Tips for Paediatricians
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Fever prophylaxis can reduce vaccine responses: A caution

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Abstract

Prophylactic administration of antipyretic/analgesic drugs, started at the time of immunization and repeated 6 and 12 hours later, is sometimes undertaken to reduce postimmunization fever and irritability in infants. Two recent studies showed that such prophylaxis can reduce immune responses to some infant vaccines, warranting judicious use. In contrast, implementing treatment 6 hours or more after immunization had no effect on vaccine responses and would reduce drug exposure of asymptomatic infants.

Keywords: *Immunization; Childhood; Ibuprophen; Acetaminophen; Vaccine immunogenicity; Fever prophylaxis.*

Pain reduction during childhood immunizations has received greater attention recently to make the experience more benign (1,2). Not recommended among pain-reducing strategies is the prophylactic administration of acetaminophen or ibuprophen (1,2). In some situations, such as in response to a previous postimmunization fever or unusual irritability, prophylactic administration of antipyretic/analgesic drugs is undertaken by parents or immunizers to prevent or reduce adverse effects. Prophylactic drugs are typically started at the time of immunization and repeated about 6 and 12 hours later. Such three-dose prophylaxis can reduce the fever rate by half during the first day after immunization but not on later days (3,4).

Two studies from Europe have raised concerns that prophylactic antipyretic use might have unintended effects on immune responses to infant vaccines. The first was a randomized trial conducted in the Czech Republic (3) in which prophylactic paracetamol (acetaminophen) was given in three doses 6 to 8 hours apart starting at the time of immunization while control infants received no intervention. After vaccinations at 2, 3 and 4 months with 10-valent pneumococcal conjugate vaccine (PHiD-CV, GSK) and hexavalent vaccine (DTaP.IPV.Hib.HepB), antibody responses were measured at 5 months. Compared to controls, antibody responses of treated infants were significantly reduced to all 10 pneumococcal serotypes and to the Hib, tetanus, diphtheria and pertussis (pertactin) components of the hexavalent vaccine. After the 12-month booster doses of the same vaccines, lower antibody levels persisted to nine pneumococcal serotypes and tetanus toxoid. Limitations of this study included lack of blinding and imprecise dosing by weight using paracetamol suppositories. The reduced antibody levels in treated infants may not have correlated with reduced clinical protection.

A more recent, well-designed study from Poland (4) has added substantially to knowledge regarding the potential for such interference as it assessed two drugs (paracetamol and ibuprophen) used as either prophylaxis (three doses, 6–8 hours apart, starting with immunization) or simulated fever treatment (two doses, starting 6–8 hours after immunization, when fevers typically begin). Healthy infants were randomly allocated to one of five groups, including an untreated control group. PCV13 pneumococcal and hexavalent vaccines (DTaP.IPV.Hib.HepB) were given at 2, 3, 4 and 12 months, with antibody responses measured at 5 and 13 months of age. Drugs were given orally and dosed by weight. At 5 months of age, the infants given three-dose paracetamol prophylaxis had significantly reduced antibody responses compared to control infants to 5 of 13 pneumococcal serotypes, although mean antibody concentrations

were above the minimum protective threshold (≥0.35 μg/ml) in both groups. No differences remained after the 12-month boosters. Paracetamol prophylaxis (0, 6 and 12 hours) did not affect responses to hexavalent antigens. Delayed 'treatment' with two doses of paracetamol (6 and 12 hours) had no effect on PCV13 or hexavalent antibody responses at 5 or 12 months.

In contrast, ibuprophen prophylaxis in this study had entirely different effects on responses. Neither three-dose prophylaxic nor delayed two-dose 'treatment' regimens had any effect on pneumococcal responses but the prophylactic regimen (0, 6 and 12 hour dosing) significantly reduced antibody responses to the FHA component of pertussis vaccine and to tetanus toxoid (but with group mean values well above the minimum protective threshold). These differences disappeared after the boosters. The delayed two-dose 'treatment' regimen (6 and 12 hours) did not reduce any response.

The different outcomes with paracetamol/acetaminophen prophylaxis between the two studies may have resulted from differences in dosing accuracy, the type of pneumococcal conjugate vaccine or the laboratory assays used. Generalizability to other infant immunization schedules (e.g., 2, 4, 6 months) is unstudied. In theory at least, the two-dose PCV13 infant immunization schedule popular in Canada might be particularly vulnerable to such interference but this schedule has not yet been studied.

The take home message? Prophylactic use of antipyretic/analgesic drugs can reduce immune responses to some infant vaccines, warranting judicious use. The clinical significance of such reduced responses is uncertain but stronger responses are obtained in the absence of prophylaxis. In contrast, using these drugs to treat symptoms once they appear is unlikely to interfere with immune responses and would reduce the number of asymptomatic children exposed to other potential drug adverse effects. The above observations that anti-inflammatory drugs only interfere with antibody responses if present during the first 6 to 8 hours after immunization serve as a reminder that injection site inflammation is an essential first step in initiating responses to vaccines, activating dendritic cells and recruiting macrophages that rapidly transport vaccine antigens to regional lymph nodes where antibody responses begin. Acetaminophen and ibuprophen target different parts of the inflammatory response cascade, likely explaining their differing effects on immune responses.

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Conflict of Interest

The authors have no conflicts of interest relevant to this report. Neither author has published in this domain within the past 3 years.

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