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Does the prophylactic antipyretics administration decrease the immune response to vaccines?

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English key words: antipyretics, immunogenicity vaccine, vaccines, pneumococcal vaccines.

Spanish key words: antipiréticos, inmunogenicidad vacunal, vacunas, vacunas neumocócicas.

Reception date: September 26, 2017 • **Acceptance date:** September 28, 2017

Publication date: October 4, 2017

Evid Pediatr. 2017;13:34.

HOW TO CITE THIS ARTICLE

Juanes de Toledo B, González Rodríguez P. Los antitérmicos profilácticos, ¿disminuyen la respuesta inmune a las vacunas? Evid Pediatr. 2017;13:34.

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This article is available at <http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:34>

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Does the prophylactic antipyretics administration decrease the immune response to vaccines?

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Original article: Wysocki J, Center KJ, Brzostek J, Majda-Stanislawski E, Szymanski H, Sxenborn L, *et al.* A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations. *Vaccine*. 2017;35:1926-35.

Abstract

Authors' 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 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.

Reviewers' commentary: this study suggests that the best immune response to vaccination is reached without the use of prophylactic antipyretics.

Key words: antipyretics, immunogenicity vaccine, vaccines, pneumococcal vaccines.

Los antitérmicos profilácticos, ¿disminuyen la respuesta inmune a las vacunas?

Resumen

Conclusiones de los autores del estudio: la administración de antitérmicos de forma profiláctica afecta a la respuesta inmune a las vacunas. Estos efectos varían según la vacuna, el antitérmico utilizado y el momento de administración. En lactantes, el paracetamol interfiere con la respuesta inmune a los antígenos neumocócicos y el ibuprofeno puede reducir la respuesta a la tosferina y al tétanos.

Comentario de los revisores: este estudio sugiere que la mejor respuesta inmune a la vacunación se alcanza sin la utilización de antitérmicos profilácticos.

Palabras clave: antipiréticos, inmunogenicidad vacunal, vacunas, vacunas neumocócicas.

STRUCTURED ABSTRACT

Objective: to determine whether the use of paracetamol or ibuprofen in vaccination interferes with the immune response to the pneumococcal conjugate vaccine (PCV13) given concomitantly with the hexavalent vaccine (HV).

Design: open-label randomised controlled clinical trial with four treatment arms.

Setting: 14 sites in Poland, between August 2011 and January 2013.

Study sample: the study included 908 infants aged 2 months. Infants were excluded in case of contraindication to vaccination,

a history of anaphylactic reaction to any vaccine component, allergy or contraindication to the antipyretic agents or chronic use of medications with known interactions with the antipyretic agents.

Intervention: patients were randomised to 5 groups using an interactive voice response system, with administration of vaccines at 2, 3 and 4 months (primary series) and 12 months (booster dose).

Groups 1 and 2 received paracetamol at 15 mg/kg/dose or ibuprofen at 10 mg/kg/dose, respectively, starting 6-8 hours after vaccination (delayed administration) and at 6-8 hours from the first dose.

Groups 3 and 4 received paracetamol and ibuprofen, respectively, at the same doses, but starting at the time of vaccination (coadministration).

The control group (group 5) did not receive prophylactic antipyretics. Use of antipyretics was permitted for all groups for treatment of fever or other symptoms.

Outcome measurement: the immune response was measured at 5 and 13 months, and results of the treatment groups and the control group were compared.

The primary endpoint was the immunogenicity of the PCV13 assessed by means of the geometric mean concentrations (GMCs) of each serotype-specific IgG.

The secondary endpoint was the measurement of the levels of specific IgG against PCV13 serotypes following the booster dose, and the immunogenicity of the components of the HV (diphtheria, tetanus, pertussis, hepatitis B, inactivated poliovirus and *H. influenzae* type B) after primary vaccination and the booster dose.

The authors used the Bonferroni correction to control for potential false positives in the multiple-group analysis, with a *p*-value of less than 0.0125. The Benjamini-Hochberg procedure, which controls false negative comparisons, was used in the analysis of the 13 PCV13 serotypes in the different groups.

Main results: Nine hundred children (99%) completed vaccination at 4 months and 892 at 12 months. Fewer than 10% of children in each group did not receive antipyretics as specified by the protocol.

Following primary vaccination, the pneumococcal IgG levels in groups 1 and 3 (paracetamol) were lower than those in group 5 for all serotypes. The reduction in group 3 (coadministration of paracetamol) was statistically significant for 5 out of the 13 serotypes (3, 4, 5, 6B and 23F) ($P < .0125$). In groups 2 and 4 (ibuprofen) there were no significant differences compared to group 5. There were no differences after the booster dose.

The immune response to the HV was lower in group 4 (coadministered ibuprofen) compared to group 5 ($P < .0125$) for tetanus and pertussis after primary vaccination, but not after the booster dose.

There were no statistically significant differences in the achievement of IgG levels considered to confer protection against PCV13 serotypes ($> 0.35 \mu\text{g/ml}$) or HV components.

In all groups, fever was mild and of short duration (< 1.5 days). Groups 2 and 4 (ibuprofen) reported more fever on day 2 (17.3-41%) compared to groups 1 and 3 (paracetamol) (11.8-26.8%) and group 5 (13.2-21.9%).

Conclusion: the administration of prophylactic antipyretics affects the immune response to vaccination. These effects vary based on the vaccine, the antipyretic used and the timing of administration. In infants, paracetamol interferes with the immune response to pneumococcal antigens and ibuprofen may diminish the response against pertussis and tetanus.

Conflicts of interest: several researchers participated in clinical trials funded by GSK, Pfizer and Novartis (refer to original article).

Funding source: funded by Pfizer.

COMMENTARY

Justification: the administration of the PCV13 may be associated with fever in up to one third of cases. Antipyretics such as paracetamol or ibuprofen are sometimes given for prophylaxis. Some studies suggest that paracetamol interferes with the immune response when it is administered at the time of vaccination.¹ However, the effect of paracetamol administered hours after the vaccine had not been studied, nor whether other commonly used drugs, such as ibuprofen, have a similar effect. Therefore, this study is important to understand the effect of these two antipyretics on vaccine immunogenicity.

Validity or scientific rigour: the clinical question was appropriately formulated, the sample of Polish infants was chosen due to the low use of antipyretics. The internal validity seems adequate, and the groups comparable, although the authors did not describe feeding modalities, attendance to child care centres or the presence of siblings. The randomisation was performed externally by an interactive voice response system, an unlikely source of selection bias; since the origin of the sample was not specified, there may have been information bias stemming from both the parents and the researchers in the assessment of the febrile response, and furthermore, the data were analysed by the sponsor (Pfizer). The external validity may also be limited, as the sample came from a population with homogeneous ethnic characteristics, which are known to influence the metabolism of paracetamol and ibuprofen. The followup was completed, with losses of less than 5%. The researchers performed a modified intention-to-treat analysis.

Clinical relevance: the immune response against PCV13 serotypes was lesser in groups that received paracetamol, even in coadministration or with delayed administration (groups 1 and 3), and the difference was significant for 5 out of the 13 vaccine serotypes ($P < .0125$). There were no differences after the booster dose. The immune response against two components of the HV (pertussis and tetanus) was reduced in the group given ibuprofen at the time of vaccination (group 4). There were no differences between groups in that they all achieved acceptable levels of protection in response to vaccination.

Although neither antipyretic has an apparent effect on the immune response, it may be that other benefits of the PCV13 may be affected, such as the protection against otitis media or the reduction in nasopharyngeal colonisation, as they may require higher levels of antibodies. Furthermore, post-vaccination fever was similar in all groups, and it was even more frequent on day 2 in the groups given ibuprofen.

Previous studies have described that this reduction in fever¹ is associated with a reduced immune response, as has been observed in studies with other vaccines, also with differences that were not statistically significant.²

Applicability to clinical practice: administration of antipyretic agents for prophylaxis affected the immune response to the vaccines under study, and thus is recommended against in everyday clinical practice.

Conflicts of interest: the authors of the commentary have no conflicts of interest to declare.

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