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Editorial

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Antipyretic drugs and vaccines: do we already know what we need to know?

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Fever and pain are the most frequent adverse effects of vaccination.

Symptomatic treatment of fever when it is high or accompanied by significant discomfort is accepted by a majority of health professionals and has been the subject of countless studies. However, there is still uncertainty as to the role of increased body temperature as a defensive physiologic mechanism against infection and the need to reduce it in every case.

Current guidelines propose a restrictive use of antipyretic agents, limiting it to specific cases with the purpose of reducing discomfort rather than fever itself. Paracetamol and ibuprofen are the drugs usually employed.

Numerous guidelines and recommendations have been published on the use of antipyretics. However, there is evidence of a widespread lack of adherence to these recommendations, both among professionals and in the routine practice of health facilities as well as in families.[1] The excessive use of antipyretics in children, be it on the initiative of the family[2] or as dictated by a health professional, is widespread despite the available evidence against it.[3]

Relief of the discomfort that accompanies fever is a reasonable therapeutic goal, despite the gaps in knowledge regarding the risks and benefits of fever and its treatment,[4] although it should be provided in conformity with current evidence and exercising prudence.

There are specific issues when it comes to the particular case of post-vaccination fever. Whereas the degree of tolerance of fever of any source is low in both families and professionals, when it comes to vaccination—an intervention performed in healthy children—it is generally even lower.

Some guidelines specify that antipyretic agents are not indicated for the prevention of fever in post-vaccine reactions,[1] and some even assert that they should not even be used for its treatment,[5] based on previous evidence that the use of antipyretic drugs may interfere with the immune response to vaccines.[6]

Indeed, Prymula[6] demonstrated in 2009 that paracetamol administered at the time of vaccination or in the following hours significantly reduced the number of episodes of moderate fever and pain (66% in primary vaccination doses, 58% in booster doses), although not the number of episodes of high fever, which were uncommon at any rate; and, what is more important, that it reduced the concentration of antibodies against several vaccine antigens (all pneumoccocus serotypes, *Haemophilus influenzae* type b, tetanus, pertactin and diphtheria), a reduction that persisted after the booster dose. The authors hypothesised that paracetamol may interfere with the early phases of the inflammatory response (which would explain why the interference was considerably lesser when paracetamol was administered hours after the onset of fever). They concluded that paracetamol should not be used in combination with vaccines.

A systematic review[7] published in 2014 confirmed the efficacy of paracetamol in reducing post-vaccination fever, and also a significant reduction in the antibody response with the prophylactic use of paracetamol, although with maintenance of levels considered protective. It concluded by underscoring the need to evaluate the real impact of these findings on the effectiveness of vaccination programmes at the population level.

Two more studies have become available on the subject. In the first, Wysocki *et al*[8] analysed the use of paracetamol and ibuprofen with the pneumococcal conjugate vaccine (PCV13) and the hexavalent vaccine. They found that antipyretic agents affected the immune response to a variable degree based on the vaccine antigens involved, the antipyretic used, and the timing of its administration:

- Paracetamol performed clearly better than ibuprofen in reducing fever after vaccination.
- Paracetamol interfered with the response against antigens contained in the pneumococcal vaccine, and ibuprofen with antigens in the pertussis and tetanus vaccines. The effect was greater when paracetamol was administered concurrently with vaccines compared to 6 to 8 hours later, and was mainly observed after primary vaccination.
- Despite the observed differences, all individuals exhibited responses that were appropriate overall.

In the current issue of *Evidencias en Pediatría*, Juanes *et al*[9] make a critical analysis of the aforementioned study,[8] declaring it a

correctly planned and implemented study, with the sole reservation that it was performed in an ethnically homogeneous population, which may limit its external validity, as it is known that genetic determinants may lead to differences in the metabolism of either drug. On the other hand, they underscored the firm evidence on the potential of paracetamol to reduce the immune response to certain vaccine antigens in primary vaccination, although it should be noted that the clinical relevance of this finding remains to be established.

The second study[10] reported findings that countered those of the first. It analysed the response to a pentavalent vaccine (DTwP-Hib-HB) in children that did not receive paracetamol or received it for either prophylactic or therapeutic purposes, and found no differences between groups. However: 1) this was a *post hoc* analysis, with no randomisation in relation to the use of paracetamol; 2) the study did not differentiate based on the doses and schedule of the use of paracetamol, and some subjects also received other drugs (ibuprofen, mefenamic acid), and lastly, 3) the authors found some degree of reduction in the response to all the antigens under study, although the reduction was not statistically significant in the overall analysis (did not go past the threshold for protection) and was therefore declared clinically irrelevant.

A critical review by De Lucas *et al*[11] of the latter study[10] highlighted that its limitations compromise the applicability of its findings to vaccination practices. Among the most relevant, they noted, in addition to what we have mentioned above, was that the results did not discriminate different paracetamol regimes, nor considered whether other drugs were taken simultaneously or successively for the same purpose, and that the vaccine under study was the whole-cell pertussis vaccine, which is no longer used in Spain.

The new meningococcal serogroup B vaccine (4CMenB) has complicated the situation. A study[12] prior to its marketing in Europe reported an increase in fever following routine vaccinations in the first months of life (4CMenB administered alone: 26-41%; other first-year vaccines administered alone: 23-36%; 4CMenB co-administered with other routine vaccines: 51-61%).

Fever in young infants causes concern in families and paediatricians and constitutes a complicated clinical challenge and a frequent reason for the performance of diagnostic evaluations and tests as well as hospital admission.

The relevance of the increased reactogenicity of the 4CMenB is, therefore, worth considering. In the United Kingdom, this vaccine was introduced in 2015 (at 8 and 16 weeks and 12 months of age), and there was a reported increase in the number of emergency department visits[13] following the introduction of this vaccine in the immunisation schedule (increase in number of visits related to post-vaccination adverse events per 1000 vaccinations from 1.03 to 3.4 [$P < .001$] at 2 months, and from 0.14 to 1.13 [$P = .005$] at 4 months). This occurred despite the recommendation of Public Health England (PHE) (2015)[14] of administering paracetamol at the time of vaccination based on previous studies[15] that demonstrated that its co-administration with the 4CMenB vaccine reduced fever after vaccination (51-65% overall) without an associated reduction in the immunogenicity of the involved vaccines (however, there was evidence of certain reductions in the response to certain antigens, although the response was never below the threshold for protection).

Another study[16] assessed the association of paracetamol and ibuprofen with the incidence of post-vaccination fever and immunogenicity following vaccination with the PCV10 co-administered with pentavalent or hexavalent vaccines in infants aged less than 12 months, and found that paracetamol reduced the incidence of post-vaccination fever, while ibuprofen did not (both administered either as prophylaxis or treatment), and that prophylactic paracetamol was associated with a reduced antibody response in primary vaccination doses, with no changes in the response to the hexavalent vaccine antigens.

In conclusion, and to summarise the above, the facts and uncertainties are the following[17]:

Antipyretics are widely used to provide relief from fever, pain and discomfort following vaccination. Paracetamol is effective in reducing post-vaccination fever.

The prophylactic use of paracetamol reduces the response to some vaccine antigens, with an effect that varies between studies, and with no evidence of a reduction in vaccine effectiveness. There are also other studies—a minority—that have found opposite or contradictory results.

Since the publication of the study by Prymula in 2009,[6] nearly all guidelines and experts have recommended against the use of antipyretics for the prevention of post-vaccine fever.[18,19]

The specific paracetamol regimen (timing and dosage) seems to be of critical importance, as the deleterious effects on immunogenicity seem to be restricted to the administration of paracetamol prior to or at the time of vaccination, as opposed to its administration a few hours after. And they also seem to be limited to primary vaccination, without affecting booster doses.

The growing number of vaccines, new manufacturing technologies, the combination of antigens and vaccines, and the increasing use of adjuvants—which tend to increase reactogenicity—complicate the risk/benefit analysis of antipyretic use.

Elucidating this question is of considerable interest for public health: to which point is it necessary to prevent or treat post-vaccine fever which, as we know, is self-limiting and of low to moderate grade? As to the observed trends in the reduction in the antibody response against certain antigens, can they reach the point of reducing the effectiveness of vaccination

programmes? And what happens in especially vulnerable populations, such as the chronically ill, the immunocompromised, pregnant women, etc, which are usually excluded from studies? Would the impact of the use of paracetamol be different in environments with suboptimal vaccination coverage?

Do we have the necessary knowledge, then, to answer these questions? We do not, and many remain unanswered. Consequently, it seems that we should uphold the prudent recommendation of not using antipyretic agents to prevent post-vaccine fever.

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