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CHEST

Should Antipyretics Be Used to Relieve Acute Adverse Events Related to COVID-19 Vaccines?

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The introduction of new vaccines against COVID-19 including those from BioNTech and Moderna, among others, will be pivotal for controlling the SARS-CoV-2 pandemic. The availability and administration of these vaccines will be a pivotal step in controlling the COVID-19 pandemic.

The BioNTech and Moderna vaccines are currently the only ones approved for use in North America. These two vaccines, like many others, also might be associated with self-limiting acute adverse drug reactions (ADRs). The overall rate of systemic ADRs, based on recently published phase 3 trial data,[1,2] is considered low. For example, in the trial that used the BioNTech vaccine (18,860 vaccine users vs 18,846 nonusers), the overall ADR rates with the first dose was 0.9%.[1] However, a considerable proportion of vaccine recipients still reported fatigue (59% vs 52%, vaccine vs placebo users) and headache (51% vs 39% among older recipients). Similarly, more patients taking the Moderna vaccine reported any systemic reaction (79.6% vs 36.6.0%). Specifically, more subjects experienced myalgia (58.0% vs 12.3%), arthralgia (42.9% vs 10.7%), and fatigue (65.7% vs 23.3%) with the vaccine.[2] Based on these data and given the availability of antipyretics as over-the-counter medications, it is expected that potentially millions around the world might be using them to control acute systemic ADRs related to the COVID-19 vaccine.

Relevance

Historically, antipyretics such as ibuprofen or acetaminophen have been used to control the acute phase adverse events secondary to different vaccines. However, some studies have suggested that taking antipyretics immediately before or shortly after receiving a vaccine might interfere with its immunogenicity,[3] but others have not.[4] A two-part landmark randomized trial evaluated the effect of acetaminophen taken prophylactically (immediately after vaccination) in infants.[3] In this study, antibody titers were significantly lowered in those taking acetaminophen prophylactically compared with control subjects. Moreover, some of the differences in these findings might be attributable to age, because the potential immune-modulating effects of antipyretics and their potential negative interaction with vaccines might differ in children and adults.

A number of regulatory bodies have made statements regarding use of antipyretics around the time of vaccination. In 2015, the World Health Organization stated that use of antipyretics is not recommended before or at the time of vaccination but approved in the days after vaccination, and the Centers for Disease Control and Prevention concurs with these recommendations.[5]

Mechanism

The mechanism of decreased circulating antibodies caused by antipyretic administration post-vaccination is not well understood; however, a few potential mechanisms have been postulated. Antipyretics such as acetaminophen and ibuprofen can interfere with the communication between the innate and adaptive immune system in lymphatic tissue, which occurs within hours of antigen administration. Most of the research on this topic has been undertaken looking at the effect of

ABBREVIATIONS: ADR = adverse drug reactions; mRNA = messenger RNA

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antibody production with antipyretics, using animal models, which warrants more human data from vaccines that use different platforms (protein, live attenuated, or messenger RNA (mRNA)-based vaccines).

No study has specifically examined the effect of antipyretics on the immunogenicity of the COVID-19 vaccines. A recent report from the $^{1}/_{2}$ single-blind randomized trial of the AstraZeneca (adenovirus-vectored vaccine) does mention that prophylactic use of acetaminophen did not interfere with the vaccine's immunogenicity, although no data were provided, and these results might not be applicable to other mRNA-type vaccines. Furthermore, no data were provided on the use of antipyretics in the Moderna[2] trial, and the Pfizer[1] trial only mentioned that the use of antipyretics was increased with increasing dose concentrations and dose number, but data on immunogenicity were not given.

Future Directions

A potential negative interaction between antipyretic use and COVID-19 vaccines might have important public health repercussions, because they potentially affect the efficacy of the vaccine directly by hindering the vaccine's immune response. Indirectly, concerns about this interaction can lead to low utilization of antipyretics and potentially lead to nonadherence with the second dose. Going forward, clinical trials need to urgently answer four questions: 1) Do either ibuprofen or acetaminophen affect antibody response by COVID-19 vaccines, and if so, is there a difference in antibody titers between the two agents? 2) Does a potential interaction with antipyretics differ with different vaccine types (mRNA vs non-mRNA vaccines)? 3) Does the timing of antipyretic administration (before vaccination or immediately after) affect antibody titers? 4) Does a possible negative interaction only affect antibody titers for the first dose, second dose, or both?

Multiple COVID-19 vaccines translating to billions of doses will be transiting through the pipeline soon, and many might use over-the-counter antipyretic medications to curb early adverse events from these vaccines. Existence of a potential negative interaction between these drugs and the vaccine will need to be examined promptly, because use of these drugs, especially with respect to the timing of vaccine administration, might be critical and potentially affect vaccines' immunogenicity.

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