

March 18, 2020

Ibuprofen and COVID-19

Regarding information that appeared in the media about the risk of using ibuprofen in COVID-19 infections, between March 15 and March 18 2020 the World Health Organization (WHO) and some regulatory authorities such as EMA, NHS in the United Kingdom, AEMPS in Spain and HPRA in Ireland have stated **that there is currently no evidence to support an aggravation of COVID-19 infection with ibuprofen or other NSAIDs**. The EMA even recommends that, when starting treatment of fever or pain in the case of COVID-19 infection, patients and professionals consider the options available including acetaminophen (i.e. paracetamol) and nonsteroidal anti-inflammatory drugs.

In short (additional information below) and *pending new data*, we believe the approach suggested by the UK NHS is appropriate. It addresses the lack of evidence regarding harmful effects of ibuprofen on COVID-19 infections and does not advise to discontinue ongoing treatments with this medicine but, if treatment is initiated, prioritizes the use of paracetamol to treat symptoms of the infection.

Background.

On March 11, 2020, The Lancet published in a comment the theory that ibuprofen may increase the expression of the angiotensin-converting enzyme 2 (ACE2), which would facilitate the development of a severe and fatal infection with COVID-19.ⁱ However, at the moment, this hypothesis is yet to be confirmed by specific experimental designs; particularly since the formulation of the hypothesis (and not a confirmation) was made in the context of treatments for diabetes and hypertension.

Subsequently, on 14 March, the Minister of Health of France, Olivier Véran, announced, through his Twitter account, that taking anti-inflammatory drugs such as ibuprofen and cortisone could be an aggravating factor for COVID-19ⁱⁱ infection. On March 16, the French Network of Regional Pharmacovigilance Centres (RFCRPV) reiterated this information, alerting the population not to use Non-Steroid Anti-Inflammatory Drugs (NSAIDs) indicating that there are a significant number of reports of serious infections in adults (cutaneous, oropharyngeal, respiratory) taking NSAIDs. The established risk of superinfection in the case of chickenpox, associated with the consumption

of these medicines ⁱⁱⁱ and the existence of previous studies where the increase in suppurative complications was associated with the use of nonsteroidal anti-inflammatory drugs in community pneumonia, was also mentioned.

In France, in March 2019, the Regional Pharmacovigilance Centres in Tours and Marseille conducted a pharmacovigilance ^{iv} study with the aim of investigating the risk of serious infectious complications associated with NSAID use in adults and children, with special emphasis on the two most commonly used NSAIDs indicated for the treatment of fever and moderate pain. The objective of this study was to determine whether these serious infectious complications were favored by the presence of NSAIDs or whether they simply reflected the evolution of the initial infectious pathology. Of all reported cases since 2000, 337 cases of infectious complications with ibuprofen and 49 cases with ketoprofen (taking into account only the most severe cases in children or adults- often young) without risk factors or comorbidities were selected. The outcomes were severe skin and soft tissue infections (dermohypodermatitis, necrotizing fasciitis, among others), sepsis, pleuro-pulmonary infections (complicated pneumonia – abscesses, pleurisy), neurological infections (brain abscesses), among others; giving rise to hospitalizations, sepsis or even death. These infectious complications (essentially caused by streptococcus or pneumococcus) were observed after short treatment periods (2-3 days) when an NSAID was associated with antibiotic therapy. They occurred when ibuprofen or ketoprofen were prescribed or self-medicated for fever, but also in various other circumstances such as benign inflammatory-looking skin lesions (local reactions, insect bites), respiratory manifestations (cough, lung infection) or others (dysphagia, otitis). It should be noted, as an important limitation, that these assessments were made based on pharmacovigilance reports and not studies.

Analysis of these cases, as well as analysis of the data from the literature (some previous experimental and pharmacoepidemiologic studies) might suggest that these infections, particularly caused by streptococcus, could be aggravated by taking the aforementioned NSAIDs. In 2019, France's National Agency for the Safety of Medicines and Healthcare Products (ANSM) warned healthcare professionals, patients and caregivers about the risk of serious infectious complications that could have serious consequences for patients' health. The NSA shared these findings with its counterparts in neighboring countries ^v; and requested the European Medicines Agency (EMA) review any possible risk. This review began in May 2019 and is carried out by the Pharmacovigilance Risk Assessment Committee (PRAC).

Conclusion.

- The evidences about the effects of ibuprofen on infections described above are not based and are not extrapolable to COVID-19 infection.
- The review about the risk of increased infectious processes associated with ibuprofen and ketoprofen, currently held by the EMA PRAC, is expected to be completed in May 2020.
- Between March 15 and March 18 2020 the World Health Organization (WHO) and some regulatory authorities such as EMA, NHS in the United Kingdom, AEMPS in Spain and HPRA in Ireland have stated **that there is currently no evidence to support an aggravation of COVID-19 infection with ibuprofen or other NSAIDs**,^{vi,vii,viii}. The EMA even recommends that, when starting treatment of fever or pain in the case of COVID-19 infection, patients and professionals consider the options available including acetaminophen and nonsteroidal anti-inflammatory drugs.
- In short and pending new data, we think it's appropriate the approach suggested by the UK NHS, which addressing the lack of evidence regarding harmful effects of ibuprofen on covid-19 infections does not advise to discontinue ongoing treatments with this medicine but, if treatment is initiated prioritizes the use of paracetamol to treat symptoms of the infection^{ix}.

References

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- ⁱⁱ Olivier Véran : <https://twitter.com/olivierveran/status/1238776545398923264>
- ⁱⁱⁱ COVID-19: no NSAs! and respect for the proper use of paracetamol... Available in:
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- ^v RAPS – EU Regulatory Roundup: France’s ANSM warns about NSAIDs following safety review. Available in: <https://www.raps.org/news-and-articles/news-articles/2019/4/eu-regulatory-roundup-frances-an-sm-warns-about-n>
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- ^{viii} EMA Statement. Available in: <https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19>
- ^{ix} NHS Declaración: <https://www.nhs.uk/medicines/paracetamol-for-adults/>