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Reçu le 23 juin 2020 ;
accepté le 9 juillet 2020

https://doi.org/10.1016/j.therap.2020.07.006

COVID-19 and NSAIDs: *Primum non nocere*

Keywords Anti-inflammatory agents; Nonsteroidal; Infections; COVID-19; Pharmacovigilance

Abbreviations

COVID-19 coronavirus disease 19
NSAIDS non-steroidal anti-inflammatory drugs
SARS-COV 2 severe acute respiratory syndrome coronavirus 2

The coronavirus disease 19 (COVID-19) emergency has brought new insights and awareness on many drugs that are widely used worldwide, such as the case of non-steroidal anti-inflammatory drugs (NSAIDs) used during short time for pain or fever with the need to analyze available data both from preclinical and clinical studies on the effects of NSAIDs in viral infections.

In this context, we read with great interest the letter of Cure et al. about the well-known harmful effects of NSAIDS such as thrombosis and acute renal failure based on pharmacological plausibility well described by the authors [1] and reported also with their over-the-counter use and in pediatric population [2].

By the way, we have underlined that almost all pharmacoepidemiological studies that assessed the risk of superinfections/complications under NSAIDs converged (NSAIDs used in a wide range of clinical situations, in particular pre-existing pleuro-pulmonary or skin and soft-tissue bacterial or viral infections) [3]. We agree that these studies taken individually are impaired by bias. But, taken together, along with the pharmacovigilance cases, the experimental studies and the pharmacological plausibility, we do believe that all these complementary data constitute a solid range of converging clinical and scientific evidence supporting an increased risk of severe bacterial complications under NSAIDs. Moreover, Pottegard et al. have also recently observed in a nationwide population-based cohort study of patients with confirmed influenza or influenza-related pneumonia, an increased risk of pleuro-pulmonary complications for NSAID users [4].

In COVID-19 infection, the scarce published data on NSAIDs cited by Moore [5] has major flaws [6,7]. Rinott et al. did not observe an increase risk for mortality or the need for respiratory support in patients treated with ibuprofen [6]. This work is a retrospective cohort study without precise characterisation of groups, adjustements, and multivariate analysis leading to criticable results. More, authors concluded that no difference was statistically observed, whereas the percentage of participants admitted to the intensive care unit, mechanically ventilated, or died was higher in the case of ibuprofen intake, probably link with a lack of power. An another paper available on *medRxiv* and also never reviewed has identify medications associated with lower risk or morbidity with COVID-19 (including ibuprofen). A such work has also major bias leading to be more cautious with a such approach based only on a comparison of ranked electronic prescribing frequency among test-positive individuals requiring hospitalisation or not [7].

Recently, we conducted an assessment of pharmacovigilance reports suspecting the involvement of an NSAID in a more serious form of COVID-19 than expected. All of the reported cases had syndrome severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection complicated with pneumonia, some with acute respiratory failure requiring resuscitation. Among the latter, patients with NSAID intake for early symptoms of SARS-CoV-2 infection had different clinical characteristics (were younger, with less co-morbidities and more frequent progression to acute respiratory distress syndrome) from the resuscitation cases described by *Santé Publique France*. On the other hand, patients with chronic NSAID treatment had similar characteristics, with the possible over-risk associated with NSAIDs being at the margin compared to that inherent in the field [8].

The example of hydroxychloroquine reminds us of the basics of clinical pharmacology. As mentioned by

Funck-Brentano et al., the risks of cardiac adverse events associated with hydroxychloroquine during the COVID-19 pandemic were increased for several reasons (hypokalaemia, increase of interleukin-6, co-prescription with QT-prolonging drugs...) [9]. The characteristics of a disease (here COVID-19) including pulmonary and extrapulmonary manifestations (for review see Gupta et al. [10]) can modify the profile of adverse effects or their characteristics in terms of frequency or severity of a drug, even used for a very long time in another indication.

As consequence, a cautious approach should be followed with the initiation of NSAIDs for fever or cough related to COVID-19 due to the increased risk of the well-known adverse effects of NSAIDs in the specific setting of COVID-19 in addition to the possible risk of worsening the disease. The existence of a safer alternative (i.e., paracetamol at the recommended dose) makes this recommendation of common sense even more legitimate.

Disclosure of interest

The authors declare that they have no competing interest.

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Received 15 July 2020;
accepted 17 July 2020

https://doi.org/10.1016/j.therap.2020.07.008