Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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No arguments for extra risk from ibuprofen in SARS-COV2 infection

Keywords COVID-19; SARS-CoV2; Ibuprofen

Abbreviations

ACE	angiotensin converting enzyme
ACEI	ACE inhibitors
COVID	coronavirus disease
NSAIDs	non-steroidal anti-inflammatory drugs
SARS-CoV2	severe acute respiratory syndrome coronavirus 2

The use of ibuprofen use to alleviate fever and pain related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection was strongly discouraged by the French ministry of health, resulting in a more than 80% decrease in its use since the beginning of the pandemic.

The apparent bases for this decision were purported cases of severe coronavirus disease (COVID) in patients exposed to ibuprofen, that were never confirmed, and theoretical considerations [1]:

- that ibuprofen could upregulate angiotensin converting enzyme 2 (ACE2), a target of SARS-COV2, much as ACE inhibitors (ACEI) [2];
- that ibuprofen could mask signs of infection leading to later diagnosis, and worsen bacterial infections such as expected respiratory superinfection in COVID;
- reducing fever might increase the severity of viral infections.

Since the beginning of the SARS-CoV2 pandemic, however, it has appeared that:

- the effect of ibuprofen on ACE2 upregulation was suggested in a single study of a streptozotocin-induced diabetic cardiac hypertrophy model [2]. Exposure to ACEI did not increase the frequency or severity of the infection [3]. Upregulation of ACE2 might in fact result in fewer and less severe infections [4];
- the severe pulmonary disease in COVID is not due to bacterial superinfection but to a cytokine storm resulting in severe inflammation, which might be improved by low-dose dexamethasone (from the Recovery trial). In such circumstances, an anti-inflammatory effect might actually be beneficial;
- fever reduction in viral disease be it with ibuprofen or paracetamol does not alter the outcome of such infections.

In addition, the acute use of ibuprofen for symptom relief in SARS-COV2 positive patients was associated with the same risk of ventilation or death as paracetamol [5]. Chronic use of ibuprofen, naproxen or valacyclovir in patients tested positive for SARS-CoV2 was associated with a lower risk of hospital admission or artificial ventilation [6].

Authors also suggest a potentially increased risk of renal failure or thrombosis, neither of which is relevant in the context: the increased risk of renal failure has been shown to be dose dependent, and was not found at 1200 mg/day, the analgesic and antipyretic dose used to relieve symptoms of viral infection. The risk of thrombosis in COVID is essentially venous and intrapulmonary, related to the cytokine storm. A potential risk of myocardial infarction with non-steroidal anti-inflammatory drugs (NSAIDs) has been shown only for durations beyond 90 days and for full anti-inflammatory doses. Short term low dose use of ibuprofen has not been associated with excess coronary events compared to paracetamol [7].

There seems to be some confusion between the well-established risks of long-term high dose NSAIDs for chronic rheumatic diseases, and the acute, short-term use of low-dose ibuprofen for the symptomatic relief of pain and fever [8].

As for the use of hydroxychloroquine [9], a recommendation was based on anecdotal reports and theoretical bases which ended up being irrelevant or unproven. Unfortunately the effective suppression of ibuprofen has made impossible any further exploration of the potential benefits or risks of ibuprofen in the early stages of the SARS-CoV2 infection in France [10].

Disclosure of interest

The author declares no direct competing interests other than longstanding interest in the use of low-dose NSAIDs, including ibuprofen. He has given advice to various pharmaceutical companies concerning the risks of these low-dose NSAIDs over the years, including manufacturers of ibuprofen, naproxen, ketoprofen and diclofenac, in addition to celecoxib, rofecoxib, aceclofenac, and others.

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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