Does Ibuprofen Worsen COVID-19?

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In March 2020, the French authorities warned against the use of ibuprofen in patients with coronavirus disease 2019 (COVID-19) symptoms [1, 2]. This advice was based on unconfirmed anecdotal reports that severe COVID-19 cases had been exposed to ibuprofen [3] and on the theories described below. In particular, concern surrounded a possible increased expression of the angiotensin-converting enzyme (ACE)-2 receptor [4], which is the target for cell penetration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5]. This was reported on by the BMJ [6–8] and resulted in an 80% decrease in the use of ibuprofen in France [9]. The European Medicines Agency urged prudence [10]. The World Health Organization initially recommended not using ibuprofen, then relented [11]. Similarly, the Medicines and Healthcare products Regulatory Agency in the UK reversed their initial recommendation to avoid nonsteroidal anti-inflammatory drugs (NSAIDs) [12], concluding “There is currently no evidence that the acute use of NSAIDs causes an increased risk of developing COVID-19 or of developing a more severe COVID-19 disease.” The Italian Society of Pharmacology released a statement along the same lines [13]. Among all NSAIDs, ibuprofen was probably targeted because it is widely used and available over the counter (OTC), unlike other NSAIDs in France.

The bases for the French Ministry’s decision appear to be as follows:

1. A suggestion that ibuprofen might upregulate ACE-2, thereby increasing the entrance of COVID-19 into the cells [4, 14]. In a single study in streptozotocin-induced diabetic rats, ibuprofen decreased cardiac fibrosis [15]. We found no corresponding human study [16]. An increased risk of severe COVID-19 was noted in patients with hypertension or diabetes, and a possible role of ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and thiazolidinedione antidiabetic drugs, which also upregulate ACE-2, was suggested [4].

2. An analogy with bacterial soft-tissue infections, where patients receiving NSAIDs had more severe infections because of the immune-depressive actions of NSAIDs or belated treatment because of initial symptom suppression [6, 17–19].

3. Fever is a natural response to viral infection and reduces viral activity: antipyretic activity would reduce natural defenses against viruses.

However, the relevance of these assertions is unclear. The relevance of the upregulation of ACE-2 in the occurrence or severity of COVID-19 is disputed [20, 21]. Several studies found no impact from previous use of ACEIs or ARBs on COVID-19 frequency [22–24] and recommended against stopping ACEIs or ARBs [21, 25, 26]. In fact, ACE-2 upregulation might also limit the severity of COVID-19 infection [25, 27], and studies reported a lower death rate in patients using ACEIs [24].

The finding that ibuprofen might upregulate ACE-2 came from a single animal experiment in myocardial fibrosis in streptozotocin-induced diabetic rats [15]. If confirmed in humans, this upregulation would be related to chronic use of NSAIDs before the infection, in which case the upregulation might increase the risk of SARS-CoV2 penetration into the cells, causing COVID-19.

However, chronic use of NSAIDs was not associated with COVID-19 [22]. Chronic use of NSAIDs might even be protective against both the occurrence and the severity of COVID-19. A study of previous exposure to a range of medicines was conducted in 12,808 patients tested for SARS-COV-2 in five Massachusetts (USA) hospitals. In total, 2271 of these patients tested positive; 707 were admitted to hospital and 213 received artificial ventilation. Exposure to ibuprofen, naproxen, oseltamivir, or atenolol was associated with a lower risk of hospital admission,
and ibuprofen was also associated with a lower, albeit non-significant for lack of power, risk of artificial ventilation (odds ratio 0.47 [95% confidence interval 0.14–1.05]) [28].

In the acute use of ibuprofen or other NSAIDs for the symptomatic treatment of COVID-19, as discouraged by the French authorities, the hypothesis of an increased risk of infection would not apply: these patients are already infected. In addition, the timeframe of upregulation is unknown, so whether any upregulation exists at that point is uncertain. The effects of any upregulation after infection are also unknown. If ACE-2 upregulation also effectively mitigates COVID-19 symptoms, might using ibuprofen actually be beneficial?

An anti-inflammatory effect masking the early symptoms of infection resulting in belated antibiotic or other treatment is not applicable here: no treatment for the virus exists to be affected by masking symptoms. The disease itself is rather unusual in that even relatively severe pulmonary infection commonly remains mostly asymptomatic until sudden decompensation apparently related to a cytokine storm, an excessive immune reaction. In this context, immune suppression or reduction might in fact be beneficial [28], as has also been suggested for the use of corticosteroids [29, 30].

An antipyretic effect increasing the risk or severity of infection would apply equally to all antipyretic agents, including paracetamol. None of the reports about the use of ibuprofen in COVID-19 mention the use or not of paracetamol while discouraging the use of paracetamol while discouraging the use of ibuprofen might induce patients to use higher doses of paracetamol rather than adding ibuprofen for symptom control, increasing the risk of hepatic injury [31, 39–41], which might also be increased by COVID-19-related alterations of liver function [42–44].

At this point, there exist no scientific data to support an increased risk of SARS-CoV-2 infection or COVID-19 severity with ibuprofen. As for chloroquine [45], it is certainly time for a properly conducted study of the potential risks and benefits of ibuprofen in COVID-19 [46, 47].

A prospective randomized trial is probably not feasible given the current circumstances [48]. Studies of claims databases or medical records could capture previous chronic use of medicines but probably not the use of OTC drugs such as ibuprofen or paracetamol for symptom relief in the early stages of COVID-19. It might be appropriate to attempt a study (e.g., case–control study such as NCT04383899) in a cohort of patients newly diagnosed with COVID-19 to explore questions related to the early treatment of COVID-19 symptoms.

Data sharing Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with ethical standards

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