Does Ibuprofen worsen COVID-19 Disease?

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Header: ibuprofen and COVID-19

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Based on unoconfirmed anecdotal reports that severe COVID-19 cases had been exposed to ibuprofen (1) and on theoretical bases described below, especially a possibly increased expression of the ACEII receptor, (2) which is the target for cell penetration of SARS-CoV2, (3) the French authorities warned against its use in patients with COVID-19 symptoms (4); (5). This was reported on by the BMJ (6-8) and has resulted in an 80% decrease in the use of ibuprofen in France. (9) The European medicines agency urged prudence: (10). WHO initially recommended not using ibuprofen, then relented.(11). MHRA in the UK similarly reversed their initial recommendation to avoid 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 has put forth a statement along the same lines. (13)
Among all NSAIDs, Ibuprofen was probably targeted because it is widely used and available OTC, which is not the case of other NSAIDs in France.

The bases for the French Ministry's decision appear to be:
a) A suggestion that ibuprofen might upregulate ACE-2 thereby increasing the entrance of COVID-19 into the cells. (2, 14) There is a single study in streptozotocin-induced diabetic rats, where ibuprofen decreased cardiac fibrosis.(15) There seems to be no study in man. (16) An increased risk of severe COVID-19 was noted in patients with hypertension or diabetes, and a possible role of Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) which also upregulate ACE-2, as do also thiazolidinedione antidiabetic drugs, was suggested (2)
b) an analogy with bacterial soft-tissue infections where more severe infections on NSAIDs are attributed to an immune-depressive action of NSAIDs, or to belated treatment because of initial symptom suppression. (6, 17-19)
c) 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:
a) The relevance of the upregulation of ACE-2in the occurrence or severity of COVID-19 is disputed. (20, 21) Several studies have found no impact of the previous use of ACE inhibitors or ARB on COVID-19 frequency (22-25) and recommend against stopping ACE inhibitors or ARB. (21, 26, 27) In fact, ACE-2 up-regulation might also limit the severity of COVID-19 infection, (26, 28) and studies found a lower death rate in patients using ACE inhibitors (23, 25)
The finding that ibuprofen might upregulate ACE-2 came from a single animal experiment on myocardial fibrosis in streptozotocin-induced diabetic rats. (15) If it were confirmed in man, 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 found not to be associated with COVID-19 (22). Chronic NSAIDs might even be protective against both the occurrence of COVID-19 and its severity: a study of previous exposure to a range of medicines was done in 2271 SARS-COV2 positive patients, of 12808 tested patients in five Massachusetts hospitals. resulting in hospital admission in 707 and artificial ventilation in 213. Exposure to ibuprofen, naproxen,

oseltamivir or atenolol was associated with a lower risk of hospital admission. Ibuprofen was also associated with a lower, albeit non-significant for lack of power, risk of artificial ventilation (0R 0.47 [0.14-1.05]). (29)

In the case of the acute use of ibuprofen or other NSAIDs for the symptomatic treatment of COVID, as discouraged by the French authorities, the hypothesis of an increased risk of infection would not apply: the patients are already infected. In addition, the time-frame of the up-regulation is unknown, so it is not certain there is any up-regulation at that point. And the effects of any upregulation after infection is unknown. If effectively ACE-2 upregulation also mitigates COVID symptoms, using ibuprofen during COVID might actually be beneficial?

b) An anti-inflammatory effect masking the early symptoms of infection resulting in belated antibiotic or other treatment is not applicable here: there is no treatment of the virus that might 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, (29) as has also been suggested for the use of corticosteroids. (30, 31)

c) An antipyretic effect increasing the risk or the severity of infection would apply equally to all antipyretic agents including paracetamol. None of the reports of ibuprofen in COVID-19 mention the use or not of paracetamol before the infection or in the early symptoms, whereas this use is widespread. (32-34)

These findings raise the question of

An indication bias: more severe cases with more symptoms and higher fever might not respond well to the first line antipyretic paracetamol, so that ibuprofen would then be used (channeling). The same has been described with soft-tissue infection. (35) This may be compounded by a reporting notoriety bias, (36) where only cases that were exposed to ibuprofen are reported.

The reality of an increased risk of severe pneumonia in patients chronically on drugs that upregulate ACE-2, such as NSAIDs, ACEI or ARB has not been shown, and in fact upregulating ACE-2 might also have beneficial effects. (20, 21, 26) Prior use of ACEI either did not change or actually reduced the risk of death in patient with COVID-19. (22, 37)
In a study of the association of the exposure to ACEI or ARB and influenza, the risk of influenza was lower with ACEI or ARB, and this protection increased with the duration of use. (38) Pre-existing diseases which may also be worsened by long-term NSAIDs, such as hypertension or heart failure seem to increase the risk of mortality in COVID-19 (22, 23, 37, 39, 40),.

A public health decision based on a few anecdotal reports, and irrelevant experimental data may have deprived patients of an effective drug to control pain and fever. Encouraging 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, (32, 41-43) which might also be increased by COVID-19-related alterations of liver function. (44-46)

At this point there is no scientific data supporting an increased risk of SARS-CoV2 infection or severity. As for chloroquine,(47) it is certainly time for a properly conducted study of the potential risks and benefits of ibuprofen in COVID-19. (48, 49)
A prospective randomized trial is probably not feasible under the circumstances. (50) Studies in 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 NCT04383899) in a cohort of patients newly diagnosed with COVID-19 infection, to explore questions related to the early treatment of COVID-19 symptoms.

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Conflicts of interests
Nicholas Moore has provided expert advice to pharmaceutical companies and regulators concerning risks associated with low-dose NSAIDs and other analgesics, over the last 30 + years.
The other authors report no conflicts of interest

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