**Canadian Society of Pharmacology and Therapeutics**

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**Ibuprofen Use and COVID-19: What Do the Data Say?**

**A Position Statement Endorsed by the Canadian Society of Pharmacology and Therapeutics**

Michael Day's News Item in the March 17, 2019 issue of the British Medical Journal: *COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists* is alarming. This position statement will examine the concerns about ibuprofen use in patients with COVID-19 and what data what exist to support and refute these concerns.

Michael Day's News Item is not a scientific study.  Four patients in France are cited in this report.  Symptoms worsened after taking ibuprofen "in the early stage of their symptoms".  Worsening symptoms after the early stage of symptoms, removing the word ibuprofen, sounds like the infection is worsening, as expected.  The issue of protopathic bias is not discussed.  A professor from Toulouse cites the advice from the French Regulator (https://dgsurgent.sante.gouv.fr/dgsurgent/inter/detailsMessageBuilder.do?id=30500&cmd=visualiserMessage) not to treat fever or infections with ibuprofen, but provides no context. In essence, the advice from the regulator provides NO evidence for their decision.  Here is the text from the Regulator:   "Serious adverse events related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported in patients with COVID19, possible or confirmed cases. We remind you that the treatment of a poorly tolerated fever or pain in the context of COVID19 or any other respiratory virosis is based on acetaminophen, without exceeding the dose of 60 mg/kg/day and 3g/ day. NSAIDs should be banned. Conversely, patients on corticosteroids or other immunosuppressants for a chronic pathology should not interrupt their treatment, unless otherwise advised by the doctor who follows them for this pathology."

Perhaps this concern was attributed to the potential for ibuprofen to upregulate angiotensin converting enzyme two (ACE-2) receptor expression thereby increasing the entrance of COVID-19 into the cells, given this is the cell surface receptor of the virus (1, 2).   This is based on a single study in streptozotocin-induced diabetic rats, where ibuprofen decreased cardiac fibrosis(3). We could not locate a study in humans. An increased risk of severe COVID-19 in patients with hypertension or diabetes, and a possible role of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has been reported (1).  These drugs also upregulate ACE-2 receptors, as do thiazolidinedione antidiabetic drugs. The relevance of this up-regulation is disputed (4). Upregulation of ACE2 receptors may increase the risk of COVID-19 infection, but not necessarily its severity.  This increase in risk would only apply to the use of NSAIDs before the infection, i.e., from chronic exposure. This would be irrelevant to the infection once the patients are infected, and experience symptoms for which ibuprofen treatment in COVID-19 infection would be used. In fact, ACE2 receptor up-regulation might also limit the severity of COVID-19 infection (5).

Another risk assumption might be based on comparisons with bacterial soft-tissue infections where more severe infections in patients taking NSAIDs are attributed to an immunosuppressive effect of NSAIDs (6) or to belated antimicrobial treatment because of effective initial symptom suppression (7).  Anti-inflammatory effects masking the early symptoms of infection and therefore resulting in later antimicrobial use is not applicable here. There is no treatment of the virus that might be affected by masking symptoms.

Yet another concern relates to fever, a natural response to viral infection which reduces virus activity: antipyretic activity would therefore reduce natural defenses against viruses. Data do not as yet support this conclusion (8). The antipyretic effect increasing the risk or the severity of infection would apply equally to all antipyretic agents including acetaminophen. In fact, none of the reports on ibuprofen in COVID-19 mention the use or non-use of acetaminophen before the infection or in the management of early symptoms.

These findings raise further questions of indication bias, where more severe cases with more symptoms and higher fever might not respond well to the first line antipyretic acetaminophen, so that ibuprofen was then used. The same had been described with soft-tissue infections (9). This may be compounded by a reporting bias, where only cases that were exposed to ibuprofen are reported.

Two trials have examined the risk of ibuprofen exacerbating respiratory illnesses. In a randomized pragmatic trial of 889 patients, there were no apparent differences between the use of steam, acetaminophen or ibuprofen (10). There were 17 complications in the ibuprofen, ibuprofen/acetaminophen combined use and acetaminophen groups. None were serious and three could have been classified as repeat medical visits based on the baseline record. There were two complications in the acetaminophen group (one cellulitis, one otitis media); 11 in the ibuprofen group (one peritonsillar abscess, three sinusitis, one meningitis, one pneumonia, three new cases of otitis media, and two repeat visits with otitis media); and four in the combined group (one peritonsillar abscess, one new case of sinusitis, one repeat visit with sinusitis, one cervical adenitis). An observational trial examined the risk of myocardial infarction in patients with acute respiratory infection and NSAID use (11). The limitations of pharmacoepidemiological studies of this nature notwithstanding, the commentary that appeared in the same issue of the journal is important to read (12). Essentially, it points out that this widely-known cardiovascular harm effect places ibuprofen and naproxen as safer agents in the class but there is much more research that needs to be done. There was no mention of any effect of ibuprofen on the respiratory infection. Coronary risks have also been assessed more recently (13). Another study found no difference in the occurrence of myocardial infarction after first dispensing of ibuprofen or acetaminophen (14).

For fever control, acetaminophen may be the drug of first choice, even if it is not the best reducer of fever. There is no reliable measure of the effect in adults, and in children it is not much better than placebo (15). In children the tolerability and safety of acetaminophen and ibuprofen were not different from placebo (16). However, encouraging the use of acetaminophen while discouraging the use of ibuprofen might increase the risk of hepatic injury from acetaminophen. Acetaminophen is the prime drug associated with liver injury and transplantation, in voluntary or inadvertent overdose and at normal doses (17-20). This might be increased by COVID-19 related alterations in liver function (21-23). Early data suggests liver injury during COVID-19 infection appears to occur in 16-50 % of patients (24).

The safety of ibuprofen use could be further assessed in this pandemic. A possible interaction with acetaminophen should be tested, along with use based on the severity of symptoms. For ibuprofen and acetaminophen, because they are used over the counter often before even seeing a physician, and because the events of interest are probably rare, a prospective randomised study of the use of analgesia in patients starting COVID may not be feasible. A well-designed nested case-control study at admission, measuring antipyretic use and the sequence of analgesics used (e.g., was ibuprofen added because symptoms were severe?) and the outcomes on the severity of COVID-19 and/or hepatic injury would provide needed data. Considering the number of patients, this could be done simply and rapidly.

There is no good evidence to suggest that ibuprofen worsens COVID-19 at this time. Some people won't get relief of other symptoms with acetaminophen. We see no reason why they could not use ibuprofen at the present time, at the lowest possible dose for the shortest time period.

We will then be better able to find out what works, what doesn't, and just as importantly, what harms the patients we serve.

**Prepared by**

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