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.

[General Interest Commentary and Announcement]

CHEST

Safety of Ibuprofen in Patients With COVID-19

Causal or Confounded?

Mohit Sodhi, MSc
Mahyar Etminan, PharmD
Vancouver, BC, Canada

As the number of cases of COVD-19 continues to rise, the mainstay therapy for those with mild-to-moderate symptoms of COVID-19 remains to be supportive therapy, which includes use of analgesics such as ibuprofen.

Recent reports of a potential harm with ibuprofen in patients with COVID-19 has received significant international media coverage. The news started when an infectious disease specialist in France anecdotally reported four cases of children who took ibuprofen and experienced worsening symptoms of COVID-19 infection in her clinic.[1] This opinion was soon endorsed by the French Health Minister and the World Health Organization (WHO).[1,2] Other professional entities including the National Health Services and the British Pharmacological Society have taken a more balanced tone suggesting that patients use acetaminophen as the first drug of choice until more evidence is collected.[1] The WHO has now retracted their earlier warning against using ibuprofen.[3]

Given this issue will be in the minds of many for the near future, physicians need to have a picture of both the strength and quality of the evidence before they can make informed decisions regarding use of ibuprofen for patients with COVID-19.

Evidence on the Safety of Ibuprofen in Patients With COVID-19

The evidence behind this controversy comes anecdotally from an infectious diseases specialist in France who reported four cases of worsening symptoms of COVID-19,[1] which we could not identify in the published literature. The second source was a letter written by Fang et al,[4] where they claimed that ibuprofen may worsen associated symptoms in those infected with COVID-19. They argued that coronaviruses bind to angiotensin-converting enzyme-2, and ibuprofen administration can increase the bioavailability of angiotensin-converting enzyme-2, therefore potentiating and enhancing the infectious processes of coronaviruses.[4]

One needs to be cautious on drawing conclusions from evidence that is derived from mechanistic or theoretical pharmacology. There are a number of examples in the literature where evidence from mechanistic studies is not always corroborated with data from clinical trials. For example, some studies have shown that coadministration of ibuprofen with aspirin can counteract the antiplatelet effectiveness of aspirin when thromboxane levels are measured.[5] This hypothesis, however, was refuted in a large randomized controlled trial.[6]

Evidence on the safety of Ibuprofen in Respiratory Infections

Other investigators[7] have also advocated to not use ibuprofen based on previous studies that have shown negative outcomes among ibuprofen users. For example, a database study from France found that patients who had prehospitalization use of nonsteroidal antiinflammatory drugs for symptoms of community-acquired pneumonia developed more severe pneumonia and stayed hospitalized longer than nonusers.[8] Another study examined risk factors for complicated community-acquired infection in children.[9] Both ibuprofen (OR, 3.27; 95% CI, 1.11-9.65) and acetaminophen (OR, 2.68; 95% CI, 1.37-5.23) were identified as risk factors.[9]

AFFILIATIONS: From the Departments of Ophthalmology and Visual Sciences (Mr Sodhi and Dr Etminan), Medicine (Dr Etminan), and Pharmacology and Therapeutics (Dr Etminan), Faculty of Medicine, University of British Columbia.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Mahyar Etminan, PharmD, Department of Ophthalmology and Visual Sciences, Faculty of Medicine, The University of British Columbia, The Eye Care Center, Room 323, 2550 Willow St, Vancouver, BC V5Z 3N9, Canada; e-mail: etminanm@mail.ubc.ca

DOI: https://doi.org/10.1016/j.chest.2020.03.040

EDI 5.6.0 DTD ■ CHEST3029_proof ■ 11 April 2020 ■ 12:24 pm ■ EO: CHEST-20-1092

Epidemiologic studies that have identified ibuprofen with negative respiratory outcomes are subject to a number of biases. These biases include protopathic bias, where ibuprofen is used to relieve symptoms of a viral infection, including COVID-19, making it seem like ibuprofen is the culprit. Confounding by disease severity (also referred to as channeling bias) should also be considered in many of these studies, especially those which compared this risk with nonusers. Patients with more severe viral infections including influenza or COVID-19 are more likely to use a stronger antiinflammatory drug such as ibuprofen than acetaminophen. Therefore, a potential harmful outcome is more likely to be caused by a more severe infection for which ibuprofen is prescribed, rather than the drug.

Where Do We Go From Here?

Because a randomized trial would not be suitable to answer this question, a large population-based observational cohort or case-control study might be the ideal study design that can answer this question. However, having the ideal data source might be a challenge for this study because it needs to adequately address confounding, especially confounding by disease severity and measurement error (also referred to as misclassification of exposure), because many people use ibuprofen over the counter in addition to prescription medication.

In summary, the current epidemiologic evidence is not strong enough to infer a causal link of a harmful effect of ibuprofen in patients with COVID-19. Evidence from mechanistic studies alone should not be used to make strong statements against use of ibuprofen. Given the current strength of the evidence on this topic, we advise that patients use acetaminophen monotherapy for fever reduction in a patient with COVID-19, as per the WHO recommendations.[3] If acetaminophen alone cannot achieve its antipyretic effect, the current evidence is not sufficient to advise against coadministration of ibuprofen with acetaminophen; however, risk of adding ibuprofen should still be assessed against its benefits.

References

1. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ*. 2020;368:m1086.
2. Edmunds DR. World Health Organization backs call to avoid ibuprofen for coronavirus. The Jerusalem Post. https://www.jpost.com/HEALTH-SCIENCE/World-Health-Organization-backs-call-to-avoid-ibuprofen-for-coronavirus-621408. Accessed March 19, 2020.
3. Weikle B. WHO clarifies guidance on ibuprofen, says there's no evidence it can worsen COVID-19. CBC website. https://www.cbc.ca/news/health/ibuprofen-covid-19-novel-coronavirus-1.5501496. Accessed March 19, 2020.
4. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? [published online ahead of print March 11, 2020]. *Lancet Respir Med*. https://doi.org/10.1016/S2213-2600(20)30116-8.
5. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345(25):1809-1817.
6. Cryer B, Berlin RG, Cooper SA, Hsu C, Wason S. Double-blind, randomized, parallel, placebo-controlled study of ibuprofen effects on thromboxane B2 concentrations in aspirin-treated healthy adult volunteers. *Clin Ther*. 2005;27(2):185-191.
7. Messika J, Sztrymf B, Bertrand F, et al. Risks of nonsteroidal antiinflammatory drugs in undiagnosed intensive care unit pneumococcal pneumonia: younger and more severely affected patients. *J Crit Care*. 2014;29(5):733-738.
8. Kotsiou OS, Zarogiannis SG, Gourgoulianis KI. Prehospital NSAIDs use prolong hospitalization in patients with pleuro-pulmonary infection. *Respir Med*. 2017;123:28-33.
9. Krenke K, Krawiec M, Kraj G, Peradzynska J, Krauze A, Kulus M. Risk factors for local complications in children with community-acquired pneumonia. *Clin Respir J*. 2018;12(1):253-261.

EDI 5.6.0 DTD ■ CHEST3029_proof ■ 11 April 2020 ■ 12:24 pm ■ EO: CHEST-20-1092