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LETTER

INFECTIOUS DISEASES

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No current evidence supporting risk of using Ibuprofen in patients with COVID-19

Dear Editor

Severe Acute Respiratory Syndrome (SARS-CoV-2) is a novel RNA virus that infects cells expressing the angiotensin-converting enzyme (ACE2) receptor and is associated with an acute respiratory disease named COVID-19. It has been hypothesized that ACE2 expression can be increased by Ibuprofen leading to a higher risk for severe COVID-19.[1] Despite the reasonable mechanistic background and results from studies suggesting that Ibuprofen may be associated with complications of community-acquired pneumonia in children,[2,3] there is no current evidence that this NSAID aggravates a SARS-CoV-2 infection in any age group.

It is possible that potential negative outcomes related to patients using Ibuprofen to relieve respiratory symptoms are more likely to be observed due to a more severe infection rather than the drug, which is known as reverse causality bias.[4] In fact, the use of Ibuprofen and its effects on ACE2 expression in patients with SARS-CoV-2 infection remains an important and controversial issue. Despite animal models have found that Ibuprofen can enhance the ACE2 expression[5] and theoretically facilitate binding, internalization and viral infection, a recent paper[6] suggested that the mechanism of lung injury during the SARS-CoV-2 infection may be through inappropriate effects of excess free angiotensin-II protein as a consequence of ACE2 downregulation leading to overstimulation of AT1 receptor (AT1R), pulmonary vasoconstriction in response to hypoxia, increased vascular tone and subsequent hydrostatic oedema formation. Angiotensin-II is recognised to act as a powerful pro-inflammatory mediator through stimulation of AT1R[7,8] and has been implicated in the pathogenesis of acute respiratory distress syndrome (ARDS),[9] a condition commonly found in patients with critical COVID-19. Although it seems counter-intuitive, it has been suggested that a higher ACE2 expression followed by the use of AT1R antagonists may result to production of the vasodilator angiotensin 1-7 and protect against acute injury.[6] Therefore, in this hypothetical scenario, it is paradoxically reasonable to assume that Ibuprofen can have positive effects against SARS-CoV-2 if used in conjunction with AT1R antagonists. To date, there is more speculation than robust scientific evidence that points to the true effect of NSAIDs, especially Ibuprofen, on COVID-19. Therefore, further studies are urgently needed to verify if strategies to enhance ACE2 expression on cell membrane and the use AT1R antagonists can lead to a decrease in lung injury.

To date, there is no evidence supporting the association between Ibuprofen and increased risk of severity of COVID-19. We strongly recommend observational studies reporting data on cases of SARS-CoV-2 treated with Ibuprofen and its consequences. This will allow the adoption of an evidence-based practice.

DISCLOSURE

None.

Paulo Ricardo Martins-Filho[1]
Edmundo Marques do Nascimento-Júnior[1]
Victor Santana Santos[2]

[1]*Investigative Pathology Laboratory, Federal University of Sergipe, Brazil*
[2]*Centre for Epidemiology and Public Health, Federal University of Alagoas, Arapiraca, Brazil*

Correspondence
Paulo Ricardo Martins-Filho, Universidade Federal de Sergipe, Hospital Universitário, Laboratório de Patologia Investigativa, Rua Cláudio Batista, s/n. Sanatório, Aracaju, Sergipe, CEP: 49060-100, Brasil.
Email: martins-filho@ufs.br

ORCID

Paulo Ricardo Martins-Filho https://orcid.org/0000-0001-8779-0727

REFERENCES

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.
2. 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;12:253-261.
3. François P, Desrumaux A, Cans C, Pin I, Pavese P, Labarère J. Prevalence and risk factors of suppurative complications in children with pneumonia. *Acta Paediatr*. 2010;99:861-866.
4. Sodhi M, Etminan M. Safety of Ibuprofen in patients with COVID-19 Causal or confounded? *Chest*. 2020;158(1):55–56.
5. Qiao W, Wang C, Chen B, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. *Cardiology*. 2015;131:97-106.
6. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res*. 2020;81(5):537–540.
7. Marchesi C, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci*. 2008;29:367-374.
8. Suzuki Y, Ruiz-Ortega M, Lorenzo O, Ruperez M, Esteban V, Egido J. Inflammation and angiotensin II. *Int J Biochem Cell Biol*. 2003;35:881-900.
9. Imai Y, Kuba K, Penninger JM. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp Physiol*. 2008;93(5):543-548.

