Rapid Response:
Re: Preventing a covid-19 pandemic

Ibuprofen may be hazardous through augmentation of some effects of bradykinin in COVID-19 and some other infections

Dear Editor,

SARS-CoV-2 binds to the respiratory cells via the angiotensin-converting enzyme 2 (ACE2) receptor. In a recent report, it has been noted that ACE2 can be increased by ACE inhibitors and ARBs and, importantly, by ibuprofen [1]. Consequently, it has been hypothesized that treatment with ACE2-stimulating drugs including ibuprofen may increase the risk of developing severe and fatal COVID-19.

Notably, the World Health Organization (WHO) has very recently officially recommended avoiding ibuprofen for COVID-19 symptoms [2]. However, the European Medicine Agency (EMA) notes that there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID 19 and in line with EU national treatment guidelines, patients and healthcare professionals can continue using NSAIDs (like ibuprofen) as per the approved product information [3]. On the other hand, prior to the COVID-19 epidemic, in May 2019, EMA's safety committee has started a review of ibuprofen and ketoprofen following a survey by the French National Agency for Medicines and Health Products Safety suggesting that infection due to chickenpox and some bacterial infections could be made worse by these medicines [3,4].

In animal studies, in the setting of endotoxin inhalation, loss of ACE2 function in lung led to activation of the des-Arg9 bradykinin /bradykinin receptor B1 axis and subsequent release of proinflammatory chemokines from airway epithelia, increased neutrophil infiltration, and exaggerated lung inflammation and injury. It seems that a reduction in pulmonary ACE2 activity contributes to the pathogenesis of lung inflammation, in part because of exaggerated bradykinin signaling [5]. Bradykinin is a potent pro-inflammatory and vasodilator peptide and a component of the contact system has important pathophysiological role in septic shock in general [6].

Of note, ibuprofen has been noted to augment some effects of bradykinin in vivo [7]. We suggest that this effect may be a further and additional mechanism of ibuprofen's potentially adverse effect in COVID-19 infection and is to be investigated.

References

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