Response to the emerging novel coronavirus outbreak

Rapid Response:

Re: Response to the emerging novel coronavirus outbreak Angiotensin converting enzyme (ACE) inhibition may have role in the symptoms and progression of COVID-19 infection

Angiotensin converting enzyme (ACE) inhibition may have a role in the symptoms and progression of COVID-19 infection

Dear Editor,

The SARS-CoV-2 virus has been shown to use angiotensin-converting enzyme 2 (ACE2) for cell entry [1]. SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity and shift to predominant ACE/AngII/AT1 axis signaling. This activation of AngII system causes deleterious effects, including vasoconstriction, inflammation, fibrosis, cellular growth and migration and fluid retention [2]. In this regard, it has been shown that serum AngII levels in patients with COVID-19 were high and associated with viral load and lung injury [3].

The pulmonary ACE expression is subject to negative feedback by AngII, meaning that increased AngII causes decreased ACE mRNA levels in the lung and decrease in pulmonary ACE activity [4]. As so, the increased AngII causes physiological ACE inhibition. This translates that there seems to be some ongoing ACE inhibition during the COVID-19 infectious process. ACE inhibition also causes decreased break down of bradykinin as ACE is also known as kininase-II. The dry cough related to the treatment of antihypertensive ACE inhibitors (ACEIs) is attributed to accumulation of bradykinin [5,6]. We suggest that the dry cough, which is present in 59% at the onset of the COVID-19 disease [7], may be related to this physiological/pathophysiological process. Therefore, we suggest that continuing ACEIs treatment in COVID-19 infection may have some deleterious effect on the disease state and outcome through the increase in the bradykinin system. The agents demonstrating the ability to attenuate cough due to ACE inhibitors in small randomized, double-blind, placebo-controlled trials include inhaled sodium cromoglycate, theophylline, sulindac, indomethacin, the calcium-channel antagonists amlodipine and nifedipine, ferrous sulfate, and the thromboxane receptor antagonist picartamide [8] and may therefore have a place in the treatment.

Another point is that the accumulated bradykinins may also be associated with other symptoms/signs of the COVID-19 infection. Bradykinin is a well-known 9 amino acid peptide with potent pro-inflammatory and vasodilator properties via its G-protein-coupled receptors [9]. It is generated as a product of the contact system. The role and pathophysiological importance of the contact system has been considered undeniable in septic shock [10]. Reducing bradykinin levels and/or effects by antagonism have been shown to reverse hypotension animal models [11,12]. In humans, a bradykinin-2-receptor antagonist deliberant reduced mortality among patients with purely gram-negative infection with the systemic inflammatory response syndrome (SIRS) [13]. Hence, we suggest that bradykinin antagonism may be an area for future therapeutics for COVID-19 infection.

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