Comment on "ACE inhibitors and COVID-19: We don't know yet"

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Abstract

We read with great interest the article by Khashkhusha TR et al "ACE inhibitors and COVID-19: We don't know yet". The authors discuss whether the use of angiotensin-converting enzyme (ACE) inhibitors (ACEIs) in novel coronavirus disease-19 (COVID-19) patients is beneficial or harmful. ACEIs and angiotensin receptor antagonists (ARBs) both upregulate ACE2 levels. We believe that ARBs should be preferred since, unlike ARBs, ACEIs may increase angiotensin II through the chymase pathway. We would like to discuss potential harms ACEI may cause through secondary bradykinin-chymase pathways.

Dear Editor,

We read with great interest the article by Khashkhusha TR et al "ACE inhibitors and COVID-19: We don't know yet".[1] The authors discuss whether the use of angiotensin-converting enzyme (ACE) inhibitors (ACEIs) in novel coronavirus disease-19 (COVID-19) patients is beneficial or harmful. ACEIs and angiotensin receptor antagonists (ARBs) both upregulate ACE2 levels.[2] We believe that ARBs should be preferred since, unlike ARBs, ACEIs may increase angiotensin II through the chymase pathway. We would like to discuss potential harms ACEI may cause through secondary bradykinin-chymase pathways.

ACEI and ARBs are extensively prescribed for their proven beneficial effects. Their potential benefit or harm in COVID-19 patients is controversial. In some trials, morbidity and mortality seem better among users than non-users of these drugs but there is no head to head comparison between the groups.[3] ACEIs catalyze the transformation of angiotensin I to angiotensin II. When this pathway is inhibited angiotensin I is increasingly converted to angiotensin 1-9 which is an intermediate product and consequently converted to angiotensin 1-7.[4] Angiotensin 1-9 and angiotensin 1-7 both have vasodilator and anti-inflammatory properties.[4] Nevertheless, there is no concrete evidence that angiotensin 1-7 prevents acute respiratory distress syndrome.[2] Continuous infusion of angiotensin 1-7 is shown to have a vasodilating effect in female rats but not in males.[2] It is not clear whether the increase of ACE2 would have a beneficial effect through increased angiotensin 1-7. On the other hand, angiotensin II is found in increased amounts in COVID-19 patients with lung injury.[3] It is proposed that blocking of ACE2 by COVID-19 decreases the conversion of angiotensin II to angiotensin 1-7 with a resultant increase in angiotensin II levels.[3]

ACE blocking of ACEIs up-regulates ACE2 while down-regulates ACE.[5] Angiotensin I is not the only substrate for ACE; another among the others is bradykinin. Bradykinin is not a substrate for ACE2, thus, ACE inhibition increases bradykinin levels.[6] Increased bradykinin, in turn, leads to mast cell degranulation and chymase activation.[6] Chymase which converts angiotensinogen derived angiotensin 1-12 to angiotensin II is very active in heart, lung, and blood and produces angiotensin II independent of renin and ACE.[6] Angiotensin II is directly responsible for vascular endothelium, heart, and lung injury. Increased synthesis of angiotensin II, levels of which has already been increased by viral blockage of ACE2,[3] by augmented

chymase activity may further damage heart and lung tissue. We propose that ARBs should be chosen instead of ACEIs in COVID-19 patients.

Conflict of interests

The authors declare that there is no conflict of interests.

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