Should ACE inhibitors and angiotensin II receptor blockers be stopped for COVID-19?

This write-up summarises a rapid evidence review related to COVID-19. The information may be revised as new evidence emerges.

Background

Two recent articles by Madeddu in the British Medical Journal (BMJ) and Fang *et al*. in the Lancet Respiratory Medicine have raised concerns about angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin II receptor blockers (ARB) potentially increasing the risk of COVID-19 and related respiratory distress syndrome.[1,2] The authors hypothesise that angiotensin-converting enzyme 2 (ACE2) is upregulated in patients treated with ACE-i or ARB, which would facilitate COVID-19 infection as ACE2 is a functional receptor of the virus.[3] Madeddu maintains that ACE-i and ARB should not be suspended due to the lack of epidemiological data,[1] and Fang *et al*. suggest that patients with cardiac disease, hypertension, or diabetes currently under treatment with ACE-i or ARB should be monitored for these medications.[2]

Clinical evidence

No published clinical trials reporting the effects of ACE-i or ARB on COVID-19 have been identified. The available literature pertaining to this topic consists of opinion pieces, observational, and laboratory studies. Evidence on the effects of ACE-i or ARB on ACE2 is scarce.

- Animal studies provide mixed results on upregulation of ACE2 in cardiac cells with ACE-i or ARB, with some showing increased ACE2 levels[4,5,6] and others observing no difference.[7,8]
- In humans, two studies in patients with atrial fibrillation or obstructive coronary heart disease showed no difference in plasma ACE2 levels between those taking ACE-i or ARB and those not taking these medications.[9,10]

In a large Chinese cohort of almost 45,000 patients with COVID-19, 17% of those with recorded medical history had cardiovascular comorbidities, including hypertension.[11] The case fatality risk of these COVID-19 patients with cardiovascular comorbidities was 7% (unadjusted for age),[11] while ACE-i and ARB use in these patients was not reported. In addition to cardiovascular comorbidities aggravating COVID-19 pneumonia, detrimental effects on the cardiovascular system from antiviral drug use may precipitate worsening of the infection and mortality.[12]

Genotypic distribution of ACE polymorphism has also been suggested to be associated with increased susceptibility to COVID-19 infection[2] as well as related respiratory distress syndrome and mortality,[1] based on the association between ACE insertion/deletion (I/D) polymorphism and mortality observed in a case series of patients with acute respiratory distress syndrome.[13] However, in a case control study of patients with severe acute respiratory syndrome (SARS) infection and healthy volunteers, there were no significant differences in genotypic distribution and allelic frequencies of ACE I/D polymorphism between the SARS patients and healthy volunteers, and ACE I/D polymorphism was not associated with acute respiratory distress syndrome or the need for intensive care in the SARS patients.[14]

Studies regarding SARS hypothesised that the infection would result in downregulation of ACE2, through binding of the virus with ACE2. As ACE2 has a protective role in severe lung failure, the downregulation due to SARS infection is thought to contribute to the severity of the disease.[15,16]

In a case series of patients admitted with viral respiratory infections (most common viral pathogens in the study were rhinovirus, influenza A, and respiratory syncytial virus), lower risks of intubation and death were associated with continued use of ACE-i during hospitalisation, having adjusted for factors including age and coinfection.[17]

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Recommendations from professional bodies

Internationally, major professional bodies have issued statements to recommend the continuation of ACE-i and ARB in the context of COVID-19, including the European Society of Hypertension, the Renal Association UK, as well as the American Heart Association, Heart Failure Society of America, and American College of Cardiology. Some professional bodies have added that the decision to change should be made on a case-by-case basis for patients who are severely ill from COVID-19.

Conclusion

Currently, there is no clear evidence that ACE-i or ARB increase the susceptibility to or severity of COVID-19.

- ACE-i and ARB are established, life-saving treatments for patients with hypertension or other chronic conditions. Discontinuing these medications could result in adverse patient outcomes, such as worsening heart failure, without a known benefit or risk on COVID-19.
- Switching medications also comes with practical issues, such as the need for additional clinic visits, thereby increasing the patient's exposure to areas of higher infection risks and workload of the already busy healthcare system.
- ACE-i and ARB use should be reviewed for patients with COVID-19 who develop complications such as sepsis or organ failure.
- Research is underway to shed more light on this topic, with two randomised controlled trials being conducted in patients with COVID-19 to assess the effects of losartan.[18,19]

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