ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Beatrice S. Vicente Pascual, MD

Introduction

The Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor Blockers (ARB) are indicated for hypertension, congestive heart failure and kidney diseases. They reduce the vasoconstrictive, proinflammatory and pro-oxidative effects of angiotensin II (Ang II) levels of the renin angiotensin system (RAS).[1,2]

Mechanism of Action

The RAS pathway begins when renin breaks down angiotensinogen to Angiotensin I (Ang I). The cleaving of Ang I to angiotensin II (Ang II) is facilitated by Angiotensin converting enzyme (ACE) (Figure 3). The activation of Type 1 angiotensin II receptor (AT1R) by Ang II, increases sympathetic tone, vasoconstriction, elevation in blood pressure, inflammation, fibrosis, and cardiac hypertrophy.[2,3]

The counter-regulatory mechanisms of the RAS occur by activating the angiotensin converting enzyme 2 (ACE2) – angiotensin 1-7 (Ang1-7) – Mas proto oncogene receptor (MasR pathway). This pathway (ACE2/Ang1-7/MasR) is activated by (ACE2) which hydrolyzes Ang II and generates (Ang1-7). The binding of the Ang I-7 to the MasR causes vasodilation, decrease in blood pressure, helps maintain homeostasis and has an anti-inflammatory effect.[2, 4.]

The ACE2 is a membrane bound aminopeptidase with a homologous structure to ACE but with distinct enzyme active sites.[5,6,7]

Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor Blockers (ARB) facilitate this counter-regulatory pathway of the RAS.[8] Angiotensin Converting Enzyme Inhibitors (ACEI) prevents the conversion of Ang I to Ang II.[9] Angiotensin II Receptor Blockers (ARB) prevents Ang II from binding to Ang II receptors on the muscles surrounding blood vessels.[9]

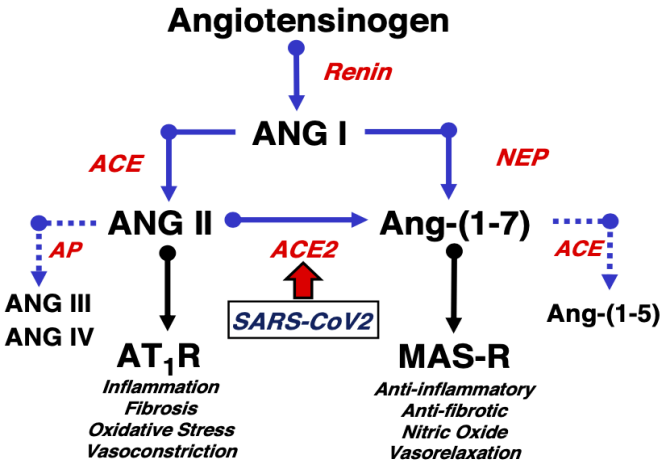

Figure 3. Processing and Functional scheme of the Renin-Angiotensin system [4]

Effect on COVID-19

The ACE2 is a known co-receptor of SARS-COV2 to gain viral entry into the target epithelial cells of the lungs, intestines, kidneys, heart, and blood vessels.[6,7]

Experimental studies have shown that SARS-CoV cause lung injury through downregulation of the lung ACE2 and in turn, shifts the balance toward the dominance of the RAS over the ACE2/Ang1-7/MasR system in the lung. As a result, noncompeting ANG II accumulation occurs, resulting in acute lung injury through AT1R activation.[10]

RAS modulation with ACEI/ARB or recombinant ACE leads to increased expression of ACE2. Hypothetically, this could increase the viral load and possibly worsen the clinical outcome of COVID-19 patients. Human studies, however showed a lack of association between increased ACE2 protein expression and the use of ARBs or ACEIs.[11] The evidence of ACE2 upregulation is limited only to animal studies using relatively high doses of several ARBs and one ACEI.[4]

Clinical Studies

Studies are ongoing on the benefits vs the risks in the utilization of ACEI/ARB among patients with cardiovascular disorders infected with COVID-19. (Appendix 5)

Recommended Dose[11]

Drug	Initial Dose adult dose	Maximum Dose adult dose
Angiotensin II Receptor Blockers		
Losartan	50 mg	100 mg
Valsartan	80 mg	320mg
Angiotensin Converting Enzyme Inhibitors		
Lisinopril	10 mg	40 mg
Ramipril	2.5 mg	20 mg
Enalapril	5 mg	40 mg
Captopril	50 mg	450 mg

Adverse Effects: [9]

Some of the common adverse effects of ACEI are cough, hyperkalemia, hypotension, kidney failure, pancreatitis, allergic reactions, angioedema.

The ARBs on the other hand may cause hyperkalemia, cough, hypotension, dizziness, headache, drowsiness, metallic taste, kidney failure, liver failure and allergic reactions.

Conclusion

We have to continue to monitor the ongoing studies on the benefits vs. the risks in the utilization of ACEI/ARB among patients with cardiovascular disorders infected with COVID-19. Scientific societies in the US and Europe namely American Heart Association, American College of Cardiology, Heart Failure Society of America, Council on Hypertension of European Society of Cardiology have stated that (in patients with COVID-19) these agents should be maintained in those using them rather than withdrawing these drugs until studies are completed.[12,13]

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