Short Commentary

Is the “respiratory stimulant, Acetazolamide” add-on therapy suitable to relieve mild respiratory insufficiency in stable COVID-19 out/inpatients?

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) and its related disease, COVID-19 is terribly spreading to 202 countries, areas or territories. Till March 29th, 2020 the values of confirmed cases and total deaths were more than 575,000 and ~ 26,500. Due to epithelial injury, as a critical event both in early stages of the disease and specifically in the development of acute respiratory distress syndrome (ARDS), patients encounter rapid vasoconstriction in the pulmonary circulation, followed by ventilation/perfusion mismatch. Acetazolamide-mediated carbonic anhydrase (CA) inhibition may attenuate the effects of hyperventilation-induced respiratory alkalosis. The evidences on chronic obstructive pulmonary disease (COPD) and acute mountain sickness (AMS) support our proposition that low doses of acetazolamide appear to stimulate ventilation in stable patients with COVID-19.

Key Words: COVID-19; CA inhibition; Acetazolamide; respiratory insufficiency

Dear Editor

Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) and its related disease, COVID-19 is terribly spreading to 202 countries, areas or territories. Till March 29th, 2020, the values of confirmed cases and total deaths were more than 575,000 and ~ 26,500 (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>). Liu et al classified patients as severe cases who had any of the following features at the time of, or after, admission (1) respiratory distress (≥ 30 breaths per min); (2) oxygen saturation at rest $\leq 93\%$; (3) severe disease complications (e.g., respiratory failure, requirement of

mechanical ventilation, septic shock, or non-respiratory organ failure) [1]. Of ~ 575,000 laboratory-confirmed patients, statistically ~5% have critical illness and almost 50% of critically ill patients have died/or may be expired [2]. Although there is no known treatment for any coronavirus infection, investigators around the globe have undertaken several clinical trials.

Respiratory insufficiency in stable patients and acute respiratory distress syndrome (ARDS) which is frequently associated with multiple organ dysfunctions leading to high mortality), are important clinical features of COVID-19. Recently, a valuable report in the Lancet has introduced important clinical characteristics in patients with COVID-19 pneumonia who developed ARDS [3]. It appears that the mechanisms underlying ARDS are multi-factorial. The renin-angiotensin system (RAS), as one of determinant factors, includes angiotensinogen, angiotensin-converting enzyme (ACE) and also angiotensin converting enzyme 2 (ACE2), and angiotensin II (Ang II) type 1 and type 2 receptors. ACE produces the octapeptide Ang II, while ACE2 cleaves a single residue from Ang II to generate Ang 1-7, which in turn blocks Ang II and inhibits ACE [4]. Great attention has been recently focused on the understanding the pathophysiological role of the RAS in lung for SARS and chronic obstructive pulmonary disease (COPD). Only 20% of capillary endothelial cells in all other organs express ACE, while it is expressed in entire capillary network of the alveoli in human lung [5], resulting in readily conversion of Ang I to Ang II in the lung pulmonary vessels. On the other hand, ACE2 is primarily produced in Clara cells and type II alveolar epithelial cells [6]. In COVID-19, the alveolar epithelial cells with ACE2 on their surfaces are the main target of SARS-CoV-2. At these conditions, due to epithelial injury, as a critical event in the development of ARDS, the ability to produce ACE2 is severely impaired. Therefore, upon dominant ACE activities during ARDS and/or ventilator-induced lung injury, patients encounter rapid vasoconstriction/low blood flow in the pulmonary circulation, followed by ventilation/perfusion mismatch (tissue hypoxia) [7].

Experimental studies had shown/proposed that some drugs (may) improve outcomes in both experimental acute lung injury and ARDS. For instance, angiotensin II receptor blockers (ARBs) and statins upregulate the activity of ACE2 [8]. The use of ARBs and statins may be like a double-edged knife and can exacerbate the disease due to the up-regulation

of ACE2 on the alveolar epithelial cells (and increasing chance of infection). Recall that ACE2 is also the receptor for the SARS-CoV-2 [9]. The use of Ang II receptor blockers or ACE inhibitors has been shown to be effective in decreasing lung injury in animal models, but systemic hypotension may be a potential side effect. Recombinant ACE2, as a potential therapeutic approach, may protect the lung from developing ARDS (and acts as a free coronavirus receptor and reduces chance of host cell-nCov interaction) [4]. A phase II trial showed that administration/infusion of a recombinant ACE2 was safe without causing significant hemodynamic changes and led to rapid decrease in plasma Ang II levels, but this pilot study needs further large trials to deeply assess clinical outcomes [10].

Drug repositioning (also called drug repurposing) – the investigation of existing drugs for new therapeutic purposes – is one line of scientific research which is followed to develop safe and effective treatment for COVID-19 (and associated complications such as respiratory insufficiency). Generally, (hydroxy)chloroquine and Kaletra (lopinavir-ritonavir) are considered as standard of care in both out-patients and hospitalized COVID-19 patients. Add-on therapy or adjuvant care is therapy that is given in addition to the primary/initial therapy to maximize its effectiveness or to relieve the (serious) disease-associated discomforts such as dyspnea, the medical term for shortness of breath. Dyspnea, hypoxia (or >50 percent lung involvement on imaging within 24 to 48 hours) has been reported in 14% of severe COVID-19 cases (<https://www.uptodate.com/contents/coronavirus-disease-2019-COVID-19>).

Acetazolamide, a potent/classic carbonic anhydrase (CA) inhibitor, is the most commonly used and standard medical prophylaxis agent for the amelioration of acute mountain sickness (AMS) and high altitude pulmonary edema (HAPE), although additional trials on the drug are still running to find more efficacious protocols [11]. According to Leaf and Goldfarb report, at high altitude, reduced barometric pressure and reduced “partial pressure of inspired oxygen” result in hypoxemia, which drives minute ventilation [12] (minute ventilation or minute volume is the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from the lungs per minute). Hyperventilation causes a respiratory alkalosis that limits the rise in ventilation and leads to symptoms of AMS. Although, the actual mechanisms by which acetazolamide reduces symptoms of AMS

remain unclear, its efficacy has been attributed to inhibition of renal CA, resulting in bicarbonaturia, followed by metabolic acidosis. By this mechanism of action, acetazolamide is able to attenuate the effects of hyperventilation-induced respiratory alkalosis and allows the chemoreceptors to respond more sufficiently to hypoxic stimuli at altitude [12]. Also, acetazolamide has been indicated to **a)** counteract periodic breathing during sleep [13, 14], **b)** significantly increase minute volume at high altitude (>4000 m) by as much as 50% relative to controls, **c)** improve arterial PO₂ (PaO₂), and oxyhemoglobin saturation and increase average arterial O₂ saturation (SaO₂ from 72 to 79%) during sleep [12, 15-18].

Moreover, respiratory failure is a common consequence of chronic obstructive pulmonary disease (COPD). Apparently, based on clinical trials (for instance: [19]), acetazolamide can be used effectively but cautiously in patients with mild to moderate COPD to stimulate ventilation and improve arterial oxygenation, particularly when supplemental oxygen cannot be provided. A number of studies on stable COPD patients have shown that acetazolamide (at 250 to 500 mg dosing) increases arterial PO₂ by 4-8 mmHg, and decreases pH by 0.04-0.07, PaCO₂ by 3-7 mmHg and HCO₃ by 6-9 mM [20-22]. Teppema and Dahan showed that the minor increase in ventilation of COPD patients will be sufficient to cause a considerable rise in arterial PO₂ (unless this is prevented by the presence of many lung regions with extremely low ventilation-perfusion ratios) [23]. Additionally, prescribing acetazolamide or any other available CA inhibitor as a respiratory stimulant for patients with COPD (with/without hypercapnia) should be done carefully; because patients with severe COPD (and COVID-19 as well) may be unable to increase ventilation in response to the acetazolamide-mediated metabolic acidosis. Furthermore, due to erythrocyte CA inhibition by acetazolamide, critically ill patient may encounter severe CO₂ retention, especially when drug clearance decreased due to severe (or even mild) renal insufficiency [20]. Low doses of acetazolamide (< 200 mg or 2.5 mg/kg) appear to be sufficient for complete renal CA inhibition to stimulate ventilation, because a secretory mechanism greatly concentrates the drug in urine and renal tissue [24]. The end-stage COPD patients that are more prone to develop acid-base disorder [25] may be excluded from this intervention.

Heming et al. believe that acetazolamide is relatively safe drug in ICU, with rare undesirable effects and reversal of post-hypercapnic alkalosis, as a complication of mechanical ventilation, by this drug may facilitate weaning from mechanical ventilation of patients with COPD [26]. In another work, Faisy and colleagues reported that the drug used at the dosage of 500 mg per day reduces metabolic alkalosis but has no benefit in terms of improving PaCO₂ patients with COPD [27]. Recently, Hudalla et al suggested a new therapeutic effect of acetazolamide against pulmonary arterial hypertension (see also above; ARDS mechanism) [28]. They suggest that protective anti-inflammatory effect of acetazolamide in pulmonary hypertension is mediated by a dual mechanism of macrophage carbonic anhydrase inhibition and systemic metabolic acidosis.

According to WHO interim guidance, “fast breathing (like breathing at altitude)” and “respiratory rate > 30 breaths/min; severe respiratory distress; or SpO₂ ≤ 93% on room air” are most common clinical features associated with mild and severe types of COVID-19, respectively [29]. However, these manifestations of hospitalized COVID-19 patients “the serious shortness of breath and acute hypoxemic respiratory failure or ARDS, requiring oxygen and ventilation therapies” have been frequently reported by different research groups [30, 31]. In Meng et al. study [32], approximately 3.2% of patients required intubation and invasive ventilation at some point in the disease course. On the other hand, about 30% of non-survivor patients (with/without non-invasive or invasive mechanical ventilation) and only 1% of survivor COVID-19 patients had acidosis outcome [33]. In another study, acidosis was classified as less common complication, even in deceased patients; actual bicarbonate and total CO₂ concentration were lower in deceased patients than in recovered patients (actual bicarbonate: 20.5 mM vs. 22.9 mM) [34]. So, it is anticipated that acetazolamide administration for stable outpatients (and hospitalized COVID-19 patients as well) leads to “respiratory distress relief” with no additional serious acid-base complications.

In summary, COVID-19 critically ill patients with severe ARDS may be unable to increase ventilation in response to a respiratory stimulant. The use of acetazolamide in such patients may expose them to all its adverse effects with no proper respiratory compensation. But low doses of acetazolamide (< 200 mg or 2.5 mg/kg) appear to be

sufficient for complete renal CA inhibition to stimulate ventilation in stable patients. Although direct targeting of nCoV-19 by anti-viral drugs [35] is of great importance, in agreement with “Pirofski and Casadevall” point of view, we must emphasize that the host response is a major determinant of the pathogenesis of infectious diseases such as COVID-19 [36]. We believe that investigators should undertake studies on patients with 2019-nCoV infection to determine whether targeting the host macromolecules/enzymes (and host responses as well) with available/inexpensive add-on drugs, like acetazolamide, will improve their chances of survival. However, the above speculation is presently at hypothesis level. It needs rigorous validation by proper trial studies.

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