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POTENTIAL ROLE OF SILDENAFIL CITRATE IN THE TREATMENT OF COVID-19 INFECTION

Ahmed M. Abbas[1,2]* and Shimaa Salah Ali[2,3]

[1]Department of Obstetrics & Gynecology, Faculty of Medicine, Assiut University, Egypt.
[2]Covid-19 Research of Assiut University Association (Corauna).
[3]House Officer, Faculty of Medicine, Assiut University, Egypt.

***Corresponding Author: Ahmed M. Abbas**
Department of Obstetrics & Gynecology, Faculty of Medicine, Assiut University, Egypt.

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The emergence of coronavirus disease-2019 (COVID-19) pandemic resulted in extreme demand for treatment. Nevertheless, it requires a relatively long time to approve new drugs to be used on humans. Therefore, researchers are reconsidering already approved drugs to be used in the treatment of COVID-19. This review summarizes the promising effect of sildenafil citrate as a potential treatment of COVID-19.

A common cause of respiratory insufficiency is acute respiratory distress syndrome (ARDS), which requires mechanical ventilation and ICU admission.[1] Respiratory distress is characterized by pulmonary edema, atelectasis, and a ventilation-perfusion mismatch; thus, hypoxemia occurs. Hypoxia leads to constriction of pulmonary arteries, a disorder is known as vasoconstriction in the hypoxic lung.[2] Pulmonary microvasculature thromboembolic occlusions, increased production of vasoconstrictive agents as endothelin-1 and thromboxane A2, and pulmonary edema further increase pulmonary hypertension.[3]

Nitric oxide (NO) Inhalation dilates the pulmonary vessels and increases the perfusion of ventilated lung areas, so improves the oxygenation of patients with ARDS.[4] However, many patients seem to be unresponsive. Simultaneously, NO inhalation as adjunctive therapy in such conditions is not devoid of side effects and could impair the renal function.[5] Nitric oxide's pulmonary vasodilating effects are regulated by its second messenger, the cyclic guanosine monophosphate (cGMP), which is rapidly degraded by phosphodiesterases (PDE). The predominant phosphodiesterase isoform of the lung which metabolizes cGMP is Phosphodiesterase type 5, and which is up-regulated in pulmonary hypertension-related conditions.[6]

Sildenafil citrate (SC) promotes intracellular cGMP accumulation by selectively inhibiting PDE type 5 and thus increases nitric oxide-mediated vasodilation; it may also have anti-proliferative effects on pulmonary smooth muscle cells.[7] Consequently, inhibition of PDE in ARDS may replace inhalational NO therapy. Phosphodiesterase inhibitors have shown beneficial effects in experimental ARDS by attenuating the vasomotor dysfunction caused by endotoxin. In addition to affecting vasoreactivity, PDE inhibitors also have anti-inflammatory effects, reducing pulmonary edema, infiltration of neutrophils, reactive oxygen species, and levels of pro-inflammatory mediators in experimental acute lung injury.[8]

These preclinical findings show a possible therapeutic effect in ARDS by inhibition of PDE. SC inhibits the cGMP-specific isoenzyme PDE type 5 (PDE5) selectively.[9] It has been shown that SC increases the exercise ability in healthy volunteers during extreme hypoxia and enhances gas exchange in patients with pulmonary hypertension by selectively dilating arteries in well-ventilated lung areas.[10]

There are varying rates of the severity of the symptoms in the novel coronavirus disease-2019 (COVID-19) pandemic, from asymptomatic to life-threatening forms. As recently reported, elevated rates of infection-related biomarkers and inflammatory cytokines (such as IL-6), neutrophilia, and lymphocytopenia (as well as low CD3 + and CD4+T-cell counts) tend to correlate with the most serious cases of Infection.[11] Along with COVID-19 Infection, there are several clinical factors significantly associated with higher risks of ARDS and death. Recent studies have reported a clear association between the extent of Infection induced by COVID-19 and the prevalence of hypertension.[12] Several studies have shown a clear association between hypertension and NO as high blood pressure is a pathological disorder characterized by endothelial dysfunction in which NO availability is compromised by increased concomitant IL-6 release by the defective endothelium.[13]

COVID-19 may cause a more severe cytokine storm (with very high IL-6 but low T cells) in patients with higher basal cytokine levels (i.e., IL-6) and lower NO levels. Starting from these considerations and concentrating on IL-6 and NO, we can postulate the potential role of phosphodiesterase type 5 inhibitors (PDE5-I), such as SC, in increasing NO levels. The function of PDE5-I in anti-viral therapy has already been tested, demonstrating an inhibiting function in the replication of coronavirus.[14] Considering the biochemical mechanisms involved in COVID-19 Infection and previous observations supporting the off-label usage of SC as an anti-viral drug, consideration should be given to a potential synergistic role of PDE5-I as an early complementary drug in treating COVID-19 Infection. If the therapy efficacy has been shown, more efficient prophylaxis will alter the evolution of this new pandemic disease.

Conflict of interest: The authors state that there are no conflicts of interest.

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