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Is it possible to use Proton Pump Inhibitors in COVID-19 treatment and prophylaxis?

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ABSTRACT

Coronaviruses (CoV), discovered after 1960, caused human life-threatening outbreaks. SARS-CoV2, which appeared in Wuhan, China in December 2019, causing Severe Acute Respiratory Syndrome and has different features than other coronaviruses, has been determined and the disease caused by the virus has been called "Coronavirus Disease-2019" (COVID-19). This disease activates both the natural and acquired immune system. The cytokin storm, in which blood levels of proinflammatory cytokines are detected excessively high is developing and the uncontrolled inflammatory response causes local and systemic tissue damages. Although a spesific drug has not been found yet, the medications currently in use for other indications, whose pharmacokinetic-pharmacodynamic properties and toxic doses are already known; are included in the treatment practice of COVID-19. These drugs affect the entry of the virus into the cell and its intracellular distribution. They also have anti-inflammatory and immunomodulating effects too. Therefore, we think that Proton Pump Inhibitors (PPI's) with similar mechanisms of action may also be involved in COVID-19 treatment and prophylaxis.

Introduction

Coronaviruses (CoV), were discovered after 1960 and have recently been brought to the agenda with outbreaks such as "Severe Acute Respiratory Syndrome" (SARS) and "Middle East Respiratory Syndrome Coronavirus" (MERS-CoV) that threaten human life [1,2].

In December 2019 Wuhan, China, a new CoV infection epidemic started with the appearence of the first cases with severe respiratory failure symptoms and World Health Organization (WHO) reported that the pandemic process started in March 2020 [3]. This new virus has been named as Severe Acute Respiratory Syndrome virus 2, (SARS-CoV2) since it has different features than other coronaviruses. The viral disease also has been named Coronavirus Disease-19 (COVID-19) [4].

COVD-19 activates both natural and acquired immune system. The problem with the infection process is the tissue damage caused by uncontrolled inflamatory response and impaired acquired immune response. Lymphopenia, especially characterized by the decline of CD8+ and CD4+ T lymphocytes, B lymphocytes and natural killer (NK) cell; is a common laboratory sign of patients with severe COVID-19 [5]. Increased neutrophil count and elevated neutrophil/ lymphocyte ratio are indicative of poor prognosis [6].

In most severe cases of COVID-19, cytokin storm develops in which blood levels of proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-8 (IL-8), interleukin-17 (IL-17), granulocyte macrophage coloni stimulating factor (GM-CSF) and tumor necrosis factor (TNF) are detected excessively high. High cytokine levels may result in shock, myocardial damage, liver and kidney damage, respiratory failure and ultimately multiple organ failure. Cytokines are also responsible for pulmonary pathology, characterized by intense neutrophil and macrophage infiltration, diffuse alveolar damage with hyalen membranes diffuse thickening in the alveolar wall [7,8].

Although a specific drug has not been found yet, the medications currently in use for other indications, whose pharmacokinetic – pharmacodynamic properties and toxic doses are already known; are included in the treatment practice of COVID-19 [9]. Antiviral compounds that inhibit the enzyme systems or the entry of the virus into the cell and the immunomodulatory drugs to reduce cytokine storm induced lung damage, are predicted to be effective for COVID-19 [10]. Pantoprazole has been previously approved by Food and Drug Administration (FDA) as an autophagy modulator in various diseases and is currently being researched as one of the candidate molecules for COVID-19 therapy [11,12]. For this reason, the scientific communities are working intensively on the drugs that can be useful for the treatment of this new disease, by considering the viral mechanism, where experience

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is insufficient.

In this article, we aimed to discuss the potential role of PPI's in the treatment and prophylaxis of COVID-19, which we believe to have activities similar to those used for this disease.

The hypothesis

Basically, hydroxychloroquine (HCQ), a molecule used in the treatment of infectious and rheumatological diseases, is among the main treatment options of COVID-19. Weak basic HCQ accumulates in organelles of acidic content, golgi vesicles, endosomes and lysosomes, raising their pH. The virus-endosome junction, which will ensure the release of viral particles into infected cells, depends on the activation of endosomal proteases in an acidic environment. HCQ prevents viral spread to cells by disrupting this acidity [13–15]. HCQ also acts through the toll-like receptor (TLR) signal pathway. Changes in endosomal pH affect TLR7 and TLR9 processing. Therefore, HCQ suppresses TLR signal activation by making changes in local pH. Although HCQ's mechanism of action on the immune system is not precisely enlightened, it is known that HCQ provides suppression in cytokine production via signal pathways and modulation in some co-stimulating molecules [16]. The immunomodülationg feature is also used in the treatment of COVID-19. HCQ; inhibits the production of cytokines such as IL-1, IL-6, interleukin-18 (IL-18), TNF- alpha and interferon-gamma (IFN-gamma), their release by T lymphocytes and micro-RNA expression. HCQ decreases the T helper lymphocyte-17 (TH17) associated cytokines and increases the levels of interferon-alpha (IFN-alpha), interleukin-2 (IL-2) and interleukin-10 (IL-10) by increasing the effectiveness of the regulatory T lymphocytes (Treg). It suppresses cytotoxic T lymphocyte and CD4+ lymphocyte activity. It reduces DNA, RNA and protein synthesis in thymocytes [17].

Another drug azithromycin is a macrolide group antibiotic and is used in combination with HCQ in the treatment of COVID-19 [18]. Since azithromycin is a weak basic drug like HCQ, it accumulates in lysosome and endosomal vesicles that are acidic and raise the pH of the environment [19]. This suppresses endocytosis, resulting in inhibition of viral entry and replication [20].

According to the data obtained by using biochemical and electron microscope in 1990, CoV was found to be very sensitive to pH changes. While the virus is stable in the environment with pH 6 and 37 °C; it is rapidly and irreversibly inactivated by forming C-shaped sediments and large aggregates in the environment with the same temperature and pH 8 [21]. Another study in 1991 revealed that CoV-cell fusion was affected by pH changes also. It has been found that RNA synthesis of viruses, that require an acidic medium for fusion, decreased significantly after the administration of weak basic chloroquine and NH_4Cl. Acidic environment dependent CoV is blocked when exposed to weak bases that increase endosomal pH [22,23].

In 2007 viral titer variabilities in pH changes were investigated in Vero cell culture infected with SARS-CoV. In the first series, viral suspensions were adjusted to pH 11 and 13 by adding NaOH. A decrease in viruses was observed at these high alkali values. While pH 11 was not sufficient for virus inactivation, pH 13 was found to provide significant inactivation [24].

As mentioned above CoV's are affected by pH changes. This is observed both experimentally and also in current treatments. In addition, anti-inflammation and immunomodulation have important roles in the treatment of COVID-19. So can we say that PPI's which make pH changes both in cell cytoplasm and organelles [25] and are also thought to have effects on inflammation and immune system are suitable candidates for COVID-19 treatment and even prophylaxis?

Estimation of the hypothesis

PPI's are drugs used in the treatment of gastric acid-related diseases that suppresses acid secretion in the gastric lümen through inhibition of H^+/K^+ATPase. However, PPI's are also effective on the immune system elements; monocytes, neutrophils and endothelial cells [26]. PPI's suppress neutrophil functions such as chemotaxis, superoxide production and degranulation via IL-8 [27]. In addition, P type proton-ATPase inhibitors are known to have anti-inflammatory effects by reducing neutrophil adhesion molecules and free oxygen radicals [28]. They are also known to provide the activation of heme oxyegenase-1 (HO-1); an endogenous antioxidant [29].

The inhibition of H^+/K^+ATPase in gastric parietal cells, as well as suppression of the same pump in lysosomal membranes, will cause an increase in endolysosomal pH. Omeprazole has been shown to provide *in-vitro* antimalarial and *in-vivo* antileishmanial activity by blocking the pump on parasitic vacuoles and phagolysosomes [30,31]. This effect is similar to HCQ.

It was revealed in a study conducted in 2019 that omeprazole increased the antiviral activity of acyclovir against herpes simplex virus (HSV) [32]. In another unpublished cell culture study conducted with the thought that omeprazole can suppress viral replication by increasing lysosomal pH, as it is a lysosomotropic agent such as HCQ, omeprazole exhibited a suppressive effect on both SARS-CoV and SARS-CoV2 in similar doses. And also omeprazole is known to suppress the double stranded RNA formation. In the study serine protease inhibitör aprotinin, which is mostly used in the treatment of bleeding and pancreatitis that can also be effective on CoV and the antiviral drug which is effective on many RNA viruses; remdesivir have been evaluated in combination with omeprazole separately. The administaration of omeprazole to the SARS-CoV2-infected cell culture at the concentration consistent with the therapeutic plasma concentration (8 μM), increased 2,7 times in the efficacy of aprotinin and 10 times in remdesivir. As a result of the study data, a candidate treatment combination has emerged for COVID-19 [33].

Interstitial fibrosis and chronic inflammation signs were observed in histophatological lung samples obtained by biopsy from SARS patients who recovered in 2009. Transforming growth factor-beta (TGF-beta) and angiotensin converting enzyme 2 (ACE2) mediated mechanisms are blamed in the pathophysiology of fibrosis [34]. The fact that patients diagnosed with interstitial pulmonary fibrosis (IPF) have a reduced level of HO-1 in bronchoalveolar lavage fluid [35], suggests that using PPI for COVID-19 in the fibrotic process may increase the expression of HO-1. PPI, which has anti-inflammatory, antioxidant and immonomodulatory effects as well as an antifibrotic effect, was evaluated in a study of graves ophtalmophaty. In the study, esomeprazole and lansoprazole have been shown to prevent TGF-beta mediated fibrosis [36]. PPI was observed to inhibit TGF-beta-mediated collagen production and proliferation in lung fibroblasts by suppressing profibrotics such as collagen 1 (COL1A1), fibronectin 1 (IFN1), matrix metalloproteinase 7 (MMP7) [37,38].

However, both HCQ and PPI tend to accumulate in an acidic environment by competing with each other since they are weakly basic. Therefore, having PPI in the environment may decrease the effectiveness of HCQ [30,39]. Based on this information, it can be thought that the use of PPI for azithromycin, which has a weak basic character, will decrease drug effectiveness. In addition to the studies emphasizing that the increase in gastric pH decreases the absorption of weak basic drugs such as HCQ [40,41], there are also studies indicating that HCQ blood level do not differ significantly in patients receiving and not receiving PPI [42]. On the other hand, the two weak basic drugs; HCQ and azithromycin are used as combination in the treatment of COVID-19. More evidence is required to say that the use of PPI with these drugs may decrease the antiviral efficacy.

Consequences of the hypothesis and discussion

In the light of all this information, we can say that PPI shows similar effects on viral entry and intracellular distribution with its effect on pH such as HCQ and azithromycin. In addition to its anti-inflammatory,

antioxidant and immunomodulatory effects, it can also take part in the treatment of COVID-19 with its antifibrotic effects. On the other hand, the demonstration that PPI's increase their effectiveness when combined with drugs that have antiviral activity such as aprotinin and remdesivir, strengthens the view that PPI can be effective in the treatment of COVID-19 through different mechanisms. Combination with the last two drugs can increase effectiveness and shorten the treatment process.

All these data especially the fact that there are no enough weapons against this disease, seem to be a sufficient reason for us to evaluate the inexpensive, widespread and immediately available PPI's in the treatment of COVID-19 which is a pandemic causes socioeconomic problems worldwide. In addition, we think that it can be used in prophlaxis too. However, *in-vitro* and *in-vivo* studies are required on PPI's that are thought to be beneficial for COVID-19 in acute and chronic processes with their anti-inflammatory, immunomodulatory and antifibrotic properties. Thus, both short and long term disease management is better evaluated and new doors can be opened about COVID-19 and the treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110018.

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