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Review Article

Proton Pump Inhibitors Versus Histamine Receptor Antagonists in Management of Patients with Covid-19

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Abstract

The seemingly unending Covid-19 still lacks a definitive treatment, which continues to remain largely symptomatic. In absence of standardized and specific treatment, the widely adopted current pharmacotherapy for Covid-19 almost invariably includes proton pump inhibitors (PPIs) in many countries, which in the author's opinion is strongly refutable, poorly justified and unwarranted. This brief paper not only discusses the adverse effects of PPIs but also presents evidence how PPIs can even be associated with enhancement and increased severity of Covid-19. In view of untoward effects due to administration of PPIs, the author justifies and recommends the replacement of PPIs with histamine antagonists based on their direct and indirect control of Covid-19 and its severity with improved prognostic outcome of the disease.

Keywords: *Gut-Lung Axis; Gut Microbiota; Kidney Disease; SARS-Cov-2*

Introduction

The current rampant and seemingly unending pandemic coronavirus disease (Covid-19) is attributed to a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 mainly affects the respiratory system but the involvement of gastrointestinal system and kidneys has also been frequently observed and reported.

There is yet no standardized and universally accepted treatment protocol specific for Covid-19 and current standard of care (SoC) is predominantly and largely symptomatic with periodic amendments as findings and results pertaining to pharmacotherapy from newer studies keep pouring in.

Proton pump inhibitors (PPIs)

Proton pump inhibitors (PPIs) are conventionally used to treat acid-related disorders in the stomach, mainly gastro-esophageal reflux disorders; they inhibit the gastric proton pump (H^+/K^+-ATPase) of parietal cells and raise the normal pH of the stomach that usually ranges from 0.9 - 1.5. A single oral PPI dose can increase the gastric pH from 2.0 to more than 6.0.

In normal situations, the gastric acidity is so strong that it practically kills all the micro-organisms that humans ingest with food and the gastric chyme is sterile when it exits the pyloric end of the stomach; hence, the major reason that accounts for higher incidence of gastro-intestinal infections in summers is due to dilution of gastric acid owing to excessive water drinking.

Proton pump inhibitors are being routinely and widely used in outpatient as well as inpatient settings for Covid-19; however, in the author's opinion, the use of PPIs appears to be strongly refutable, poorly justified and unwarranted, and several studies have also argued against the use of PPIs. The objective of administration of PPIs appears to be in anticipation of likelihood or imminent development of hyperacidity and its related symptoms due to parallel/simultaneous pharmacotherapy for Covid-19 that has been initiated or is to be initiated.

In the author's opinion, replacement of PPIs with histamine receptor antagonists offers far better efficacy and superiority in not only controlling Covid-19, but also in preventing PPIs-associated multiple side effects, some of which can potentially exacerbate the Covid-19. Furthermore, the purpose of controlling acidity, gastro-esophageal reflux (and associated symptoms) pre-required for pharmacotherapy of Covid-19 can be adequately accomplished by histamine receptor antagonists.

This brief paper proposes and justifies the replacement of PPIs with histamine antagonists for improved control of Covid-19 along with elimination of unwarranted adverse effects associated with administration of PPIs.

PPIs, gut microbiota and gut-lung axis

The stomach, upper gastrointestinal tract, and oral cavity are inhabited with naturally occurring microbiota, some of which are acid-producing and contain ATPase enzymes; PPIs probably exert a direct effect on the proton pumps of the microbiota and by altering the pH can affect the microenvironment of the flora [1]. Proton pump inhibitors used to treat indigestion, peptic ulcers and acid reflux disrupt the normal balance of the beneficial bacteria living in the gut and reduce the diversity of gut bacteria.

The role of microbiome is of paramount importance in immunity and inflammation also and influences pulmonary functions through the gut-lung axis [2,3].

Covid-19, gut microbiota and gut-lung axis

Although SARS-CoV-2 predominantly affects the lungs, GIT involvement is also described in Covid-19 patients and the finding of viral RNA in feces of infected patients suggests a potential interaction with the host's gut microbiome and may account for a possible fecal-oral transmission route of SARS-CoV-2. Normally, in old people, the diversity in the gut microbiota reduces with aging, which renders them more vulnerable to severe Covid-19.

Authors of one study [4] believe that gut microbiota represents a link between immune system and lung and affects the progress of Covid-19 and dysbiosis in gut microbiota also results in gut permeability leading to secondary infection and multiple organ failure. On the other hand, dysbiosis by disrupting the gut barrier may also translocate the SARS-CoV-2 from the lungs into the intestinal lumen via circulatory and lymphatic system and vice versa.

The bidirectional interactions between the respiratory mucosa and the gut microbiota is termed gut-lung axis and one study [5] has shown that dysbiosis of the gut microbiota may also be responsible for delayed SARS-CoV-2 clearance; thus, the PPIs are likely to increase the survival of SARS-CoV-2 in the GIT and allowing time enough for the virus to invade gastrointestinal epithelial cells and increase the risk of exacerbating the Covid-19.

In this manner, intestinal dysbiosis by exacerbating inflammation in presence of reduced anti-inflammatory mechanisms in the gut and lungs may result in increased mortality in other respiratory infections. These findings could potentially pave the way for adjunctive therapies based on the re-establishment of eubiosis and modulation of the gut microbiota for restraining the harmful effects of Covid-19 [5].

In view of above studies and evidence, the author opines that preservation of normal gut microbiota could form an important objective of effective management of Covid-19, which can be achieved to a large extent by avoiding administration of PPIs.

Gastric juice plays a main role in inactivation of swallowed microorganisms, preventing their onward passage in the GIT. In one study [6], the authors admit the widespread injudicious use of PPIs and caution against the possibility of greater risk of infection with SARS-CoV-2 in patients treated with PPIs. This is particularly in view of earlier studies that have documented that PPIs are a risk factor for rotavirus, influenza virus, norovirus, and Middle East respiratory coronavirus infections. Indeed, one study [7] did find that patients administered PPIs were at increased risk for higher morbidity due to Covid-19.

PPIs and kidney

In addition to involvement of lungs and GIT, both PPIs and Covid-19 can adversely affect kidneys also. In one study on the effects of PPIs on kidney [8], the authors found association of PPIs with a wide array of kidney disorders like hypomagnesemia, acute kidney injury, acute interstitial nephritis, incident chronic kidney disease, kidney disease progression, kidney failure, and increased risk for all-cause mortality and mortality due to chronic kidney disease. Furthermore, the authors also go on to admit that PPIs are frequently prescribed and often injudiciously used in absence of a therapeutic indication, and when medically indicated, they are often used for prolonged periods than required. Another study [9] also showed that PPI usage was associated with adverse kidney outcomes; whereas, some research studies have found that PPIs were associated with inflammatory processes in the kidneys [10].

Some researchers have linked kidney damage to PPIs. Investigators in one study [11] observed a higher risk of acute kidney injury (AKI) and chronic kidney disease (CKD) associated with PPIs. This large study included 93,335 patients with AKI and 84,600 patients with CKD; of the patients in the AKI and CKD cohorts, 16,593 and 14,514 used PPIs, respectively. The incidence rate of AKI was significantly higher in patients on PPIs as compared to those without (36.4 vs 3.54 per 1000 person-years); incidence of CKD also showed similar association with PPIs (34.3 vs 8.75 per 1000 person-years).

In another study [12], investigators reported that PPIs users exhibited a 26% greater risk of CKD in comparison to patients that were on H2 blockers; in addition, PPI users were 22% more likely to experience CKD progression. The cohort included 144,032 incident users of acid suppression therapy that consisted of 125,596 PPI and 18,436 consumers of H2 blockers.

Covid-19 and kidney

Recently, there have been reports of nonelderly Covid-19 patients who developed an acute kidney injury (AKI) in absence of prior underlying medical conditions. Proteinuria is very frequent among hospitalized Covid-19 patients and may precede AKI. Elevated levels of urine retinol binding protein and low degree of albuminuria suggest a predominantly tubular origin of affliction. Acute kidney injury in Covid-19 may be due to possible direct damage to kidney cells (or acute tubular necrosis) with septic shock and/or increase in blood clotting.

Involvement of the renal system is common in moderate to severe SARS-CoV-2 infection with proteinuria as an independent risk factor for increased duration of hospitalization and intensive care unit admission in patients with Covid-19. Proteinuria was a frequent finding among patients hospitalized with Covid-19 [13] and researchers of one study [14] even suggest that proteinuria can function as a biomarker for Covid-19 severity.

Thus, Covid-19 and PPIs can exert a combined or synergistic adverse effect on kidneys.

Covid-19, histamine and antihistamines

Many studies have shown that mast cells and basophils release mediators such as histamine and cytokines in response to viruses in view of which role of mast cell-derived histamine in combination with interleukin-1 (IL-1) has been proposed in Covid-19 lung inflammation. Role of histamine is further strengthened by reports of potential efficacy of histamine-2 receptor antagonist famotidine in the treatment of Covid-19.

Histamine is known to act as a chemical mediator in acute inflammatory events promoting vascular and tissue changes with possession of strong chemo-tactic activity. It is an inflammatory mediator that impacts the immune system usually as a proinflammatory factor [15].

Histamine also modulates the functions of monocytes, T cells, macrophages, neutrophils, eosinophils, B cells, and dendritic cells [16]. It is found in high concentrations in intestinal mucosa, skin, and bronchial tissues where it regulates a variety of pathophysiological and physiological processes, namely secretion of gastric acid, inflammation, and the regulation of vasodilatation and bronchoconstriction.

Clinical improvement of Covid-19 can be achieved by controlling lung inflammation, a common feature in severe Covid-19 [17]. On the other hand, recently it has emerged that H1 receptor antagonists display significant promise as anti-SARS-CoV-2 agents and in combating SARS-CoV-2 infection.

Antiviral tests using native SARS-CoV-2 virus in Vero E6 cells confirmed that 7 drugs namely (clemastine, amiodarone, trimeprazine, bosutinib, toremifene, flupenthixol, and azelastine) significantly inhibited SARS2 replication, reducing supernatant viral RNA load with a promising level of activity. Three of the drugs were classified as histamine receptor antagonists with clemastine showing the strongest anti-SARS2 activity (EC50 = 0.95 ± 0.83 μM) [18].

Examination of reports on interactions between SARS-CoV-2 and histamine receptor antagonists have hypothesized the positive effects of famotidine to be due to H2 receptor-mediated immunomodulatory actions on mast cell histamine-cytokine cross-talk, rather than a direct action on SARS-CoV-2; in view of these observations, the researchers propose that the principal mechanism of action of famotidine for relieving Covid-19 symptoms involves on-target histamine receptor H2 activity, and that dysfunctional mast cell activation and histamine release may account for the development of clinical Covid-19 [19,20].

Montelukast in combination with fexofenadine/levocetirizine forms a frequent (almost invariable) component/ingredient of standard of care (SoC) for Covid-19, obviously for the purpose of antihistaminic actions as Montelukast prevents release of histamine from mast cells and fexofenadine/levocetirizine (both) are antihistamines. The administration of Montelukast in combination with fexofenadine/levocetirizine emphasizes the significance of antihistaminic actions in the management of Covid-19.

Fexofenadine and levocetirizine are predominantly H1 receptor antagonists; whereas, famotidine and ranitine are predominantly H2 receptor antagonists. The author recommends replacement of PPIs with H2 receptor antagonists to check gastric hyperacidity, if required, due to pharmacotherapy and the combination of both histamine (H1 and H2) antagonists would be supplementary to each other and exert a synergistic action in combating not only histamine-induced widespread inflammation in the body but also exercise direct control over coronavirus spread and viral load along with elimination of PPIs-induced adverse effects.

Conclusion

Thus, avoidance of PPIs and their replacement with histamine antagonists (that posses multi-purpose action) is likely to reduce gastric acidity and its related symptoms, reduce viral load in GIT and its invasion into body via GIT, reduce incidence and/or severity of

PPIs-associated adverse effects, help in controlling coronavirus infection as some studies have exhibited, reduce histamine mediated inflammation-induced tissue injury and speed up recovery.

Therefore, in view of above evidence and contention, it is strongly recommended that PPIs be replaced by histamine antagonists to enhance the management of Covid-19 and eliminate the risks and adverse effects associated with the use of PPIs.

Declarations of Interest

None.

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