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PROTON PUMP INHIBITORS (PPIs): INCREASED RISK OF COVID-19?

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Abstract : SARS-CoV2, a novel coronavirus of Coronaviridae family, has caused a worldwide pandemic of COVID-19 infections. Most patients had respiratory symptoms causing pneumonia in severe cases, thus droplets have been focus of investigations in disease-transmission. However, gastrointestinal (GI) symptoms in some cases have warranted research, revealing possible fecal-oral routes.

Proton Pump Inhibitors (PPIs), one of the most commonly-used drugs in gastric acid-related disorders, act by inhibiting H+-K+-ATPase pumps in parietal cells of oxyntic glands of stomach.This paper aims at finding the risk of COVID-19 infections in patients on PPI therapy.

SARS-CoV2 enters human body through ACE-2 receptors. These receptors, though present extensively, are expressed primarily in alveolar tissue of lungs, enterocytes of small intestine. Surface expression of ACE2 receptors in alveolar epithelium explains widespread respiratory symptoms of COVID-19. To access ACE-2 receptors of small intestinal enterocytes, the virus has to pass through the stomach, where normal pH is around 2. SARS-CoV2, being pH-dependant, cannot tolerate this acidification and its half-life is greatly reduced.

This study focuses on 150 patients across India, positive for COVID-19 infections by RT-PCR, where medication-history, specially PPIs were noted. PPIs increased risk of GI symptoms in COVID-19 from 14% to 61.9% with odds ratio of 5.6, proving PPIs greatly affect chances of GI symptoms.

The explanation is by reducing gastric HCl, PPIs increase gastric pH from 2 to around 6. Once pH of 5-6 is achieved, virus can easily pass through stomach and reach ACE-2 receptors of small intestine, explaining a route for fecal-oral transmission.

Index Terms - PPI, COVID-19

Introduction:

SARS-Cov2, a novel coronavirus, initially presented as a cluster of pneumonia cases in Wuhan, China (December, 2019). Since then, there has been a worldwide outbreak wreaking havoc over 160 countries. Till the 3rd week of April, there have been over 2,750,000 cases causing at least 190,000 deaths globally. Death rates are reported to be specially high in Italy, UK and parts of USA. Though droplet infections have been shown to be the primary mode of spread, fecal-oral routes of transmission have also been reported[1].

Clinical Features:

Fever, cough, fatigue and dyspnea are the respiratory symptoms with which most patients present[2]. Other presenting complains of COVID-19 infections include gastrointestinal symptoms (such as anorexia, nausea vomiting, pain abdomen and diarrhea)[3], olfactory dysfunction[4] and even conjunctivitis[5]. The reason for this wide array of symptoms may be attributed to the fact that SARS-COV2 enters the body through Angiotensin Converting Enzyme2 (ACE2) receptors. These receptors though present abundantly in various organs and smooth muscle cells, surface expression of the receptor was found mostly in alveolar epithelium and small intestinal enterocytes[6]. ACE2 receptors are Type1 transmembrane metallocarboxypeptidases[7].The main function of ACE2 is converting Angiotensin ll to Angiotensin 1-7. Angiotensin ll is a potent vasoconstrictor and acts via Renin-Angiotensin-System (RAS) to increase systematic blood pressure[8]. Thus ACE2 by degrading Angiotensin ll, negatively regulates RAS[9].

ACE2 contains in its extracellular portion, the first α-helix and lysine 353, also proximal residence of the N terminus of β-sheet 5. This interacts with high affinity to the receptor binding domain of the SARS-CoV S glycoprotein.

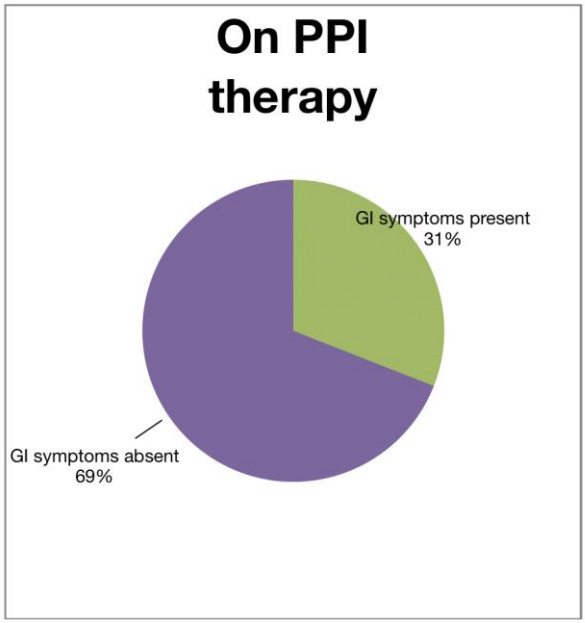
Though most cases report a mild course of disease, severe illnesses including deaths are constantly being reported worldwide. Fatalities from COVID-19 infections have been mostly seen in elderly populations, though deaths among younger patients are not rare. The affected countries have been fatalities across all genders, religions, ethnicities and cultures; however there have been some reports of males being more affected than females[10] . African-Americans are having greater death rates than Caucasians[11] . While most of these fatalities have come from respiratory manifestations of the disease, gastrointestinal symptoms alone are often severe enough to warrant admission in Intensive Care Units (ICU).

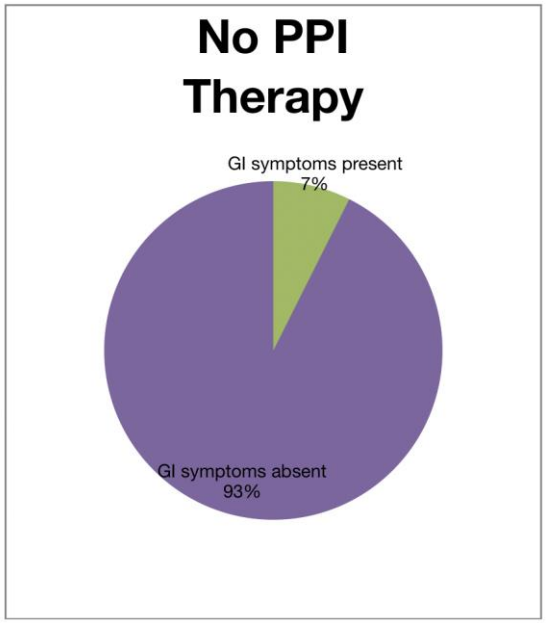
Not much data has been published regarding severe COVID-19 infections including deaths and their relationship with preexisting co-morbidities and ongoing medications. This study aims at a correlation between patients on Proton Pump Inhibitor (PPI) therapy and the severity of gastrointestinal symptoms from COVID-19.

Proton Pump Inhibitors such as Pantoprazole, Lansoprazole and Esmoprazole act by blocking the H^+ -K^+ -ATPase pumps on the walls of gastric mucosa thus inhibiting acid secretion resulting in reduced acidity of the gastric contents. Since the introduction of Omeprazole in 1989[12], PPIs have become the first line drug for a wide spectrum of acid-related disorders ranging from hyperacidity to peptic ulcer disease. It is also very commonly used with other drugs such as NSAIDS for gastric protection. Due to very little interactions with other drugs, very high safety profile and patient compliance, PPIs are extremely common drugs used both in the clinics and for in-patients. Some patients with digestive disturbances often take long-term courses of oral PPIs.

Methods:

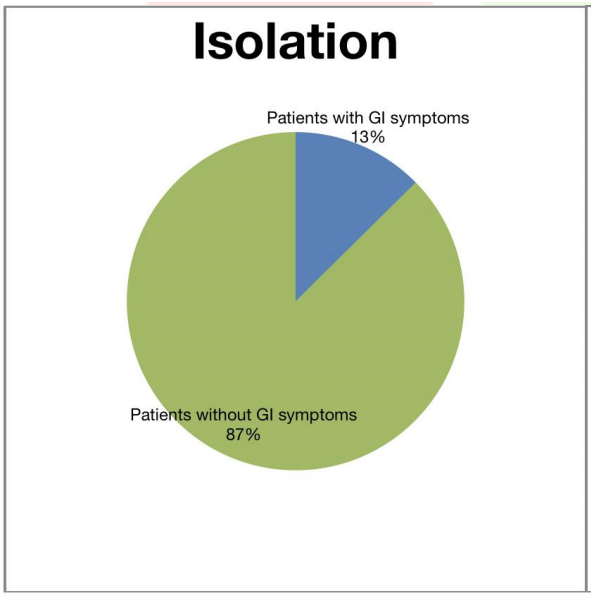
A cross-sectional study was conducted across 8 Hospitals in India. 150 consecutive patients who tested positive for COVID-19 infections were chosen. Each of them had tested positive for SARS-CoV2 by RT-PCR, as recommended by World Health Organization[13]. Of these 150 patients, 119 were in isolation ward with mild symptoms, while 31 patients were admitted in ICUs due to the severity of their illness. Along with routine history taken during admission and subsequent examinations, history of medications over the past 1months were taken from each patient (or patient's relatives in cases where the patients were unable to communicate), with special emphasis on Proton Pump Inhibitors.

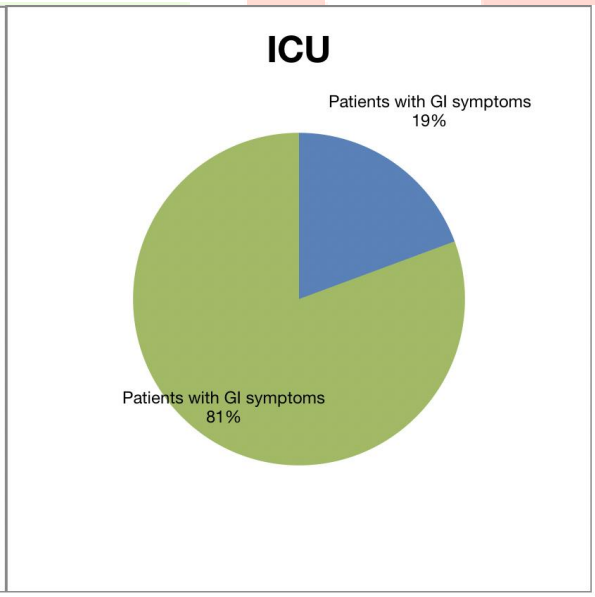




Results:

Out of the 150 patients admitted, 21 had gastrointestinal symptoms (15 from isolation wards and 6 amongst ICU admissions).





Upon thorough history taking, it was found that 42 patients had been on PPI therapy (at least 2weeks) within the past 3-4 weeks. Correlation of the data showed 13 (of these 42 patients) patients exhibiting symptoms of Gastrointestinal involvement. Thus an ongoing or recently completed course of PPIs increases the risk of GI symptoms from 14% to 61·9% (odds ratio = 5.6).

Discussion:

SARS-CoV2, similar in structure to type ll coronavirus of the *Coronaviridae* family, has an unique genetic sequence, thus separating itself from animal coronaviruses. The genome has been seen to contain at least 14 open reading frames (ORFs). While the 5' portion of the genome has replicase/ transcriptase genes, its 3'end contains four major structural proteins- S,M,N and E (made through subgenomic RNAs)[14]. Laboratory investigations confirm that these glycoproteins, specially spike or 'S' proteins mediate attachment, fusion and entry by utilizing a pH-dependant endocytic pathway[15], similar to Influenza and Ebola viruses.

Coronavirus (MHV-A59) had its half-life reduced from 24hrs to 30mins when pH is increased from 6 to 8, keeping the temperature constant at 37°C [16]. Studies conducted on other coronavirus confirm that a pH of 5 (at 37°C) is optimum for fusion of the viral cell into the host cells with a half-maximal rate of fusion at pH 5·5 [17].

The human gastrointestinal tract has been automatically divided into different parts to aid the process of digestion, absorption and elimination of food. Each component of the GI tract- namely mouth, esophagus, stomach, small intestine and large intestine has their own specialized epithelial cells to facilitate their function. Apart from different epithelial linings, each part of the GI tract maintains its own pH levels.

Organ	Epithelium	pH
Mouth	Stratified squamous with or without keratin	≈7[18]
Esophagus	Stratified squamous without keratin	≈7[19]
Stomach	Mucous columnar cells	1-2·5[20]
Small- intestine	Columnar with evaginations	≈6[21]
Large- intestine	Columnar with invaginations	≈7·5[22]

Under normal physiological conditions, the strong acidity of the gastric juice creates an environment unfit for the fusion of pH-dependant viruses to the host body. Functionally, the stomach may be divided into two areas: Oxyntic and Pyloric glands. Around 80% of the stomach is the oxyntic area which contains parietal cells[23]. These parietal cells have specialized pumps called H^+ -K^+ -ATPase pumps, which in presence of Gastrin, secrete H^+ ions into the gastric lumen. Cl^- ion secretion occurs simultaneously Hydrochloric acid (HCl) formation in the stomach.

The gastric H^+ -K^+ -ATPase is an α,β heterodimeric enzyme wherein the α-subunit (catalytic site) shares a strong non-covalent bond with the β-subunit[24]. This α-subunit, composed of 10 transmembrane helices and 3 cytoplasmic domains, has conserved sequences along with other P_2 type ATPases, the sarcoplasmic reticulum Ca^{2+} ATPase and the Na^+ -K^+ -ATPase, for the ATP binding site and the phosphorylation site[25].

Proton pump inhibitors are weak bases with a pKa between 4.0 and 5.0. They accumulate in the acidic space of the secretory canaliculus of the parietal cells in the form of prodrug from which they are converted to the activated species – highly reactive cationic thiophilic reagent. This protonation is required for their activation to form disulphides with the cysteines of the H^+ -K^+ -ATPase[26]. The binding of PPIs to the H^+ -K^+ -ATPase pumps lead to reduced H^+ secretion in the gastric lumen, causing less HCl production – the net effect being a rise in gastric pH.

While the normal gastric pH is around 2, it increases to around 6 within 3-4 hours after PPI introduction[27]. Again the average pH of the distal duodenum was reduced from 5.95 to 5.85 after 1 week of PPI use[28]. This suggests that the sudden and extreme change of pH in the GI tract (2 in stomach and 5.95 in distal duodenum) changes to a rather uniform and homogenous pH of around 5 to 6 after PPI therapy. Incidentally, this is the pH where the pH-dependant viruses reach their maximal rate of fusion into the host cell. Thus, PPIs provide the ideal gastrointestinal pH for viral proliferation and entry.

ACE-2 receptors, which are required by the SARS-CoV2 for entry into the human cells are expressed in the small intestine more than any other part of the GI tract. In normal individuals the entry of the virus through the ACE2 receptors of the small intestines are restricted by the acidity of stomach. In patients receiving PPIs, the pH of gastric lumen is increased many folds to allow passing of the virus in active form into the small intestine, where it freely binds with ACE-2 receptors to gain entry into the human body.

Conclusion

Though viral load from stool samples should be assessed to get more appropriate results, the data from this study suggests that proton pump inhibitors should be used with caution during the global COVID-19 pandemic since they are a risk factor in the fecal-oral transmission of the disease and also an important history in patients suffering from gastrointestinal symptoms because of the illness.

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