Review article: Acid suppressant therapy and risk of COVID-19 infection - to use, to alter or not to use?

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Abstract

Recently there have been many concerns regarding the use of acid suppression therapy in the setting of the COVID-19 pandemic. We review here the biological plausibility, the evidence and the recommendations for acid suppressant use in the present COVID-19 pandemic. After adjusting for confounding factors, PPI use, especially twice-daily dosing, seem to be associated with acquiring COVID-19 infection and worse outcomes among patients with COVID-19, compared to non-users. PPI induced hypochlorhydria may be responsible for the observed effects. Famotidine seems to protect against clinical deterioration among hospitalised and improves patient-reported outcomes among non-hospitalised patients with COVID-19, compared to non-users. Famotidine interfering maturation of SARS-CoV-2 and reducing inflammation may be responsible for the observed effect. The knowledge from the recent studies could help by reminding PPI users to be especially vigilant about following protective health behaviours and should also encourage physicians to prescribe PPIs rationally during and after the pandemic.

Keywords

Acid suppression, proton pump inhibitor, PPI, H2 receptor antagonist, H2RA, COVID-19, SARS-CoV-2, pandemic

Introduction

Acid suppression therapy is one of the most commonly prescribed medications worldwide. These medications include proton pump inhibitors (PPI) and Histamine-2 receptor antagonists (H2RA). They have been game-changing for treating people with gastroesophageal reflux disease (GORD) and peptic ulcers (1). Acidic stomach secretions with a pH level of 3 or lower can kill the bacteria, and thus guard the intestines against harm (2). Acid suppression therapy, while reducing stomach acid can be beneficial to patients with acid-related diseases, may also leave the gut vulnerable to some enteric infections (4, 5).

The coronavirus 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). COVID-19 has been continuously affecting populations worldwide, creating a global outbreak, since it was initially reported in China in December 2019 (6). COVID-19 related mortality rates vary widely among different populations, and risk factors are still being identified. Some of the confirmed risk factors include old age, chronic lung disease and smoking, cardiovascular disease, chronic kidney disease, diabetes mellitus and obesity, malignancy and chronic HIV infection (7). Use of various medications have also been described to increase the risk of COVID-19; nevertheless, these issues have not been ultimately confirmed.

COVID-19 can infect the GI system (8). Given the high expression of ACE2 receptor (the cellular receptor for SARS-CoV-2) in the intestinal epithelium, it is highly plausible that the gut is a site of active viral replication leading to GI involvement in COVID-19 (9, 10). This raises the possibility of increased susceptibility to and severity of COVID-19 infection among those using acid suppressant therapy.

Recently published observational studies highlight the various impacts of the use of acid suppressant therapy in COVID-19 infection (11-14). We review here the biological plausibility, the evidence and the recommendations that can be made for acid suppressant use in the present COVID-19 pandemic.

PPI and COVID-19

PPIs are medicines that are primarily used to suppress gastric acid production. Examples of PPIs include dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. PPIs can be very useful in treating acid-related symptoms such as acid reflux, heartburn, and dyspepsia, and to treat and protect from acid-related complications such as reflux oesophagitis and peptic ulcers.

Stomach acid helps to keep the digestive system free of infections by killing swallowed viruses and bacteria that might be in saliva or in food (2). Many viruses are sensitive to low gastric pH, and hence theoretically, hypochlorhydria induced by PPI agents can increase the risk of viral infections (15). It has already been established that PPIs can increase the risk for enteric diseases such as food poisoning, traveller's diarrhoea and *Clostridium diffcile* infections (4, 5). Similarly, PPIs may also increase the risk of community-acquired pneumonia (16-18).

Earlier studies have shown that stomach acid can kill coronaviruses (19). Coronaviruses shed into saliva. SARS-CoV-2 uses the angiotensin-converting enzyme–2 receptor to invade enterocytes (10). Therefore, the virus can rapidly invade and replicate within cells lining the intestinal tract (10, 20). As stomach acid can be protective against the acquisition of coronavirus, PPIs induced hypochlorhydria may facilitate an environment in which coronavirus may thrive. As a result of the use of PPIs, the stomach pH will increase above 3. This rise in the gastric pH might allow the virus to enter the GI tract more efficiently, leading to enteritis, colitis, and systemic spread to other organs, including the lungs. Therefore, there is a theoretical concern that the use of PPIs could diminish or abolish the neutralising effects of gastric acid on SARS-CoV-2, which could potentially increase the risk of GI manifestations and severity in COVID-19.

In a recently published extensive, nationwide survey of over 53,000 Americans, PPI use was independently associated with increased odds for COVID-19, compared to those not using PPIs (11). Moreover, there was a dose-response relationship between PPI use and the risk of COVID-19.

After adjusting for confounding factors (age, sex, race/ethnicity, education, marital status, household income, body mass index, smoking, alcohol consumption, US region, insurance status, and the GI diseases, diabetes, and HIV/AIDS), the highest risk was seen among those taking PPIs twice a day. This group had almost 4-times the odds of being positive for COVID-19 when compared to people not using PPIs [odds ratio (OR) 3.67; 95% CI, 2.93 – 4.60]. Those taking PPIs up to once a day were twice as likely to have had a positive COVID-19 test result than those who did not take the drugs (OR 2.15; 95% CI, 1.90 – 2.44). The risk of PPIs remained significant regardless of the duration of use, including those who had been on PPIs for six months or greater, before the start of the pandemic (11).

In contrast, the use of the less powerful H2RAs was not associated with an increased risk for COVID-19. The use of lower-dose H2RAs was associated with 15% decreased odds of reporting a positive test, while no association was seen for the higher dose of H2RAs.

Importantly, this study was not a randomised, controlled trial; it does not definitively prove that PPIs increase the risk for COVID-19. Future research is needed to confirm the findings in this new study.

Contrarily to the findings of the above study by Almario et al., a recent survey of a Korean nationwide cohort with propensity score matching, revealed PPI usage, including current and past use, did not increase susceptibility to SARS-CoV-2 infection (12). However, current PPI usage was associated with worse outcomes of COVID-19. The ongoing short-term use of PPIs (<1 month) conferred a 90% increased risk of worse clinical outcomes of COVID-19. These findings continue to highlight the potential risk of continued PPI use in the setting of COVID-19 infection.

H2RAs and COVID-19

H2RA also suppresses the production of gastric acid. Cimetidine, ranitidine, famotidine and nizatidine are examples of H2RAs. Early data show that H2RAs had antiviral properties inhibiting HIV replication in vitro (21). Famotidine's role in SARS-CoV-2 was elucidated in a study by Wu et al. (22). There is a potential role of famotidine in interfering maturation of SARS-CoV-2 and reducing inflammation. This knowledge has spurred an interest in the potential of the drug.

The results of a recent propensity score-matched retrospective cohort study involving hospitalised COVID-19 patients in New York were promising (13). This study by Freedberg et al. showed that in patients hospitalised with COVID-19 and not initially intubated, famotidine use was associated with a two-fold reduction in clinical deterioration leading to intubation or death (adjusted hazard ratio 0.42, 95% CI 0.21–0.85). However, this effect was not observed in PPI users for unclear reasons.

Similarly, a study by Janowitz et al., revealed self-administration of famotidine is associated with symptomatic improvements in a case series of 10 consecutive patients (14). The results of this case series suggest that high-dose oral famotidine is well tolerated and associated with improved patient-reported outcomes in non-hospitalised patients with COVID-19.

The findings of the above two studies are observational and should not be interpreted to mean that famotidine has a protective effect against COVID-19. Currently, clinical trials are underway to determine whether H2RAs might protect against the COVID-19 for reasons unrelated to pH balance. The results of a multicentre, randomised controlled trial (RCT) (NCT04370262) of intravenous famotidine in COVID-19 is eagerly awaited (23).

Recommendations for acid suppressant use

As always, the decision about whether, when, and how to modify PPIs dosing should be based on a thoughtful assessment of the risk-benefit ratio for individual patients. Therefore, patients should not immediately stop their PPIs as there are many important reasons to be on a PPI. Patients are encouraged to discuss the benefits and risks of continuing PPIs with their doctor before making any treatment changes. As with any medication, the lowest effective dose should be used, when clinically indicated, for the shortest possible time.

The main result of the study by Almario et al., was that use of PPIs, particularly twice-daily PPIs, appears to increase the risk of COVID-19. Clinicians should carefully consider whether twice-daily PPI dosing is necessary for their patients. This is particularly important for those who are vulnerable to severe COVID-19 infection (e.g., the elderly and those with co-morbidities). Twice-daily PPI use can lead to 24-hour median intragastric pH >6 and sustain pH >4 for more than 20 hours (24-26). Moreover, previous studies suggest that twice-daily PPI does not offer clinically meaningful benefits over once-daily dosing for GORD. Although some patients may undoubtedly benefit from twice-daily dosing, it is always useful to re-evaluate the need for high-dose PPIs, particularly when the population prevalence of COVID-19 remains high.

The other thing to consider is that the above studies did not find an increased risk for COVID-19 among those who use H2RAs, and one study revealed its role in reducing clinical deterioration of COVID-19 infection. Therefore, H2RAs may be considered as an alternative for PPIs in treatment for acid-related conditions during the present pandemic.

For patients who need to continue a PPI for an appropriate reason, it is essential to emphasise the best ways to reduce the risk of getting COVID-19: regular hand washing, social distancing and wearing a mask when around others.

Conclusion

Following the recommended public health practices will have a more significant impact on personal risk of COVID-19 for patrients more than PPI use or dosing. The knowledge from the recent studies could certainly help by reminding users to be especially vigilant about following protective health behaviours and should also encourage physicians to prescribe PPIs rationally during the pandemic and beyond.

Declarations

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Conflict of interest

The authors declare no conflict of interest.

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