EDITORIAL

H$_2$ antagonists, proton pump inhibitors and COVID-19

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Introduction

Agents that reduce gastric acid secretion such as H$_2$ antagonists and proton pump inhibitors (PPIs) are often used in perioperative care, e.g., for the prevention of aspiration pneumonia as an anesthetic premedication and for prophylaxis of stress-induced gastritis and ulcer formation in the intensive care unit (ICU). However, I have previously suggested that these agents may affect SARS-CoV-2 infection [1]. It has been reported that the H$_2$ antagonist famotidine may prevent SARS-CoV-2 infection, while PPIs might increase the risk of SARS-CoV-2 infection [1]. Since writing [1] several new pieces if data have accumulated on both mechanism and clinical picture so editorial reappraises the effects of H$_2$ antagonists and PPIs on SARS-CoV-2 and COVID-19.

H$_2$ antagonists

Basic studies

It has been suggested that histamine release by mast cells activates H$_2$ receptors to enhance SARS-CoV-2 infection-induced lung inflammation [2]. Histamine from the mast cells increases expression of Toll-like receptor 3 (TLR3) in SARS-CoV-2 infected cells. H$_2$ antagonists may, therefore, reduce TLR3-dependent inflammatory signalling processes [3]. and H$_2$ antagonists including famotidine may ameliorate systemic inflammation caused by SARS-CoV-2 infection. In addition, the H$_2$ antagonists have been reported to activate the innate immune system. Regarding neutrophils H$_2$

antagonists increase count and bactericidal actions, enhance phagocytosis, and decrease adhesion and peroxide production. H$_2$ antagonists also increase natural killer cell count and cytotoxicity, enhance production of Interleukin (IL)-2, IL-13 and TNFα and expression of MHC-2 and caspase-1 activity in macrophages/monocytes, and increase MHC-1, CD40, CD80, CD89 and IL-12 in dendritic cells [4].

Clinical studies

Several reports [5–8] suggest that famotidine administration may improve outcome in COVID-19 patients. Freedberg et al. [5] performed a retrospective analysis of 1620 COVID-19 patients including 84 patients (5.1%) receiving famotidine (of these 28% patients received intravenous; 17% received 10 mg, 47% received 20 mg and 35% received 40 mg). They found that famotidine significantly reduced the risk of aggravation of COVID-19. Similarly, Mather and colleagues [6] performed a retrospective analysis of 878 COVID-19 patients of which 83 (9.5%) patients received famotidine. Using logistic regression analysis, they found that famotidine use was an independent predictor of both lower mortality and combined death/intubation. In addition, serum biomarkers of the systemic inflammatory response syndrome including CRP and procalcitonin were significantly lower in patients receiving famotidine compared to those without. Janowitz and colleagues [7] also reported a case series showing that high-dose oral famotidine from 20 to 80 mg three times daily significantly improved patient-reported outcomes in non-hospitalized COVID-19 patients. However, Sun and colleagues [8] performed a systematic review and meta-analysis using 5 studies including 36,635 subjects and found that famotidine medication was associated with a statistically non-significant reduced risk of severe course in COVID-19 patients. Although the above basic research data suggest that H$_2$ antagonists may reduce systemic inflammation and might produce antiviral actions,

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recent systematic review and meta-analysis do not show beneficial effects of famotidine. The discrepancy between clinical and basic data might be explained by rapid tolerance as intravenous administration of H_2 antagonists causes development of tolerance in a few days [9].

PPIs

Basic studies

Gastric juice is the first defence line against pathogens as gastric acid can inactivate swallowed pathogens to prevent infection [10]. Reduction in gastric acid by PPIs may cause impairment of this defence. Indeed, pantoprazole, PPI improved the viability of Middle East respiratory syndrome coronavirus (MERS-CoV) in the mouse stomach and exaggerated inflammation, and epithelial degeneration in the small intestine followed by the development of respiratory infection [11]. As SARS-CoV-2 is also known to infect gastrointestinal glandular epithelial cells [12], PPI may worsen SARS-CoV-2 infection. Saheb Sharif-Askari [13] performed bioinformatic analyses to evaluate the effect of various medications on mRNA expression of ACE2, TMPRSS2, and CD147 in rat kidney tissues. They found that PPIs such as omeprazol may increase expression of ACE2 a target site of SARS-CoV-2 infection. In contrast, several articles suggest that PPIs may ameliorate SARS-CoV-2 infection. Endosomal acidic environment activates viral fusion proteins to promote viral fusion processes. As PPIs can induce cytosolic acidification and lysosomal and endosomal alkalinization, PPIs may interfere with pH-dependent viral endocytosis [14]. Jimenez and colleagues [15] found that pH reduction may increase ACE2 expression and facilitate internalization of SARS-CoV-2 into human cells. As ACE2 can be expressed in the stomach [16], PPI may reduce the entry of SARS-CoV-2 into gastric cells by neutralization of gastric pH. Touret and colleagues [17] performed in vitro screening of clinically available agents producing inhibition of SARS-CoV-2 replication, and found that PPIs such as omeprazole and vonoprazan showed antiviral potency. They also suggested that antiviral actions of PPIs may be due to inhibiting ATPase proton pump or buffering the pH as endosomal pH neutralization would restrict spike protein processing to interfere with membrane fusion process of SARS-CoV-2 for endocytosis.

Clinical studies

Basic research data do not confirm whether PPIs may produce beneficial or harmful effects on SARS-CoV-2 infection. However, in a recent meta-analysis, patients with current use of PPI showed significantly higher risk of SARS-CoV-2 infection than those without PPI use (Odds ratio 1.94, 95% confidence interval 1.59 to 2.36, $p < 0.0001$) when Korean nationwide cohort [18] is excluded as this cohort unduly affected association between PPI use and SARS-CoV-2 infection [19]. In addition, another meta-analysis and systematic review suggested that risk of mortality due to COVID-19 may be significantly higher in PPI users compared to non-PPI users although the quality of evidence was weak [20]. Liu and colleagues [21] found that salivary ACE2 mRNA levels were significantly higher in PPI users than non-PPI users. Salivary ACE2 levels and stool SARS-CoV-2 RNA detection rates were comparable between users and nonusers of PPI. In addition, the mortality rate in COVID-19 patients was significantly higher in PPI users compared to non-PPI users, and logistic regression showed that predictors of mortality were PPI use, age, race (African Americans), cancer and diabetes.

In conclusion, published data to date suggest that modulation of gastric pH by antiacid medication (H_2 antagonists and PPIs) may greatly influence SARS-CoV-2 infection and COVID-19 severity. We must be cautious in our use of PPIs until more data are accumulated.

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