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LETTER TO THE EDITOR

An Additional Perspective on Proton Pump Inhibitors as Risk Factors for COVID-19

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Dear Editor,

We read with great interest a recent paper in *Clinical Drug Investigation* by Charpiat et al. entitled "Proton Pump Inhibitors are Risk Factors for Viral Infections: Even for COVID-19?" [1]. The authors discuss potential implications of the use of proton pump inhibitors (PPIs) amidst the COVID-19 pandemic and suggest they should be used with caution as (i) alkalinisation of gastric acid removes the protective barrier towards ingested microorganisms; (ii) PPI treatment has been proposed as a risk factor for some viral infections (rotavirus, influenza virus, norovirus, and Middle East respiratory syndrome coronavirus); and (iii) evidence of faecal-oral transmission has been reported for SARS-CoV-2. Considering the widespread use of PPIs and the serious situation regarding the ongoing COVID-19 pandemic, we recognise the manuscript by Charpiat et al. as highly relevant and wish to put forward an additional perspective that is pertinent to the discussion of PPIs as risk factors for COVID-19.

1 PPIs and Viral Infections

As argued by Charpiat et al, PPIs have been associated with an increased risk of some viral infections (e.g. [2, 3]). However, as emphasised in a comprehensive review on acid-suppressive therapy and the risk of infections, "data on pathophysiology and clinical significance of acid suppression drugs in human viral infections are scarce" [4] and not indicative of increasing risk mediated by alkalinisation of the gastric acid. A systematic review/meta-analysis of high-quality randomised, double-blind, placebo-controlled trials of PPIs in patients with gastro-oesophageal reflux disease or peptic ulcer disease failed to detect an association between the treatment and respiratory infections reported as adverse events [5]. High-quality pharmacoepidemiological studies have indicated an increased risk of gastroenteritis during periods of highest circulation of enteric viruses in continuous PPI users versus non-users (RR 1.81, 95 % CI 1.72–1.90) [3], but failed to demonstrate an association between PPIs (or histamine H_2 receptor antagonists) in new nonsteroidal anti-inflammatory drug users and the risk of hospitalisation for community-acquired pneumonia [6]. In contrast, some authors have suggested that PPIs should be investigated as potential treatment for viral infections [7]; however, it should be emphasised that, at the moment, this has only been supported by sporadic in vitro experiments and indirect findings.

The complex relationship between PPIs and viral infections dates back to the time of their invention and synthesis of timoprazole, a drug that would later become a prototype of novel antisecretory agents. A core antisecretory compound used by Hässle (Astra) in the process of development of the first PPI, pyridyl-2-acetamide, was originally obtained from Servier as an antiviral agent. Conversion to pyridyl-2-thioacetamide, followed by the introduction of benzimidazole ring and addition of sulfoxide (as the obtained compound was already covered by a Hungarian patent) yielded a completely new group of drugs known today as PPIs [8–11]. Apart from this particular curiosity, the antiviral effects of PPIs have been reported by several groups. Moormann et al. filed a patent with priority in 1994 (US-5945425-A) claiming the use of PPIs as antiviral agents [12], Sasaki et al. demonstrated inhibition of rhinovirus infection in cultured human tracheal cells by lansoprazole, by interruption of the RNA endosomal entry reducing the expression of intercellular adhesion molecule-1 [13]. Esomeprazole and omeprazole inhibited entrance of several types of pseudoviruses (EBOV-Z, EBOV-B, MARV, FLU-H5, GALV) in a screen

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of commonly used FDA-approved drugs for the antiviral effects against Ebola [14].

Altogether, evidence suggestive of both the potential detrimental and protective effect of PPIs in the context of viral infections exists. However, the evidence is limited and its invocation and interpretation in the context of COVID-19 requires great caution. Suggested mechanisms responsible for either an increased risk (e.g. removing the protective barrier towards ingested microorganisms [1]) or antiviral effect of PPIs (e.g. modulation of endolysosomal pH [15]) are still speculative, and studies on other viruses may not be informative about the possible effect of PPIs on the SARS-CoV-2 and COVID-19. For example, although alkalinisation of endolysosomal pH seems to inhibit the viral entrance of some viruses [16], it has also been shown to increase the infectivity of others [17].

2. PPIs and COVID-19

Disclosure of uncertainty and evidence quality is an indispensable part of a well-balanced communication of science [18]. In the light of this fact, we emphasise that both our initial proposal that PPIs might exert beneficial effect [15] and a warning by Charpiat et al. that PPIs might be a risk factor for COVID-19 [1] are based on limited evidence on speculative pathophysiological concepts that should be further explored before affecting clinical decision making. This is particularly so considering that gastroprotection (PPIs) is a standard supportive treatment in severely ill/intubated patients. In order to provide a more balanced overview of the topic of PPIs and COVID-19, we here address several clinical/epidemiological studies published so far dealing with this question.

In a recent retrospective observational study on 152 hospitalised patients with confirmed SARS-CoV-2, Luxenburger et al. reported an increased risk of secondary infections and ARDS after accounting for other predisposing comorbidities [19]. Won Lee et al. conducted a nationwide cohort study on 132,316 patients based on propensity score matching that suggested short-term current, but not long-term current or previous use of PPI might be a risk factor for the development of severe COVID-19, although treatment didn't seem to affect the susceptibility to SARS-CoV-2 infection [20]. Zhou et al. found an association between the risk of severe COVID-19 and the use of either PPIs or famotidine in a Chinese cohort of 4445 people after propensity score matching [21]. Almario et al. performed an online survey of 53,130 Americans and reported an independent, dose-response relationship between the use of antisecretory medications and COVID-19 positivity [22]. Ramachandran et al. reported an independent association of prehospitalisation PPI-exposure and worse clinical outcomes in 295 COVID-19 patients [23].

Taken together, the above-mentioned reports support a possibility that the use of PPIs might be a risk factor for developing a more severe clinical presentation of COVID-19 [24–26]. However, they should be interpreted with caution as (i) most of the studies offer limited information on the type, dose, duration, compliance, frequency, concomitant therapy, as well as indication related to PPI treatment [24]; (ii) strength of the observed associations was consistently relatively weak and "in the zone of potential bias" [24, 27]; (iii) most of the studies are retrospective observational cohorts that are prone to bias even after apparently appropriate adjustments. For example, there is a substantial risk of *indication bias*, and concerns have been raised about the susceptibility to *protopathic bias* [28], just as in the case of the PPI-pneumonia relationship [27, 29]; (iv) some of the studies included in the meta-analyses suffer from obvious design flaws. For example, the questionable validity of the sampling method evident from the demographics of the cohort in the study by Almario et al. has already been recognised and brought up by others [30–35].

PPIs are a part of a standard supportive care in the most severe COVID-19 patients, but, in the light of the current evidence, the hypothesis that they might confer a significant clinical benefit due to their anti-viral effect [15, 36–38] does not seem likely to be proven correct. Nevertheless, well-controlled prospective studies are needed to provide more solid evidence on the topic as the discovery of either detrimental or beneficial effects of PPIs will likely affect guidelines and clinical decision making given the current widespread use of these drugs.

Declarations

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Conflict of interest Authors declare no conflict of interest.

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Authors' contributions JH wrote the first draft of the manuscript. IK and VT provided a critical revision of the manuscript. All authors provided final approval of the version to be published.

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