Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL

Proton pump inhibitors in the COVID-19 pandemic☆

Los inhibidores de la bomba de protones en la pandemia por la COVID-19

The 2018 annual report on the Sistema Nacional de Salud (SNS) [National Health System] by the Ministry of Health states that the chemical subgroup with the highest consumption by number of packages through medical prescriptions corresponds to the antiulcer agents, particularly the proton pump inhibitors (PPIs). Omeprazole is the drug of choice in this group and is the most widely used active ingredient, with 50 million packages sold, representing 5.3% of all medicinal products.[1]

PPIs are also among the most widely used medicines in other European Union countries and in the United States, and they have been linked to a number of adverse side effects, such as bone fractures, chronic kidney disease, vitamin B deficiency$_{12}$ and gastrointestinal infections, among others.[2] However, not all the possible side effects and risks of the long-term use of PPIs reported are real. In some cases, such as their possible association with dementia, myocardial infarction or kidney disease, the studies in which they were reported could have had biases due to the failure to consider that patients who start PPIs have more comorbidities and are more polymedicated than patients who do not, which is particularly true of older adults. This, rather than the exposure to the actual PPIs, may account for the differences in the rates of certain adverse effects.[3]

Furthermore, a study carried out in 2019 by Vilcu et al.[4] reported that the continuous use of PPIs is associated with an increased risk of viral infection during periods of high endemic prevalence, such as the one we are experiencing. This effect is probably related to the secondary hypochlorhydria induced by these drugs, which lowers the upper gastrointestinal tract's defences against ingested bacteria and viruses,[2] and the fact that long-term use of PPIs appears to reduce microbial diversity in the gut.[5] This may all be relevant, since the SARS-CoV-2 virus can enter the body not only through the respiratory system but also through the digestive tract.[6]

In this vein, Almario et al. recently published a controversial study in the *American Journal of Gastroenterology*, carried out via a self-administered *online* survey in the United States, which found that individuals who used PPIs at least once a day were significantly more likely to have test positive for COVID-19 (*aOR2,15*; confidence interval (CI) 95%, 1.90–2.44 and *aOR3,67*; CI 95%, 2.93–4.60, if they took them once or twice a day, respectively) compared to those not on PPIs. Individuals taking histamine-2 receptor antagonists (H_2 blockers) do not have an elevated risk.[7]

The actual authors acknowledge that the study has a number of limitations, apart from methodological shortcomings, hence the data should be approached with caution.

However, as the authors comment, the results of the study may constitute evidence of an *association* between the use of PPIs and the probability of testing positive for COVID-19, although this study does not provide evidence of *causality*, in the absence of a prospective clinical trial, and further investigation is called for in different populations and settings through specifically designed prospective randomised clinical trials.[7]

Other authors[8,9] contribute data that patients with COVID-19 who were regularly treated with PPIs before hospitalisation had a significantly higher mortality rate than non-users and the consumption of these drugs was a negative predictive factor for the development of secondary diseases such as COVID-19.

Several letters were soon published[10–12] in response to the Almario study on account of its methodological deficiencies and inconsistencies: this association lost its potency following correction for age and renal, pulmonary and cardiovascular comorbidities, which indicated that the effect of PPIs on mortality could be related to other factors associated with the use of PPIs and not the actual drug. These authors convey the concern that the data published could generate unnecessary anxiety among some patients and perhaps lead to the interruption of these drugs in those who need them for an adequate clinical indication, possi-

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bly entailing a significant risk or harm to the patient if they are suspended.

Simultaneously to the aforementioned Almario et al.[7] study, Lee et al.[13] conducted another study with a large Korean cohort of present and past PPI users. Among the patients with confirmed COVID-19, the *current use* of PPIs conferred a 79% higher risk of a serious clinical outcome (need for oxygen therapy, admission to the Intensive Care Unit (ICU), need for invasive ventilation or death), while the relationship with *previous use* of PPIs was insignificant. In turn, the current use of PPIs initiated in the previous 30 days was associated with a 90% greater risk of severe clinical evolution of COVID-19 (admission to the ICU, need for invasive ventilation or death).

In the same line, Li et al.[14] performed their own meta-analysis on the subject, also underlining the fact that current or regular PPI users were more likely to have severe COVID-19 than non-PPI users, with a pooled odds ratio (OR) of 1.67 (95% CI: 1.19–2.33, $p = 0.003$) and a pooled hazard ratio (HR) of 1.87 (95% CI: 1.29–2.70, $p < 0.001$), emphasising that extreme caution should be exercised with patients receiving PPIs during this pandemic.

The results of the Lee et al.[13] study were also conflicting, and the study was criticised for its limitations and methodological deficiencies, which also prompted letters of response. In this regard, Roulet[15] also reports that the results should be interpreted with caution, since the patients in the current PPI use group were older and presented more comorbidities than those in the other groups, which could have caused some type of bias. In any case, they report that in patients most severely affected by COVID-19 who require treatment with a PPI in intensive care, it must be ensured that the proven benefits of such drugs outweigh the potential risks of using them. To date, the risks of these drugs are only hypothetical.

In January this year, Fan et al.[16] published a study including 9469 participants who had been tested for COVID-19 in the UK Biobank, 16% of whom were regularly taking a gastric acid suppressant, PPI or H_2 blocker versus 84% who were not taking them.

For the study, 1516 users and 1516 non-users of gastric acid suppressants finally underwent a matched analysis. The characteristics of the participants in these two groups were well balanced.

Among the regular users of acid suppressants there was a higher proportion of patients aged <65 years and a higher prevalence of comorbidities compared to the non-users, thus reducing the confounding effects of the possible risk factors, biases, in the results.

The OR of testing positive for COVID-19 associated with PPI therapy or an H_2 blocker in the matched cohort was 1.08 (95% CI, 0.89–1.31) and 0.94 (95% CI, 0.65–1.38), respectively. On the other hand, in the analysis, neither the use of PPIs or H_2 blockers was associated with the risk of SARS-CoV-2 infection in patients with upper gastrointestinal tract diseases. However, they found that the use of omeprazole alone was significantly related to an increased risk of SARS-CoV-2 infection based on the subgroup analysis in patients with upper gastrointestinal diseases (OR, 1.35; 95% CI, 1.01–1.82), which was not observed with the use of other types of PPI. On the other hand, neither PPIs (HR, 0.80; CI 95%, 0.58–1.11) nor the use of H_2 blockers (HR, 1.18; CI 95%, 0.62–2.23) were associated with risk of death in COVID-19 patients in the matched cohort.

The obvious advantage of this latest study compared to the others is the detailed and validated information in a well-characterised cohort that includes the types of gastric acid suppressants used and the potential confounding risk factors, all of which affords it greater credibility.

In any case, when assessing the possible side effects of any drug, we should not forget that most of the associations reported in observational clinical research are false and that the minority of the associations that are true are usually exaggerated. This issue is especially problematic in the case of associations of RRs or ORs below 4, such as the studies that have been reviewed. These associations, commonly reported in the medical literature, are more likely to be attributable to a bias than to a causal association. All observational research has a bias. Generally speaking, unless the RRs of the cohort studies exceed 2 or 3, or the ORs of the case-control studies exceed 3 or 4, the associations in the observed observational research should not be considered credible.[17]

In any event, these authors are reminding physicians to regularly review the need for gastric acid suppression in all patients on PPIs: physicians must ensure that the expected benefits and the risks of PPI therapy are balanced and that the lowest and most effective dose is used for the shortest recommended duration.

In the light of all these studies on the possible effects of PPIs on the incidence and evolution of COVID-19, some studies have emerged[18,19] on famotidine, an H_2 blocker, that seem to attribute a protective effect to it. Mather et al.[18] report that the use of this preparation in *hospitalised patients* with COVID-19 is associated with a lower risk of mortality, a combined result of mortality and the need for tracheal intubation and with lower levels of serum markers of severe disease (CRP, ferritin, D-dimer) in hospitalised patients with COVID-19. Similarly, Janowitz et al.[19] suggest that high-dose oral famotidine is well tolerated and is associated with improved outcomes and evolution as reported by *non-hospitalised* COVID-19 patients.

For the time being, there is no explanation, or none is known, for the possible protective mechanism of famotidine in a patient with COVID-19, although a prospective randomised clinical trial has already been sponsored for this purpose,[20] the results of which remain to be seen.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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