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Observational Study of More than 53,000 Americans Suggests an Association Between Proton Pump Inhibitors and Risk of COVID-19

(Bethesda, MD, July 7, 2020) Findings from an online survey of more than 53,000 Americans suggest that using heartburn medications known as proton pump inhibitors (PPIs) once or twice daily significantly increases the odds of a positive test for COVID-19 compared to those who do not take PPIs. This research appears online today in pre-print format in *The American Journal of Gastroenterology.*

Researchers Christopher V. Almario, MD, MSHPM and Brennan M. R. Spiegel, MD, MSHS, FACG of Cedars-Sinai in Los Angeles along with William D. Chey, MD, FACG of the University of Michigan conducted a large population-based, online survey to evaluate whether use of PPIs increases risk of COVID-19.

"We developed this hypothesis at the beginning of the COVID-19 pandemic when we started to see a high incidence of GI symptoms and learned that the virus sheds into saliva, and thus can be swallowed into the stomach. We have now tested the hypothesis in a rigorous study of more than 50,000 Americans and found it to bear out, albeit in an observational study," commented Dr. Almario.

According to the investigators, PPIs increase the risk for enteric infections which is likely related to PPI-induced hypochlorhydria, or low levels of gastric acid. "Although the impact of acid suppression on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown thus far, prior data revealed that pH ≤3 impairs the infectivity of the similar SARS-CoV-1. Thus, we aimed to determine whether use of PPIs increases the odds for acquiring COVID-19 among community-dwelling Americans," they write.

Of 53,130 participants, 3,386 (6.4%) reported a positive COVID-19 test. In regression analysis, individuals using PPIs up to once daily (OR 2.15; 95% CI, 1.90–2.44) or twice daily (OR 3.67; 95% CI, 2.93–4.60) had significantly increased odds for reporting a positive COVID-19 test when compared to those not taking PPIs. Individuals taking histamine-2 receptor antagonists (H_2RAs) were not at elevated risk.

"There is a reason we have acid in our stomach, namely, to kill pathogens before they enter the digestive tract," commented Dr. Spiegel, Co-Editor-in Chief of *The American Journal of Gastroenterology*. "Coronaviruses are easily destroyed at a gastric pH of less than 3, but survive in a more neutral pH, including the range created by drugs like omeprazole and esomeprazole."

"We found a strong, independent effect of using PPIs on risk of COVID-19, including a dose-response relationship with nearly a four-fold increased risk for twice daily dosing. But we found no relationship with the less powerful H_2RAs, such as famotidine or cimetidine," he added.

According to Dr. Spiegel, "previous research has already demonstrated that PPIs slightly increase the risk of enteric infections, but the strong link found here speaks to COVID-19 pathogenesis through the GI tract, where the expression of the receptors the virus uses to enter the body, known as ACE-2 receptors, is roughly 100-fold higher than in any other part of the body, including the lungs."

While these data arise from a large sample, demonstrate a large effect size, reveal a dose-response relationship, are controlled for confounders, and are different from a control group using H_2RAs, all strengthening the results, the investigators note that further studies examining the association between PPIs and COVID-19 are needed.

Brian E. Lacy, MD, PhD, FACG, Co-Editor-in-Chief of *The American Journal of Gastroenterology* commented, "The results of this large survey study, from an experienced team of clinicians and researchers, are intriguing and add novel, clinically relevant information to the rapidly evolving field of COVID-19 during this devastating pandemic. Prior research studies have shown that PPIs slightly increase the risk of an infection developing in the gastrointestinal tract. We now recognize that receptors for COVID-19, (ACE-2) are found throughout the gastrointestinal tract, which supports the biologic plausibility that PPI use could be associated with an increased risk for COIVD-19. However, as the authors carefully point out in their thoughtful analysis, this is not a randomized, placebo-controlled study, but rather a study demonstrating an association, and thus studies from other groups should be analyzed to confirm these novel findings."

Patients who take PPIs should not make any changes in their treatment due to this study without consulting with their physician, especially if the patients need PPIs to treat their digestive disorders. Everyone should be mindful about the spread of COVID-19 and wear a mask, observe social distancing, and meticulously wash or sanitize their hands.

Information Sheet and FAQs About Proton Pump Inhibitors (PPIs) and Risk of COVID-19
The authors provide more information about this research in the form of Frequently Asked Questions (FAQ) here.

The full study in pre-print format can be found here. Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. *Am J Gastroenterol* 2020 (pre-print posted online July 7, 2020)

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