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Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors

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ABSTRACT

Background: Proton pump inhibitors (PPIs) increase the risk for enteric infections which is likely related to PPI-induced hypochlorhydria. 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.

Methods: From May 3 to June 24, 2020, we performed a population-based, online survey described to participating adults as a "national health survey." A multivariable logistic regression was performed on reporting a positive COVID-19 test in order to adjust for a wide range of confounding factors and to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results: 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 (H2RAs) were not at elevated risk.

Conclusions: We found evidence of an independent, dose-response relationship between the use of anti-secretory medications and COVID-19 positivity; individuals taking PPIs twice daily have higher odds for reporting a positive test when compared to those using PPIs up to once daily, and those taking the less potent H2RAs are not at increased risk. Further studies examining the association between PPIs and COVID-19 are needed.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly used medications in the U.S. and have been linked to side effects including bone fracture, chronic kidney disease, and gastrointestinal (GI) infections, among others (1). While a recent randomized controlled trial did not confirm most of these purported complications, it found that once daily PPI use increased the odds for enteric infection by 33% (2). This is likely related to PPI-induced hypochlorhydria, which impairs the body's proximal defense against ingested bacteria and viruses (1).

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 (3). As SARS-CoV-2 employs the angiotensin-converting enzyme-2 receptor to rapidly invade and replicate within enterocytes (4), increases in stomach pH >3 from PPI use might allow it to gain entry into the GI tract more easily, leading to enteritis, colitis, and systemic spread to other organs, including the lungs (5). We thus hypothesized that PPIs may increase the risk of acquiring COVID-19.

METHODS

To test our *a priori* hypothesis, we used data from a population-based, online, self-administered survey of Americans collected from May 3 to June 24, 2020. We collaborated with an online survey research firm (Cint) that recruited a nationwide, representative sample based on U.S. Census data on age, sex and region. Panelists who were ≥18 years of age received an email inviting them to complete a "national health survey," which was administered solely in English. The Cedars-Sinai Institutional Review Board approved this study (Pro56183).

All participants were asked which GI symptoms they have ever experienced and those who reported prior abdominal pain or discomfort, acid reflux, heartburn, or regurgitation were separately asked about any current PPI and/or histamine-2 receptor antagonist (H2RA) use. For those currently taking PPIs and H2RAs, we assessed their frequency and duration of use. We also examined whether respondents were tested for COVID-19; those with a positive test were asked about new symptoms they experienced, if any, at the time of diagnosis, including ageusia, anosmia, GI (abdominal pain, diarrhea, nausea/vomiting), respiratory, or systemic symptoms. Of note, individuals taking a PPI or H2RA for ≤1 month and who were diagnosed with COVID-19 at least two months prior to survey completion were classified as non-users to help reduce the risk of protopathic bias.

All statistical analyses were performed in Stata 13.1 (StataCorp LP, College Station, TX) and a two-tailed p-value <.05 was considered statistically significant. We performed a multivariable logistic regression on reporting a positive COVID-19 test in order to adjust for a wide range of potentially confounding factors and to calculate odds ratios (OR) and 95%

confidence intervals (CI). Among respondents who were COVID-19 positive, we also conducted a regression model on the presence of GI symptoms associated with COVID-19 (abdominal pain, diarrhea, nausea/vomiting). Both regression models included PPI and H2RA exposures as well as relevant demographic, socioeconomic, lifestyle, and comorbidity variables.

RESULTS

Overall, 264,058 individuals were invited by Cint to complete the survey, of whom 128,847 (48.8%) accessed the site. Of the 86,602 eligible respondents who completed the survey, 53,130 (61.3%) noted prior abdominal pain or discomfort, acid reflux, heartburn, or regurgitation and were thus asked about use of anti-secretory medications. The study cohort's demographics are shown in **Table 1**.

We found that 3,386 (6.4%) participants reported a positive COVID-19 test (**Table 1**). In multivariable regression analysis, PPI use was independently associated with increased odds for reporting a positive test, even after adjusting for a wide range of sociodemographic, lifestyle, and clinical variables (**Table 2**). When compared to individuals not using PPIs, those taking 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. Regarding H2RAs, which cause less hypochlorhydria than PPIs, use of lower-dose H2RAs was associated with slightly decreased odds for reporting a positive test while no association was seen for higher-dose H2RAs. In addition to PPI usage, we found that males, current smokers, non-Hispanic blacks, and Latinxs were significantly more likely to report being positive for COVID-19 (all $p<.001$), consistent with previous research (6-11) and thus supporting the generalizability of this dataset.

In a separate regression analysis that included duration of anti-secretory use, we found the following with respect to PPI exposure: no current PPI use—reference; up to once-daily PPI for ≤6 months—OR 3.25 (95% CI, 2.81–3.77); up to once-daily PPI use for >6 months—OR 1.44

(95% CI, 1.22–1.70); twice daily PPI use for ≤6 months—OR 2.31 (95% CI, 1.42–3.77); twice daily PPI use for >6 months—OR 3.81 (95% CI, 2.97–4.87).

Among those who tested positive for COVID-19 (n=3,386), 3,267 (96.5%) were symptomatic (ageusia, anosmia, GI, respiratory, or systemic symptoms) and 674 (19.9%) reported new onset of abdominal pain, diarrhea, or nausea/vomiting. In regression analysis, we found that individuals taking lower-dose PPIs (n=266, 10.9%; OR 0.62 [95% CI, 0.49–0.78]) had lower odds for reporting GI COVID-19 symptoms versus those not on PPIs (n=297, 39.5%; reference). Conversely, no association was seen with twice daily use (n=111, 56.1%; OR 1.04 [95% CI, 0.70–1.57]).

DISCUSSION

In a large, nationwide study, we found that use of PPIs is associated with increased odds for reporting a positive COVID-19 test. The highest risk is seen among individuals taking PPIs twice daily—a common practice in both primary and secondary care (12, 13)—as they are nearly four-times more likely to report COVID-19 positivity when compared to those not on PPIs. Since meta-analysis reveals that twice daily PPIs do not offer clinically meaningful benefits over once daily dosing for gastroesophageal reflux disease (14), our findings further emphasize that PPIs should only be used when clinically indicated at the lowest effective dose.

Our study has several strengths. To our knowledge, this is the first study examining the relationship between PPIs and COVID-19 among a population-based sample of Americans. Our finding that PPI use is associated with increased odds for acquiring SARS-CoV-2, which invades and replicates within enterocytes (4), is consistent with prior literature showing that PPIs also increase the risk for other enteric infections (1, 2, 15, 16). Most of these studies, though, did not assess the impact of twice-daily dosing; further research examining whether PPI twice daily increases the risk for such infections over once-daily dosing are needed. We also examined the association between PPIs and GI COVID-19 symptoms and found that PPIs do not increase the odds for reporting such symptoms. As GI symptoms are prevalent in those with COVID-19 (5), further studies assessing the mechanisms behind its differential presentations are needed. Moreover, unlike many studies that use retrospective data to examine potential PPI side effects (1), we prospectively constructed this survey to test an *a priori* hypothesis. Our survey was also

generically positioned to participants at the outset as a “national health survey” and not as a COVID- or PPI-focused study in an effort to minimize participation bias.

There are also limitations to our study. First, as with all observational studies, our study is susceptible to residual confounding and selection bias; those severely ill and hospitalized with COVID-19 were unlikely to have taken the survey. Second, our findings are also subject to protopathic bias, as some may have started a PPI in response to certain COVID-19 symptoms (e.g., nausea, abdominal pain) or related treatments (e.g., nonsteroidal anti-inflammatory drugs for prolonged fevers). We attempted to address this by identifying those who started a PPI after their COVID-19 diagnosis and classifying them as non-users. Moreover, protopathic bias would not have impacted our positive finding seen in those using a PPI for >6 months as they started it before the pandemic. Third, there are also potential risks for misclassification and recall biases because the medication and COVID-19 testing data were self-reported. It is unclear, however, why an individual would falsify their COVID-19 status, or why variations in self-reported COVID-19 positivity would positively correlate with PPI usage but not H2RA use. Additionally, self-reported COVID-19 status has been used in other widely-publicized surveys regarding pandemic epidemiology (17, 18). The short recall period also reduces risk of recall bias and it is less of a concern for the medication data as we asked respondents about their current usage. Fourth, we did not determine how respondents tested positive for COVID-19 (e.g., polymerase chain reaction [PCR] or serology testing) nor did we measure disease severity. We suspect, though, that most participants underwent PCR testing, in contrast to antibody surveillance, as the vast majority of respondents had symptomatic COVID-19. Fifth, while our survey was described generically as a “national health survey,” most questions focused on GI symptoms and those with

such symptoms may have been predisposed to completing the survey. On the other hand, respondents without GI symptoms remained eligible for the survey and received the same incentive despite needing to answer fewer questions than those with symptoms. Finally, there are limitations related to generalizability as the survey was administered only in English and did not assess reading ability; the findings may not be generalizable to non-English speakers or those with limited literacy. Our survey was also conducted solely online, but 90% of all Americans and 73% of those 65 years of age and older currently use the internet (19).

These potential limitations notwithstanding, there is biological plausibility for our findings as the similar SARS-CoV-1 is pH-sensitive and remains infective at a pH >3 (3); twice daily PPI use can lead to 24-hour median intragastric pH >6 and sustain pH >4 for more than 20 hours (20-22). We also found evidence of a dose-response relationship as those using PPIs twice daily have higher odds for COVID-19 positivity when compared to those taking lower-dose PPIs or those not using PPIs at all. Moreover, individuals taking the less potent H2RAs are not at increased risk. Further studies examining the association between PPIs and COVID-19 and whether they increase the risk for more severe disease are needed.

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TABLE 1. Demographics of the study cohort

Variable	Overall cohort (N=53,130)	Tested positive for COVID-19 (n=3,386)
Age:		
18-29 yo	12,064 (22.7)	385 (11.4)
30-39 yo	14,400 (27.1)	2,524 (74.5)
40-49 yo	10,498 (19.8)	320 (9.5)
50-59 yo	9,078 (17.1)	106 (3.1)
≥60 yo	7,090 (13.3)	51 (1.5)
Sex:		
Male	25,492 (48.0)	1,168 (34.5)
Female	27,071 (51.0)	2,192 (64.7)
Prefer not to say	567 (1.1)	26 (0.8)
Race/ethnicity:		
Non-Hispanic white	34,401 (64.8)	624 (18.4)
Non-Hispanic black	4,261 (8.0)	119 (3.5)
Latinx	8,115 (15.3)	2,360 (69.7)
Non-Hispanic Asian	2,388 (4.5)	48 (1.4)
Other/prefer not to say	3,965 (7.5)	235 (6.9)
Education level:		
High school degree or less	15,248 (28.7)	2,357 (69.6)
Some college	13,499 (25.4)	299 (8.8)
College degree	17,470 (32.9)	506 (14.9)
Graduate degree	6,913 (13.0)	224 (6.6)
Marital status:		
Married	24,547 (46.2)	2,752 (81.3)
Not married	28,583 (53.8)	634 (18.7)
Employment status:		
Not employed (unemployed, on disability, on leave of absence from work, retired, or homemaker)	19,906 (37.5)	697 (20.6)
Employed or student	33,224 (62.5)	2,689 (79.4)
Total household annual income:		
≤$50,000	22,489 (42.3)	495 (14.6)
$50,001–$100,000	15,721 (29.6)	309 (9.1)
$100,001–$200,000	8,146 (15.3)	380 (11.2)
≥$200,001	3,950 (7.4)	2,151 (63.5)
Prefer not to say	2,824 (5.3)	51 (1.5)
Body mass index (kg/m^2):		
Normal or underweight (<25)	20,591 (38.8)	2,554 (75.4)
Overweight (25–29.9)	14,879 (28.0)	266 (7.9)

Obese (≥30)	17,554 (33.0)	563 (16.6)
Unknown	106 (0.2)	3 (0.1)
Current smoking status:		
Not at all	36,528 (68.8)	461 (13.6)
Some days	4,649 (8.8)	451 (13.3)
Every day	11,953 (22.5)	2,474 (73.1)
Average alcohol use per week:		
No days	26,468 (49.8)	495 (14.6)
1–3 days	19,386 (36.5)	2,344 (69.2)
4–6 days	4,641 (8.7)	341 (10.1)
Every day	2,635 (5.0)	206 (6.1)
U.S. region:		
Northeast	9,779 (18.4)	321 (9.5)
South	22,175 (41.7)	2,321 (68.5)
Midwest	10,875 (20.5)	205 (6.1)
West	10,301 (19.4)	539 (15.9)
Insurance status:		
Insured	47,010 (88.5)	3,304 (97.6)
Not insured	6,120 (11.5)	82 (2.4)
Has usual source of care:		
Yes	41,089 (77.3)	3,004 (88.7)
No	12,041 (22.7)	382 (11.3)
Rome IV irritable bowel syndrome	7,214 (13.6)	438 (12.9)
Celiac disease[a]	1,430 (2.7)	214 (6.3)
Gastroesophageal reflux disease[a]	6,662 (12.5)	109 (3.2)
Liver cirrhosis[a]	1,227 (2.3)	182 (5.4)
Crohn's disease[a]	1,176 (2.2)	114 (3.4)
Ulcerative colitis[a]	911 (1.7)	40 (1.2)
Diabetes[a]	5,634 (10.6)	243 (7.2)
HIV/AIDS[a]	610 (1.1)	54 (1.6)
PPI exposure:		
No current PPI use	36,583 (68.9)	752 (22.2)
Daily PPI use or less	14,855 (28.0)	2,436 (71.9)
Twice daily PPI use	1,692 (3.2)	198 (5.8)
H2RA exposure:		
No current H2RA use	44,586 (83.9)	2,828 (83.5)
Daily H2RA use or less	7,387 (13.9)	415 (12.3)
Twice daily H2RA use	1,157 (2.2)	143 (4.2)

H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

a Respondents were asked whether they were ever diagnosed by a healthcare provider with the condition.

TABLE 2. Results from the multivariable logistic regression model on reporting a positive COVID-19 test (N=53,130)

Variable	Positive COVID-19 Test (n=3,386)	OR [95% CI][a]
PPI exposure:		
No current PPI use	752 (2.1)	Reference
Once daily PPI use or less	2,436 (16.4)	2.15 [1.90–2.44][b]
Twice daily PPI use	198 (11.7)	3.67 [2.93–4.60][b]
H2RA exposure:		
No current H2RA use	2,828 (6.3)	Reference
Once daily H2RA use or less	415 (5.6)	0.85 [0.74–0.99][c]
Twice daily H2RA use	143 (12.4)	0.86 [0.66–1.11]

Note: data are presented as n (% of row).

CI, confidence interval; H2RA, histamine-2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

a The multivariable logistic regression model included PPI use, H2RA use, age, sex, race/ethnicity, education level, marital status, employment status, total household annual income, body mass index, current smoking status, alcohol use per week, U.S. region, insurance status, usual source of care, and presence of Rome IV irritable bowel syndrome, celiac disease, gastroesophageal reflux disease, liver cirrhosis, Crohn's disease, ulcerative colitis, diabetes, and HIV/AIDS.

b $p<.001$

c $p=.032$