Original Investigation

Proton Pump Inhibitors and Risk for Recurrent Clostridium difficile Infection

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Background: Proton pump inhibitors (PPIs) are widely used gastric acid suppressants, but they are often prescribed without clear indications and may increase risk of Clostridium difficile infection (CDI). We sought to determine the association between PPI use and the risk of recurrent CDI.

Methods: Retrospective, cohort study using administrative databases of the New England Veterans Healthcare System from October 1, 2003, through September 30, 2008. We identified 1166 inpatients and outpatients with metronidazole- or vancomycin hydrochloride-treated incident CDI, of whom 527 (45.2%) received oral PPIs within 14 days of diagnosis and 639 (54.8%) did not. We determined the hazard ratio (HR) for recurrent CDI, defined by a positive toxin finding in the 15 to 90 days after incident CDI.

Results: Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.5%). Using Cox proportional survival methods, we determined that the adjusted HR of recurrent CDI was greater in those exposed to PPIs during treatment (1.42; 95% confidence interval [CI], 1.11-1.82). Risks among exposed patients were highest among those older than 80 years (HR, 1.86; 95% CI, 1.15-3.01) and those receiving antibiotics not targeted to C difficile during follow-up (HR, 1.71; 95% CI, 1.11-1.64).

Conclusions: Proton pump inhibitor use during incident CDI treatment was associated with a 42% increased risk of recurrence. Our findings warrant further studies to examine this association and careful consideration of the indications for prescribing PPIs during treatment of CDI.

Arch Intern Med. 2010;170(9):772-778

Proton pump inhibitors (PPIs) are among the most commonly prescribed agents in outpatient and inpatient settings, but they are often used without a clear indication. Although PPIs have been considered relatively safe, studies have demonstrated that PPI use and the use of other gastric acid suppressants are associated with a variety of infections, including Salmonella and Campylobacter gastroenteritis and community-acquired and nosocomial pneumonia. Several observational studies have associated community-acquired and nosocomial CDI with PPI use, finding risks of CDI 2 to 3 times higher in PPI users compared with nonusers. Other putative risk factors include older age, frailty, and environmental factors. Proton pump inhibitors have also been associated with Clostridium difficile infection (CDI). Clostridium difficile is a spore-forming bacterium with a toxin that is associated with diarrheal illnesses. Symptomatic recurrence occurs in approximately 20% of patients after treatment, with even higher rates after subsequent episodes. The incidence of CDI in the United States has nearly tripled in the past decade, with antibiotic and hospital exposures recognized as the preeminent risks for infection. Other research has failed to associate PPIs with CDI. The exact relationship between PPI use and incident CDI remains elusive, and no causative pathway has been demonstrated. The relationship between PPI exposure and the risk of recurrent CDI is even less clear, with fewer studies and conflicting findings. To further address this question, we conducted a retrospective cohort analysis using data from the New England Veterans Healthcare System (VISN 1) to determine the association between PPI use and the risk of recurrent CDI.
STUDY SETTING

We used linked pharmacy and administrative databases from VISN 1 from October 1, 2003, through September 30, 2008. The New England region consists of 8 Veterans Affairs (VA) medical centers and affiliated clinics, including 3 large, urban, tertiary care centers and 5 smaller facilities providing inpatient and outpatient care. The VISN 1 pharmacy files were obtained from Veterans Health Information Systems and Technology Architecture. The data elements of the outpatient and inpatient pharmacy files used in this study include patient identification, date of birth, drug name and dose, drug administration route, quantity, VA drug class, date of original prescription, number of days of medication supplied, and refill date. Laboratory data were obtained from the electronic medical record. Comorbidities were captured via the VA national patient care database located at the Austin Automation Center, Austin, Texas. Analyses were conducted at the Massachusetts Veterans Epidemiology Research and Information Center, VA Cooperative Studies coordinating center, VA Boston Healthcare System. The study was approved by the institutional review board of the VA Boston Healthcare System, which waived informed consent and Health Insurance Portability and Accountability Act of 1996 authorization.

STUDY POPULATION

From the data sets, we identified patients with a first positive finding of a C. difficile toxin from October 1, 2004, through September 30, 2008. This search yielded the index date for 1549 patients. The laboratories of VISN 1 use enzyme immunoassay tests for toxins A and B, with a standard practice of testing only loose stool samples. This sample of incident cases was then restricted to 1546 patients with a minimum of 1 year of prior VA health care system use to establish their use of the VA system. We further limited the study population to 1408 patients for whom treatment was initiated within the VA system with metronidazole or oral vancomycin hydrochloride and then to 1166 patients whose treatment started within 3 days before or after the index CDI (Figure 1).

PRIMARY EXPOSURE AND OUTCOMES

The main exposure variable was the use of any oral PPI during the 14 days after incident CDI diagnosis, coinciding with the treatment window. For inpatients (n = 981), PPI exposure was defined as any pharmaceutical dispensing of a PPI during this postdiagnosis window. For outpatients (n = 185), the end date of the most recent antecedent prescription was extended by 10% (eg, 9 days for a 90-day prescription) to account for potentially missed doses. If the predicted prescription end date fell after the index date, then the subject was placed in the PPI-exposed group. For all outpatients, actual prescription end dates fell beyond the index date. With these exposure criteria, 527 patients (45.2%) were categorized as PPI exposed and 639 patients (54.8%) as non–PPI exposed (Figure 1).

The primary outcome measure was a positive finding for a C. difficile toxin occurring 15 to 90 days after the incident CDI diagnosis date. We established a 15- to 90-day follow-up window to provide a period of observation that would capture the greatest number of possible recurrent cases based on clinical observations and previous studies. Patients were censored at death or 90 days after the index date. We also calculated the time to recurrence, defined as the number of days from the later of either the index date or the start of incident CDI treatment until the recurrent diagnosis date. Thus, the calculated time to recurrence could be as short as 12 days.

COVARIATES

Covariates that may influence the risk of recurrent CDI and those that may influence exposure to PPIs were included in our analysis. These variables were age, sex, comorbid conditions, medication used before the index date, initial incident CDI antibiotic treatment (metronidazole or vancomycin), non–CDI-targeted antibiotic exposure during follow-up, VA nursing home admission during the study period, and, for those who were inpatients, the duration of hospitalization after the index date.

Comorbidities were determined from administrative records using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, including selected diagnoses recorded in the 2 years before the index date. Comorbidities and their ICD-9-CM codes were hypertension (codes 401-404), diabetes (250), ischemic heart disease (410-414), chronic obstructive pulmonary disease (491, 492, and 496), esophageal disease (530), peptic ulcer disease (531-535), solid tumors (140-199), and rheumatologic disease (710, 714, and 720). Medication used in the 90 days before the index date was included to represent the acuity and severity of the comorbid conditions and those drugs that might directly increase susceptibility to infections. Specific medications were antibiotics, systemic and inhaled corticosteroids, chemotherapeutics, and immunomodulators. In addition, we recorded inpatient and outpatient prescriptions for H2 receptor antagonists.

We determined the initial antibiotic treatment for CDI because differences in clinical severity may affect the choice of antibiotic. There may also be different treatment success rates. We evaluated how many patients changed from metronidazole to vancomycin therapy within the 14 days after diagnosis. Because antibiotic exposure is a major risk factor for CDI, we determined whether patients were exposed to non–CDI-targeted antibiotics during follow-up. Similarly, because hospital exposure is a major risk factor, we determined the number of days patients were hospitalized after incident CDI diagnosis. We categorized this variable as 0 days, discharged fewer than 14 days after the index diagnosis, and discharged at least 14 days after the index diagnosis.

To account for the possible effect of PPI exposure from day 15 to censorship, we determined whether patients were dispensed or prescribed PPIs by using the same criteria as during the treatment window.
Sensitivity Analysis

Positive toxin findings alone may not represent clinically relevant, recurrent CDI. Thus, we determined HRs excluding 34 patients (13.5% of 251 total cases of recurrence) with a new positive toxin finding for whom there was no VA pharmacy record of additional CDI antibiotic treatment. Because continued hospital exposure could favor CDI recurrence, we determined whether alternative categorization of inpatient time to discharge influenced hazard rates. We also analyzed to what extent patients with recurrent CDI had intervening positive toxin results. All analyses were performed using SAS statistical software (version 9.1.3; SAS Institute Inc, Cary, North Carolina).

Results

Study Population

The study population of 1166 veteran patients meeting criteria for recurrent CDI was predominantly male (97.2%), with a median age of 74 (interquartile range, 63-82) years. Overall, 527 (45.2%) of the patients were exposed to a PPI concurrent with antibiotic treatment (PPI-exposed group) and 639 (54.8%) were not exposed to concurrent PPI use (non-PPI-exposed group) (Figure 1 and Table 1). Almost all PPI-exposed patients (96.7%) were prescribed omeprazole, 20 mg once daily, or the equivalent dose of another PPI; the remaining patients received lower or higher PPI doses. Age and sex were similar among the PPI-exposed and non-PPI-exposed patients. The PPI-exposed group had a higher prevalence of ICD-9-CM coded ischemic heart disease, chronic obstructive pulmonary disease, esophageal disease, peptic ulcer disease, and rheumatologic disease. This group also had greater exposure to systemic corticosteroids. Metronidazole was the initial antibiotic used for treatment of incident CDI in more than 90% of both groups. Similar proportions (11%) in each group were switched from metronidazole to oral vancomycin within 14 days than those in the non-PPI-exposed group. Also, those in the PPI-exposed group were more likely to have been admitted to a VA nursing home during the study window. However, patients in the PPI-exposed group were more likely to have been inpatients and were more likely to have inpatient stays exceeding 14 days than those in the non-PPI-exposed group. Also, those in the PPI-exposed group were more likely to have been exposed to non-CDI antibiotics during follow-up. Of those in the PPI-exposed group, 434 (82.4%) had continued exposure to PPIs during follow-up days 15 to 90. In the non-PPI-exposed group, there were only 41 patients (6.4%) exposed to PPIs during this follow-up. Similar proportions of each group had an admission to a VA nursing home during the study window.

Relationship of PPI to Recurrent CDI

The primary outcome of additional positive findings for C difficile toxin occurred in 251 patients (21.5%). The unadjusted incidence of recurrent toxin in the 15 to 90 days after incident CDI was greater in the PPI-exposed compared with the non-PPI-exposed group (133 of 527 [25.2%] vs 118 of 639 [18.5%]). Unadjusted Kaplan-Meier recurrence-free survival curves are seen in Figure 2, with an associated HR of 1.42 (95% CI, 1.11-
1.82; \( P = .006 \) for those in the PPI-exposed group compared with those in the non-PPI-exposed group. After adjusting for age, initial incident CDI antibiotic treatment (metronidazole or vancomycin), additional antibiotic exposure (yes or no), duration of hospital exposure (0, <14, or \( \geq 14 \) days), and differing baseline comorbidities (ischemic heart, esophageal, peptic ulcer, pulmonary, and rheumatologic diseases) and medications (systemic corticosteroids), the HR associated with PPI exposure remained elevated at 1.42 (95% CI, 1.10-1.83; \( P = .008 \)) (Table 2). The proportional hazards assumption was met for the adjusted model because the interaction term between exposure and the logarithm of time was not significant (\( P = .65 \)).

**EFFECT MODIFICATION**

We evaluated potential effect modification by age, non-CDI antibiotic exposure during follow-up, and PPI exposure during follow-up. We found an increasing risk of recurrence associated with PPI use with increasing age (Table 2). Stratification by non-CDI antibiotic exposure in the follow-up window modified the association of PPIs and recurrent CDI on the ratio scale. Those exposed to additional antibiotics had a 71% greater risk of recurrence associated with PPIs, whereas those not exposed to antibiotics had a 30% greater risk of recurrence. However, we were not sufficiently powered to detect a statistically significant effect modification for age or non-CDI antibiotic exposure.

Most patients in the PPI-exposed group (434 of 527 [82.4%]) and very few of the non-PPI-exposed group (41 of 639 [6.4%]) received PPIs during the 15- to 90-day follow-up (Table 1). Patients prescribed PPIs during both treatment and follow-up had an increased risk of recurrence compared with those who were not exposed to PPIs in either time window (HR, 1.44; 95% CI, 1.09-1.89; \( P = .01 \)). Greater risk for recurrence, although not powered for statistical significance, was also seen in the smaller subgroups who were exposed to PPIs in the treatment period only (41 patients; HR, 1.30; 95% CI, 0.68-2.51; \( P = .43 \)) or in the follow-up period only (93 patients; HR, 1.51; 95% CI, 0.93-2.46; \( P = .10 \)).

**SENSITIVITY ANALYSES**

We determined the proportion of those classified as having recurrent CDI whose treatment with CDI-targeted antibiotics was documented in the VA pharmacy. Of the 251 cases meeting our criteria for recurrent CDI, 217 (86.5%) were prescribed metronidazole or oral vancomycin at the time of the additional positive toxin finding. Restricting our risk analyses to those patients did not change our estimates (adjusted HR, 1.52; 95% CI, 1.15-2.01; \( P = .003 \)).

Because a change from metronidazole to vancomycin therapy may reflect more severe disease clinically or failure to respond to the original CDI treatment antibiotic, we evaluated the influence of any exposure to vancomycin on the association of PPIs and recurrence. Controlling for any vancomycin treatment within the first 14 days did not alter our findings (adjusted HR, 1.42; 95% CI, 1.10-1.84; \( P = .008 \)).

We conducted adjusted analyses using varied categorical lengths of hospitalization following incident CDI diagnosis and found no differences in the HRs associating PPI exposure with recurrent CDI (data not shown).

Of the 251 recurrent cases, 121 (48.2%) had no intervening test for \( C \) difficile toxin, 100 (39.8%) had an intervening test with a negative result, and 30 (12.0%) had an intervening test with positive results, mostly within several days of the index date. There was no difference in PPI exposure among those with intervening negative test results or no intervening tests (\( P = .43 \)).

**COMMENT**

Our findings indicate that PPI use concurrent with treatment for CDI was associated with a 42% increased risk of recurrent CDI in the subsequent 15 to 90 days. In stratified analyses, exposure during treatment and within the follow-up window was associated with a 44% greater recurrence, whereas patients prescribed PPIs in only 1 of the 2 exposure windows (ie, treatment only or follow-up only) demonstrated a higher but nonstatistically significant risk of recurrent infection.
Proton pump inhibitors have been linked to higher risks of community-acquired and nosocomial CDI, but other studies have not shown this association. Few studies have specifically focused on the association of PPIs with recurrent CDI. A retrospective medical record review of 140 patients in a single VA medical center demonstrated 4-fold increased odds of recurrence in those exposed to PPIs concurrently with CDI treatment, although HRs accounting for time to recurrence were not analyzed. A small prospective medical record review of patients with endoscopically proved pseudomembranous colitis found higher relapse rates in those prescribed antiulcer medications but did not distinguish between PPIs and other gastric acid suppressants. Similarly, a case-control study showed a slightly greater risk of recurrence in patients exposed to H2 receptor antagonists, but the investigators did not assess the risk of PPIs. Others have not found a difference in recurrence rates due to acid-suppressing medications; however, those investigators did not distinguish between PPIs and H2 receptor antagonists, which are generally less potent. The data presented herein represent, to our knowledge, the largest evaluation of this potentially modifiable exposure to PPIs and risk of CDI recurrence.

One potential mechanism to explain this association may be that elevated gastric pH levels facilitate the growth of potentially pathogenic upper and lower gastrointestinal tract flora. Although C. difficile spores are acid resistant, vegetative forms are susceptible to acidity. Furthermore, elevated gastric pH levels may allow or facilitate conversion from spore to vegetative forms of C. difficile in the upper gastrointestinal tract. Other potential mechanisms include impairment of leukocytes and other immune responses and antimicrobial properties of PPIs.

Our study had several strengths, including use of data from the VA’s large, multisite, integrated health care system. The ability to link information from laboratory, pharmacy, and administrative data enabled comprehensive assessment of multiple aspects of patients’ health care. We also incorporated time to recurrence into our analyses, and stratified and sensitivity analyses supported the association of PPI use with recurrent CDI. Finally, our data are compatible with plausible biological mechanisms and with results from previous studies indicating increased risk of infections, including CDI, with PPI exposure.

As with all studies using administrative and clinical data extracts, our findings should be viewed in the context of the following limitations. Use of observational databases allows for potential misclassification of exposure (e.g., for outpatients, use of non-VA prescribed or over-the-counter PPIs or other gastric acid suppressants, and conversely, nonadherence to VA-prescribed PPI therapy). However, there exists significant financial incentive for most veterans to obtain prescriptions directly from the VA. Furthermore, because most of our sample initially had CDI treatment as inpatients, we are confident in the quality of our PPI exposure data.

A positive test result for a C. difficile toxin by itself does not necessarily indicate a clinically relevant recurrence and could lead to potential misclassifications of the outcome. However, our findings remained robust when we assessed overdiagnosis of recurrent CDI by analyzing only the 217 subjects (86.5%) who had an additional positive toxin finding and additional documented treatment with CDI-targeted antibiotics. The hazards of recurrence in this restricted sample were similar to those of the entire study population (adjusted HRs, 1.52 vs 1.42, respectively).

Our data cannot, with certainty, determine to what extent the patients had recurrent CDI after a short period of treatment success or experienced treatment failure. Further examination revealed that 39.8% of the recurrent cases had an intervening negative stool toxin finding and 48.2% had no intervening tests. There was no difference in PPI exposure among these subgroups. From these data, there was little evidence to suggest that patients classified as having recurrent CDI had persistently positive toxin results between their index and recurrence dates. Nevertheless, to distinguish recurrent disease from treatment failure would require a prospective, systematic testing of subjects receiving treatment for CDI.

Patient frailty has been associated with CDI. Although we controlled for differences in comorbid conditions, other than incorporating use of selected medications to treat these conditions, we did not directly assess the severity of illnesses. In addition, our study was conducted in a predominantly male veteran population, and our results may not generalize to all patients. Previous studies have found women to be at greater risk for CDI than men, but other large investigations have associated PPIs with C. difficile in both sexes. Overall, these findings may be generalized to other elderly populations with similar access to PPIs.

After incident CDI diagnosis, our sample had other potentially important exposures increasing their risk of recurrent CDI. Although we controlled for patients’ time in the hospital after incident disease, we were unable to incorporate C. difficile pressure in specific settings such as hospital wards. We also did not find any difference between groups for nursing home admissions during the study window. In our adjusted analyses, controlling for non-CDI antibiotic exposure during follow-up did not affect the risk associated with PPI exposure during treatment. When stratifying results, the risk associated with PPIs increased for those with additional antibiotic exposure, and statistical significance was no longer reached in those who received no further antibiotic treatment. Given the direction of the association, lack of further antibiotic treatment does not necessarily negate the effect of PPIs.

Most patients remained exposed or nonexposed to PPIs during the treatment and follow-up windows; very few received PPIs only during days 1 to 14 or only during days 15 to 90. Continued exposure to PPIs was associated with a risk of recurrent CDI similar to that found for the originally defined PPI-exposed group. Thus, to what extent the PPI exposure concurrent with CDI treatment, during follow-up, or during both periods is driving the association with recurrence is unclear.

The effect of any risk attributable to PPIs, regardless of magnitude, is increased owing to the high prevalence of use for this class of medication. Proton pump inhibi-
tors are often used without a clear indication. Studies of outpatients have found that of those receiving long-term acid-suppressive therapy, only 61% had a relevant gastrointestinal tract–related diagnosis.4 Similarly, studies of inpatients found acid-suppressing medications frequently prescribed for stress ulcer prophylaxis in non-intensive care unit settings,41-43 a practice contrary to the American Society of Health System Pharmacists guidelines.44 Choudhry et al45 studied patients with CDI and PPI use for prescription indication; an appropriate indication was not identified in 53.4% of the patients. We did not assess the indications for PPI use in our patients.

In conclusion, the study identified a 42% increased risk of recurrent CDI related to PPI use. Given the morbidity and cost associated with recurrent CDI and the lack of readily modifiable risk factors, our findings have important clinical implications. The data presented herein support the need for critical assessment of PPI use in patients being treated for CDI as well as further research to test this association.

Accepted for Publication: November 20, 2009.
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Author Contributions: Dr Linsky had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis. Study concept and design: Linsky, Gupta, Lawler, and Hermos. Acquisition of data: Linsky and Fonda. Analysis and interpretation of data: Linsky, Gupta, Lawler, Fonda, and Hermos. Drafting of the manuscript: Linsky and Hermos. Critical revision of the manuscript for important intellectual content: Linsky, Gupta, Lawler, Fonda, and Hermos. Statistical analysis: Linsky, Lawler, and Fonda. Administrative, technical, and material support: Linsky, Lawler, Fonda, and Hermos. Study supervision: Linsky, Gupta, and Hermos.

Financial Disclosure: None reported.

Funding/Support: The study was supported by the resources of the VA Cooperative Studies Program and using the facilities of the VA Boston Healthcare System.

Previous Presentations: This study was presented at the 32nd Annual Meeting of the Society for General Internal Medicine; May 14, 2009; Miami, Florida; and at the 25th International Conference on Pharmacoepidemiology and Therapeutic Risk Management; August 16, 2009; Providence, Rhode Island.

Additional Contributions: Galina Sokolovskaya, MS, provided programming assistance and David Gagnon, MD, provided statistical consultation.

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It is now time to test the various hypotheses generated by observational studies of vitamin D, including that of Llewellyn et al,2 in adequately designed and conducted RCTs. Repeating and updating meta-analyses of existing data sets, which has the potential to confuse rather than clarify,18 will not suffice. Very importantly, such trials will also provide an opportunity to systematically assess potential harms of vitamin D supplementation, an issue that has been largely overlooked or dismissed. We should invest in trials that provide the best possible evidence on the benefits and risks of vitamin D before we invest in costly, difficult, and potentially unrewarding interventional strategies.

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Financial Disclosure: None reported.

Funding/Support: This work received funding from the Health Research Council of New Zealand (Drs Grey and Bolland).

Additional Contributions: Ian Reid, MD, provided critical review of the manuscript.