Gastric Acid Suppression by Proton Pump Inhibitors as an Independent Risk Factor for Clostridium difficile–Associated Diarrhea

Keithen Branch, PharmD, Vince Yahl, PharmD, BCPS, Karen Kier, PhD, MSc, BPharm, Nancy Mertz, BBA, and Suzanne Marques, PharmD, BCPS

ABSTRACT

Purpose: We analyzed the relationship between the use of proton pump inhibitors (PPIs) and the development of Clostridium difficile–associated diarrhea (CDAD) in hospitalized patients.

Methods: We conducted a retrospective case–control study in a 420-bed tertiary hospital serving a rural population in a 10-county region. We identified all patients in the hospital who had been tested for the presence of C. difficile toxin A in the stool from January 1, 2005, to October 31, 2005. Potential case subjects were those who tested positive for toxin A (n = 81); potential control subjects tested negative (n = 706). Each case subject was matched to a control subject based on age (within five years), sex, chronic dialysis, acute dialysis, and the use of nutrition. Fifty-seven case subjects were randomly matched to 57 control subjects. Thirty-four case subjects and 37 controls were exposed to a PPI.

Results: No statistically significant differences were observed between the study groups (P = 0.442).

Conclusion: In hospitalized patients with significant risk factors for the development of CDAD, PPIs did not escalate the incidence of the disease. Until further prospective research is conducted, this study supports the use of PPIs in hospitalized patients when indicated.

INTRODUCTION

Clostridium difficile–associated diarrhea (CDAD) has become a national concern with widespread implications in health care. The incidence and morbidity of CDAD are on the rise; in fact, CDAD rates doubled from 1996 to 2003. There has also been much concern regarding outbreaks of a strain of C. difficile identified as group BI by restriction-endonuclease analysis and North American pulse-field type 1 by pulse-field gel electrophoresis (BI/NAP1), which increases the severity of the disease via increased toxin production. In addition, newer hypervirulent strains of C. difficile have shown diminished responses to traditional treatments such as oral metronidazole (Flagyl, Pfizer). CDAD has a significant impact on the health care system, because it increases both medical costs and hospital length of stay.

The use of proton pump inhibitors (PPIs) in the hospital has recently increased because of the availability of intravenous (IV) formulations, competitive marketing, and expanded indications. Exposure to PPI therapy increases the incidence of gastric and duodenal bacterial overgrowth. Subsequently, several studies have analyzed the relationship between PPIs and the development of CDAD. Reports in the literature have been conflicting.

Several trials have shown a positive association between PPIs and the development of CDAD. Although Cunningham et al. noted an association in hospitalized patients, details of the study groups were not included in the report, thus making it difficult to assess subject demographics.

In a case–control and cohort study, Dial et al. also found an increased risk of CDAD development after PPI exposure, but several significant differences between the study groups might have accounted for the increased risk. Case subjects were more likely to have renal failure requiring dialysis, methicillin-resistant Staphylococcus aureus (MRSA) infection, and exposure to clindamycin (Cleocin, Pfizer). Each of these factors might have increased the risk of CDAD in these patients.

In another case–control study by Dial et al., the risk of CDAD increased following exposure to PPIs in the outpatient setting; however, clinical diagnoses of CDAD were included in the case group of patients without laboratory confirmation for the presence of, or a definitive diagnosis of, C. difficile.

In another study of outpatients by Dial et al., those who received a prescription for oral vancomycin (Vancocin, Roche) were also more likely to be taking a PPI. The authors assumed that the patients taking oral vancomycin were being treated for CDAD. In this study, the case subjects were more likely to have renal failure, inflammatory bowel disease, MRSA infection, and leukemia or lymphoma. These comorbidities might have influenced the results.

In other reports, PPIs were not associated with the development of CDAD. In a retrospective case–control analysis, Shah et al. noted no association with the use of gastric acid–suppressive medications and CDAD in hospitalized patients older than 65 years of age. This study included both histamine H₂-receptor antagonists (H₂RAs) and PPIs in the case patients; this might have affected the results, because H₂RAs do not suppress gastric acid secretion to the same extent that PPIs do.

In a prospective trial from Montreal, Quebec, Loo et al. found no association between CDAD and PPIs. In this study, designed to observe risk factors for CDAD, the administration

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of fluoroquinolones and cephalosporins increased the risk for the development of CDAD.

In a retrospective cohort study, Pepin et al.14 found no association with PPI use. Again, the use of fluoroquinolones emerged as the most important risk factor for the development of CDAD.

PPIs have become an integral part of treating patients in the hospital, particularly in preventing stress ulcers in the critically ill. To date, the literature is controversial and inconclusive in terms of the association between PPIs and CDAD, especially in hospitalized patients. To better understand this matter, we designed a case–control study at a rural hospital to examine the institutional use of PPIs and their potential role for increasing the risk of CDAD.

**METHODS**

**Study Design**

Our study was a retrospective case–control review that included patients admitted to the hospital over a 10-month period. All study subjects developed diarrhea and were subsequently tested for the presence of *C. difficile* toxin A in the stool, as determined by an enhanced optical immunoassay. The study took place in a 420-bed tertiary hospital serving a rural population in a 10-county region.

**Primary Outcome**

The primary outcome of our study was the detection of differences in PPI exposure between case and control patients.

**Inclusion and Exclusion Criteria**

Patients who developed diarrhea and who were tested for *C. difficile* toxin A were eligible to be included in the study. They had to be at least 18 years of age and had to be admitted to the hospital during the study period.

Patients were excluded from the study if they experienced a recurrent episode of CDAD. Recurrent episodes were defined as a positive test for toxin A within the previous six months. Subjects with an unconfirmed diagnosis of CDAD were excluded; subjects were also excluded if they were not successfully matched to controls.

**Cases and Controls**

Patients who met the inclusion criteria during the study period and who tested positive for toxin A were considered possible case subjects (n = 81). Patients who met the inclusion criteria and who tested negative for toxin A were potential control subjects (n = 706).

After exclusion criteria were applied, each remaining case subject was randomly matched to a control subject to account for risk factors for CDAD and for severity of illness. Matching criteria included age within five years, sex, acute dialysis, chronic dialysis, the use of H2RAs, and the use of total parenteral nutrition.

**Exposure to Antibiotics and Proton Pump Inhibitors**

Medication histories or inpatient dispensing records were used to determine any antibiotic exposure within 30 days of *C. difficile* toxin assay testing. We analyzed all preoperative and single-dose antibiotic exposures. We performed a second analysis to eliminate exposures to a single dose of an antibiotic. For this analysis, exposure was defined as (1) having taken an antibiotic on three consecutive days in the previous month or (2) having taken an antibiotic 48 consecutive hours immediately before toxin A testing.

Subjects were considered to have been exposed to a PPI (1) if they had used a PPI at least three consecutive days before testing for toxin A; (2) if they had used a PPI at least seven consecutive days within the previous month during a hospital stay; or (3) if they had received active treatment with a PPI before hospital admission.

**Statistical Analysis**

We tested primary outcomes for significant differences using the Pearson chi-square test. To assess differences between case and control groups, we applied this test or Fisher’s exact test to patient demographic characteristics. For parameters that indicated a statistically significant difference, we estimated odds ratios (ORs) and 95% confidence intervals (CIs). Values were considered statistically significant if *P* was less than 0.05. SPSS for Windows, version 12.0, was used to perform the statistical analyses.

**Patient Enrollment**

During the study period, 81 patients tested positive for toxin A. Nineteen subjects were excluded: 15 had recurrent episodes of CDAD, and four were younger than 18 years of age. In all, 62 potential case subjects remained. After matching criteria were applied, 57 case subjects were successfully matched to 57 control subjects.

**RESULTS**

**Primary Outcome**

The difference in the rate of exposure to a PPI in the case and control groups was not statistically significant. Thirty-four case subjects and 37 controls were exposed to a PPI (*P* = 0.442). In a separate analysis, we examined each of the criteria for PPI exposure independently and found no statistical difference between case subjects and controls for each variable (*P* = 0.424) (Table 1).

**Patient Demographics**

We analyzed age, length of stay (LOS), and antibiotic exposure. The average age of patients in the case group was 66.02 years; the average age of controls was 65.95 years (*P* = 0.258).

We then stratified age into three categories: younger than 60

<table>
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<th>Table 1</th>
<th>Number of Subjects Exposed to a Proton Pump Inhibitor</th>
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<tr>
<td></td>
<td>Group</td>
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<tr>
<td>Case</td>
<td>34</td>
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<tr>
<td>Control</td>
<td>37</td>
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* Definitions of proton pump inhibitor exposure are given in the text.
† Subjects who met requirements for a combination of exposure criteria.

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years, 61 to 79 years, and older than 80 years. No statistically significant differences were noted between these categories ($P = 0.810$) (Table 2).

The average LOS was 11.02 days for case subjects and 9.96 days for controls ($P = 0.439$).

Antibiotic exposure within the previous 30 days did not differ significantly between cases and controls ($P = 0.841$). When antibiotic exposure was stratified by class, there was a significant difference between these two groups in their exposure to penicillin with a beta-lactamase inhibitor ($P = 0.023$; OR, 0.38; 95% CI, 0.163–0.887). Because the literature had suggested that exposure to a single antibiotic dose might contribute to the development of CDAD, we considered it necessary to analyze inpatient antibiotics both with and without single dose exposures (Tables 3 and 4).

According to the criteria for antibiotic exposure, 26 case subjects and 26 controls had not been exposed to an antibiotic. Patients who had been exposed to a PPI, and not to an antibiotic, were analyzed separately; of 34 case subjects who had been exposed to a PPI, nine were not exposed to an antibiotic. Of 37 controls exposed to a PPI, 14 were not exposed to an antibiotic. These figures were not statistically significant ($P = 0.221$).

In each case and control group, nine patients had received parenteral nutrition, eight patients had undergone dialysis, and five subjects had previously received H$_2$RAs.

**DISCUSSION**

In studies evaluating PPIs as a risk factor for CDAD, results have been mixed.$^8$–$^{14}$ This relationship has been somewhat ambiguous, and the exact mechanism of action is only speculative. *C. difficile* is a gram-positive, spore-forming anaerobic bacillus. The spores are acid-resistant, and they are not affected by the gastric pH. By contrast, a vegetative inoculum of *C. difficile* is easily destroyed by stomach acid.$^15$ Suppressing gastric acid secretion may allow actively growing bacteria and ingested spores that germinate in the stomach to survive until they pass into the bowel, increasing the likelihood of colonization. PPIs have also been implicated in diminishing neutrophil activity, thereby further increasing the risk of an infectious disease.$^{16,17}$ Overall, it has been proposed that PPIs either suppress the body’s natural barrier defense to infection or alter the immune response to infection.

To assess potential differences between the case and control groups that might explain our results, we evaluated several demographic characteristics and well-documented risk factors for CDAD. Both groups of subjects were similar in age, LOS, and antibiotic exposure. These three risk factors, arguably, are the most important in the development of CDAD.

On average, our study population was older than 65 years of age. Most *C. difficile* infections occur in the elderly, who are more likely to have pre-existing hypochlorhydria.$^{18}$ PPIs might not affect the risk of CDAD in older patients, because the change in gastric pH induced by PPIs might be less profound. This might partially explain our study results.

As supported in other studies,$^{19,20}$ penicillin plus a beta-lactamase inhibitor was associated with less *C. difficile* overgrowth, compared with other broad-spectrum antibiotics. Piperacillin–tazobactam (Zosyn, Wyeth) significantly alters the intestinal flora, but it does not increase the germination of *C. difficile* spores.$^{21}$

We analyzed therapy for CDAD to determine whether either patient group was receiving more empirical treatment before *C. difficile* toxin assay testing. IV metronidazole (Baxter) has also been infrequently implicated in the development of CDAD.$^{22}$ There was no statistical difference between case and control groups for any antibiotic exposures except penicillin with a beta-lactamase inhibitor.

**LIMITATIONS OF THE STUDY**

Our results should be viewed in the context of the study’s limitations. For instance, subjects were not matched or assessed.
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according to their location; therefore, we could not detect outbreaks of CDAD that were potentially specific to a particular patient-care area within the institution. We considered it unnecessary to match subjects in this fashion, because they were matched according to other robust controlling factors in play. The laboratory test used in this study detects toxin A exclusively. Some strains of pathogenic C. difficile produce only toxin B or scant amounts of toxin A. To control for this, we excluded all clinical diagnoses of CDAD that were not confirmed by laboratory testing.

We analyzed antibiotic exposure only 30 days before toxin A assay testing. However, it has been reported that CDAD symptoms can develop six weeks or longer following antibiotic exposure.23

As for the small number of patients enrolled in the study, we analyzed consecutive patients admitted to the hospital over a recent 10-month period in order to limit the data to the most recent C. difficile diagnoses and to be consistent with our institution’s current PPI usage. To increase the number of patients in the study, it might have been prudent to match each case subject to several control subjects. Although the low number of subjects could imply a lack of statistical power, our results show credibility, in that cases and controls were markedly similar in age, LOS, and antibiotic exposure, as well as in the other predefined matching criteria that assessed for severity of illness.

CONCLUSION

CDAD is a problem of growing concern as both the incidence and the severity of this disease continue to escalate. One possible explanation for the results of inpatient studies associating PPI exposure with CDAD includes a potential detection of a regional strain of C. difficile; it is also possible that the case subjects were already more susceptible to a C. difficile infection because of an increased incidence of other comorbid conditions when they were compared with control groups. The few studies that evaluated risk factors for CDAD development in the hospital have not implicated PPIs as increasing the risk of CDAD. Our results support this conclusion; in our study, PPIs were not associated with CDAD in hospitalized patients.

CDAD is a complicated disease process, with multiple factors contributing to significant infection. It is difficult to assess whether one single factor, such as PPI exposure, contributes significantly to the development of CDAD. It is more likely that a combination of multiple factors causes CDAD in susceptible patients.

Until further definitive research is conducted, practitioners should focus on modifying well-known and accepted risk factors for CDAD, such as improving hygiene practices among health care providers and using broad-spectrum antibiotics appropriately. PPIs remain effective for various gastrointestinal conditions, and they are well tolerated.

Our study conclusions do not support suggestions of an increased risk of CDAD with PPIs. These medications should be considered in hospitalized patients when indicated. Further prospective research is warranted to evaluate the potential risks for CDAD development.

REFERENCES