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ORIGINAL PAPER

Association between Proton Pump Inhibitor Use and Spontaneous Bacterial Peritonitis

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Abstract Proton pump inhibitors (PPIs) increase enteric bacterial colonization, overgrowth, and translocation, all effects which might predispose to spontaneous bacterial peritonitis. We investigated whether PPI usage is associated with spontaneous bacterial peritonitis. Our retrospective case-control study included 116 consecutive cirrhotic patients with ascites who underwent diagnostic paracentesis upon hospital admission (2002–2005). Spontaneous bacterial peritonitis was defined as paracentesis yielding ≥250 polymorphonuclear leukocytes/ml. We performed logistic regression to determine the risk of spontaneous bacterial peritonitis by PPI usage. Of the 116 subjects, 32 had spontaneous bacterial peritonitis. Patient characteristics were similar between groups with and without infection, with the exception of the Model for End-Stage Liver Disease score (median: 23 and 18, respectively; $P = 0.002$). Crude and adjusted odds ratios for the development of spontaneous bacterial peritonitis by exposure to PPIs were 1.22 (95% confidence interval: 0.52–2.87) and 1.05 (0.43–2.57), respectively. In conclusion, we did not find a positive association between PPI use and spontaneous bacterial peritonitis.

Keywords Acid suppression · Ascites · Cirrhosis · Heartburn · Proton pump inhibitors · Spontaneous bacterial peritonitis)

Abbreviations

H2RA	Histamine 2 receptor antagonist
MELD	Model for end-stage liver disease
PMN	Polymorphonuclear leukocytes
PPI	Proton pump inhibitor
SBP	Spontaneous bacterial peritonitis

Introduction

Spontaneous bacterial peritonitis (SBP) is a common and serious infection occurring in cirrhotic patients with ascites [1]. Intestinal permeability to bacteria is increased in patients with cirrhosis[2, 3], and one mechanism that has been suggested to explain SBP in these patients is that it evolves because bacteria translocate across the leaky gut [4–6]. Uncontrolled bacterial growth in ascitic fluid then develops as a result of an impaired host immune response [7, 8].

Because of the significant morbidity and mortality related to SBP, identifying predisposing factors is of great importance. Gastric acid is a key defense against enteric pathogens, and the suppression of gastric acid has been associated with increased bacterial colonization and an enhanced viability of pathogenic bacteria in the gastroin-

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testinal tract [9, 10], thereby leading to an increased risk of infection. For example, both community-acquired pneumonia and ventilator-related pneumonia among intensive care unit (ICU) patients [11, 12] have been associated with the administration of proton pump inhibitors (PPIs), presumably through increased bacterial colonization in the stomach [12]. Moreover, PPI use has been identified as an important risk factor for the development of *Clostridium difficile*-associated disease in some [13–15] – but not all [16, 17] – studies. In addition, impairment of gastrointestinal motility by PPIs or histamine 2 receptor antagonists (H2RAs) can predispose to bacterial overgrowth and bacterial translocation [5, 9, 18, 19]. Finally, PPIs may impair neutrophil function, potentially predisposing to bacterial infection [20, 21]. A recent study showed, as a secondary finding, that acid-suppressive therapy was associated with a trend towards a markedly increased risk for development of SBP [9]. Against this background, we sought to specifically determine whether PPI use was associated with SBP among hospitalized cirrhotic patients who underwent diagnostic paracentesis.

Methods

Study population

We conducted a retrospective review of 214 consecutive cirrhotic inpatients who underwent diagnostic paracentesis within 5 days of admission to the University of Pennsylvania Health System from January 2002 to December 2005. Thirty of these patients were immunosuppressed due to HIV infection or prior transplantation. Such patients may have been more predisposed to developing SBP regardless of PPI exposure and were therefore excluded from further analysis. Seventy-eight patients had been exposed to antibiotics either within 2 weeks prior to hospitalization or prior to paracentesis following hospital admission. These patients were excluded because antibiotic administration may have prevented the development of SBP, thus masking a possible effect of PPI use on SBP development. A second reason for this exclusion was that initiation of antibiotic treatment may have rendered paracentesis insensitive for the diagnosis of SBP. Of these 78 patients, ten met both immunosuppression and antibiotic exposure exclusion criteria. The remaining 116 patients were included in the study.

Cases and controls

We reviewed consecutive inpatient records of all patients admitted to the University of Pennsylvania Health System who had ascites and had undergone diagnostic paracentesis. Diagnostic paracentesis to identify SBP is standardly performed on all cirrhotics with ascites admitted to our hospital, regardless of the reason for admission. SBP was defined as a paracentesis yielding ≥250 polymorphonuclear leukocytes (PMN)/ml in the ascitic fluid. We did not require positive ascitic fluid cultures to diagnose SBP. The case group consisted of patients who met the SBP criteria on their first paracentesis after admission. Patients with ascites fluid PMN cell counts of <250 cells/ml were considered not to have SBP and constituted the control group. We did not collect data on subsequent paracenteses performed in the same patient.

Exposure

Exposure to PPIs and H2RAs was assessed by manually reviewing medication history recorded in the inpatient medical record upon hospital admission. We did not separate PPI or H2RA usage by individual drugs and daily dosages, as there were too few patients in some of the strata to yield interpretable results. In all cases, the medications had been prescribed on a daily basis.

Statistical analysis

Non-parametric data were compared using rank-sum tests. Categorical data were compared with Fisher's exact test. Logistic regression was performed to determine the crude and adjusted odds ratios (ORs) of developing SBP associated with use of PPI or any acid-suppressive agent (H2RA or PPI). Multivariate analysis was performed to assess for potential confounding effects of age, bilirubin, prothrombin time (INR), creatinine, Model for End-Stage Liver Disease (MELD) score, diabetes mellitus, gender, race, history of SBP, and etiology of liver disease. MELD scores were calculated according to the method used by the United Network of Organ Sharing (http://www.unos.org). Histories of prior spontaneous bacterial peritonitis, diabetes mellitus, and etiology of liver disease were obtained from inpatient medical histories. Laboratory data at time of admission were used. Only confounders affecting the unadjusted point estimate by 10% or more were included in the final multivariate model [22]. P-values < 0.05 were considered to be significant, and two-sided tests were used. All analyses were performed using STATA ver. 8.1 (Stata Corp, College Station, Tex.).

Results

Of the 116 eligible study subjects 32 patients had SBP, and 84 did not. Clinical characteristics of the two groups are summarized in Table 1. SBP patients tended to have higher

Table 1 Clinical chacteristics of patients with and without spontaneous bacterial peritonitis

Variable[a]	SBP present (n = 32)[b]	SBP absent (n = 84)[b]	P-value
PMN count in ascites (cells/ml)	2077 (739, 4,183)	13 (5, 41)	<0.001*
Acid suppression			0.89
None	17 (53%)	48 (57%)	
Proton pump inhibitor	13 (41%)	30 (36%)	
H2RA	2 (6%)	6 (7%)	
Age (years)	53.9 ± 10.1	54.9 ± 11.0	0.65
Male gender	23 (72%)	55 (65%)	0.66
Race			0.42
Caucasian	23 (72%)	49 (58%)	
African–American	5 (16%)	21 (25%)	
Other or unknown	4 (13%)	14 (17%)	
Etiology of liver disease			0.77
HCV ± alcohol	20 (63%)	42 (51%)	
Alcohol	5 (16%)	17 (20%)	
NASH/Cryptogenic	3 (9%)	10 (12%)	
PBC/PSC/AIH	2 (6%)	4 (5%)	
Hepatitis B	0 (0%)	5 (6%)	
Other	2 (6%)	5 (6%)	
Diabetes mellitus	10 (31%)	19 (23%)	0.35
History of SBP	3 (9%)	2 (2%)	0.13
INR	1.8 (1.6, 2.3)	1.5 (1.3, 1.8)	<0.001*
Creatinine (mg/dl)	1.3 (0.9, 2.3)	1.1 (0.8, 2.0)	0.48
Bilirubin (mg/dl)	4.1 (2.6, 7.0)	2.6 (1.3, 5.6)	0.01*
MELD score	23 (18, 29)	18 (13, 22)	0.002*
MELD group			0.02*
≤15	5 (16%)	30 (36%)	
16–24	14 (44%)	40 (48%)	
≥25	13 (41%)	14 (17%)	

* $P < 0.05$

[a] SBP, Spontaneous bacterial peritonitis; H2RA, histamine 2 receptor antagonist; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; INR, prothrombin time; PMN, polymorphonuclear leukocytes

[b] Values are given as the median (25%, 75%), or as n (%)

INR, bilirubin, and MELD scores than subjects without SBP (Table 1). The two groups were otherwise similar. Moreover, rates of PPI and H2RA use were similar between those with and without SBP; 41% of SBP patients and 36% of subjects without SBP were taking PPIs (Table 1).

The crude ORs for the development of SBP among PPI users versus non-users was 1.22 [95%confidence interval (95% CI): 0.52, 2.87], P = 0.64 (Table 2). Broadening the definition of acid suppression to also include those exposed to H2RAs did not significantly alter this point estimate (Table 2). Multivariate analysis did not result in either MELD or its separate components (bilirubin, INR, and creatinine) significantly affecting our unadjusted point estimate. The only significant confounder was race, which was included in the final multivariable model. After adjusting for race, the ORs for SBP among subjects taking PPIs was 1.05 (95%CI: 0.43, 2.57), P = 0.91 (Table 2).

Discussion

We did not find evidence in this study that the use of PPIs was associated with a markedly increased risk of development of SBP. Biologically, PPI use might be expected to predispose to infection because gastric acidity is an important defense against enteric pathogens. Some investigators have demonstrated positive associations between

Table 2 Risk of spontaneous bacterial according to acid suppression

Exposure	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
PPI	1.22 (0.52, 2.87)	1.05 (0.43, 2.57)
PPI or H2RA	1.18 (0.52, 2.67)	1.03 (0.44, 2.40)

OR, Odds ratio; 95% CI, 95% confidence interval; PPI, proton pump inhibitor; H2RA, histamine 2 receptor antagonist

[a] Adjusted for race

the administration of acid suppression therapy and the development of *Clostridium difficile*-associated diseases as well as community-acquired and nosocomial pneumonia [11–15], although the association between PPI therapy and the risk of infection remains controversial. [16, 17] Furthermore, a small-scale previous study suggested a markedly increased risk of SBP with the use of PPIs (OR = 7.0, $P = 0.08$) [9]. Although we did not observe an increase of such a large magnitude in the risk of SBP associated with PPI therapy in this study, we could not rule out the possibility of a modest increase in SBP risk due to acid-suppressive therapy. Given how commonly acid-suppressive therapy is used in cirrhotics with ascites, it will be important for other studies to exclude a possible small increased risk of SBP in PPI users.

Our study has several important strengths. Compared to the previous study that addressed the association between SBP risk and PPI therapy in a secondary fashion, our study was specifically designed to investigate this issue. Our study also included more patients than the previous study, which may have enhanced the precision of our point estimates.

SBP is a common infection among cirrhotics and often presents with subtle manifestations. As a standard of practice, diagnostic paracentesis to identify SBP is performed on all cirrhotics with ascites admitted to our hospital, regardless of the reason for admission. Therefore, we were able to capture all cases of SBP in our study cohort. Patients who have been immunosuppressed or recently exposed to antibiotics might be more or less likely, respectively, to develop SBP, independent of PPI exposure. We excluded all such patients so that our results are more generalizable to the average end-stage liver disease (ESLD) patients with ascites.

As expected, the median MELD score in SBP patients was higher – 23 – than that in non-SBP patients – 18. This difference was statistically significant and likely reflects the fact that patients with more advanced liver disease are more likely to develop life-threatening complications such as SBP. An alternative plausible explanation is that SBP may lead to transiently worsening hepatic synthetic function and renal function, resulting in a higher MELD score on presentation. In any case, MELD score was not a significant confounder in the association between PPI therapy and SBP.

A diagnosis of SBP was made for patients with ≥250 PMN/ml of ascites fluid. We did not use ascites fluid culture data to aid in the diagnosis because the reliability the culture data in our cohort is questionable. Ascites cultures have a high yield when done properly (i.e., in blood culture bottles with an adequate inoculum of 10 cc at bedside) [23, 24]. However, uniform proper techniques and high yield are attainable only when relatively few people – who are also well-trained – are involved. Given the large volume and high turnover rate of the housestaff and students involved in our institution, one cannot be confident that proper culture collection techniques were followed consistently. In any case, since neutrocytic ascites has the same clinical course as culture-positive ascites, it is not likely we over-diagnosed SBP in the absence of a positive culture. Moreover, bacterascites, defined as a positive culture without an elevation in ascitic fluid neutrophil count, may in some cases represent a contaminant in culture media. Our definition of SBP may have lead to misclassification of early SBP cases as controls. However, given the rarity of bacterascites, it is unlikely to have biased our results significantly.

Several other potential limitations of our study warrant consideration. We relied on nursing and physician admission notes to identify exposure to acid-suppressive therapy. It is possible that other methods of identifying medication exposure, such as corroboration with pharmacy records or outpatient physician records, may have enhanced reporting accuracy. Such an approach was impractical for our study. We do not suspect that patients ultimately diagnosed with SBP would have been more or less likely to have reported acid-suppressive therapy on their hospital admission histories compared with the controls. We did not perform separate analyses for different PPI formulations because of the limited sample size, but there is no obvious reason why the risk, if any, would be different among different formulations. Lastly, we were unable to perform an analysis of PPI dosage and frequency of administration upon development of SBP due to lack of sufficient statistical power. Therefore, we instead report whether patients were regularly taking PPI or H2RA prior to hospital admission.

In conclusion, our study addressed an important clinical question, as PPI use is very common in cirrhotic patients with ascites. We did not find a relationship between acid-suppressive therapy and the development of SBP in this patient population. Further studies are needed to confirm our results.

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