Research Article

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Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: A multicenter prospective study

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Background & Aim: Retrospective studies show an association between proton pump inhibitor (PPI) therapy and spontaneous bacterial peritonitis (SBP). We investigate the relationship between PPI and SBP in decompensated cirrhotic patients in a large nationwide prospective study.

Methods: Seven hundred seventy patients with a diagnosis of decompensated cirrhosis were admitted consecutively in 23 hospitals in Argentina from March 2011 to April 2012; the patients were carefully investigated for PPI consumption in the previous 3 months. In total, 251 patients were excluded because of active gastrointestinal hemorrhage, antibiotic use during the preceding weeks, HIV-positive status and immunosuppressive therapy.

Results: Two hundred twenty-six out of 519 patients (43.5%) had received PPI therapy within the last 3 months. In 135 patients, PPIs were administered for longer than 2 weeks. A bacterial infection was shown in 255 patients (49.1%). SBP was diagnosed in 95 patients out of 394 patients with ascites (24.7%). There was no significant difference in the rate of PPI consumption between the infected and the non-infected patients (44.3% *vs.* 42.8%) or between the SBP patients and the patients with ascites without SBP (46% *vs.* 42%). In the SBP patients, the duration of PPI administration did not influence the rate of SBP occurrence. The type of bacteria and the origin of SBP infection were similar in the patients with and without PPI.

Conclusion: In the current large, multicenter, prospective study, PPI therapy, specifically evaluated at admission of consecutive cirrhotic patients, was not associated with a higher risk of SBP.

Introduction

Proton pump inhibitors (PPIs) have been associated with a modest increased risk of spine and total fractures in 130,487 postmenopausal women (risk factor 1.25 [1,2]), with a significant increase in the rate of *Clostridium difficile* infections and recurrences in hospitalized patients [3] and with an increased risk of community- and nosocomially-acquired pneumonia [4].

Recent retrospective studies show controversial results regarding an increased risk of spontaneous bacterial peritonitis (SBP) in cirrhotic patients taking PPIs [5–11].

These studies had a similar design, which might constitute a source of error: (1) the studies were retrospective reviews of the list of medications taken by the cirrhotic hospitalized patients, and most were performed in a single center; (2) patients with documented PPI ingestion were considered PPI users, and those with an absence of data were considered PPI non-users; and (3) the inclusion criteria were heterogeneous.

Difficulties in data collection are clearly shown by the high number of medical records invalidated for the final analysis in these studies.

A retrospective analysis may lead to a false estimation of patients taking PPIs because this issue was not specifically investigated at admission.

Total PPI sales in Argentina represent approximately 169 million dollars annually and because SBP represents one of the most frequent causes of bacterial infection in decompensated

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Abbreviations: PPI, proton pump inhibitor; SBP, spontaneal bacterial peritonitis; HBV, hepatitis B virus; SIBO, small intestinal bacterial overgrowth; GHBT, glucose hydrogen breath testing.

cirrhotic patients, the impact of the potential increase in SBP in cirrhotic patients taking PPIs should be urgently clarified.

The aim of the study was to investigate the relationship between PPI therapy and the development of SBP in decompensated cirrhotic patients in a nationwide multicenter, prospective study.

Patients and methods

We prospectively collected and analyzed the data of 770 patients with decompensated cirrhosis who were consecutively hospitalized in 23 hospitals in Argentina from March 2011 to April 2012.

All of the patients were specifically asked about PPI consumption in the 3 months prior to hospitalization and were classified as PPI users or non-users.

The inclusion criteria were as follows: A diagnosis of cirrhosis established either with a liver biopsy or by a combination of physical, endoscopic, laboratory and ultrasonographic findings.

The exclusion criteria were as follows: a) active gastrointestinal bleeding; b) antibiotic treatment in the previous 2 weeks including quinolone or rifaximin prophylaxis c) HIV-positive status; and d) immunosuppressive therapy.

Two hundred fifty-one patients were excluded for the following reasons: active gastrointestinal bleeding in 126 cases (50.2%), antibiotic use in the previous 2 weeks in 54 cases (21.5%), HIV-positive status in 46 cases (18.3%), and use of immunosuppressive therapy in 25 cases (10%).

A complete medical history including information regarding the ingestion of PPIs in the last 3 months was obtained. In every center involved in the study there were two investigators responsible of assessing PPI intake. In the case of an affirmative answer, the date of intake, the duration of PPI treatment as well as the medical indication were investigated.

A physical examination, renal and liver function tests, serum sodium and potassium, and red and white blood cell counts were performed in all the patients at admission. A diagnostic paracentesis was performed at the time of admission in all of the patients with ascites and was repeated during hospitalization if a clinical suspicion of infection or decompensation occurred. The criterion for the diagnosis of SBP was a polymorphonuclear cell count in ascitic fluid $\geqslant 250$ cells/mm^3. The criterion for the diagnosis of spontaneous bacteremia was a positive blood culture without any associated cause, and the diagnostic criterion for a urinary infection was a positive urine culture. The diagnosis of other infections was performed according to the conventional criteria.

The infections diagnosed at the time of admission were classified as community acquired. The infections diagnosed 2 days after hospitalization were classified as nosocomial.

Statistical analysis: The SPSS program (version 20.0, IBM) was used for the analysis. ANOVA and Student's *t* tests were performed to evaluate differences in demographic variables among groups and χ^2 test was used for independent variables. Age, gender, MELD score, Child-Pugh score, alcohol, hepatitis B virus (HBV), hepatitis C virus, encephalopathy, serum bilirubin, serum creatinine, serum sodium, INR, peripheral leukocyte count, platelet count, protein in ascitic fluid and PPI consumption were analyzed. Significant risk factors for SBP in the univariate analysis were entered into the multivariate analysis using the logistic regression model. Differences were considered statistically significant at $p < 0.05$.

The study was approved by the Ethics Committee of each hospital, and patients' written informed consent was required for participation.

Results

A total of 521 patients were included in the study. There were 255 patients with bacterial infections and 264 without bacterial infections. Only the MELD score (19 ± 7 *vs.* 17 ± 6) and the serum albumin (2.53 ± 0.54 *vs.* 2.69 ± 0.62 gr/dl) were significantly different in the infected patients compared with the non-infected patients.

A history of PPI consumption was found in 114 (44.3%) of the infected patients and in 112 (42.8%) of the non-infected patients (n.s.).

The causes of the bacterial infection were SBP in 95 cases (37%), urinary infection in 40 (15.6%), pneumonia in 39 (15%), cellulitis in 31 (12%), bacteremia in 30 (11.7%) and other infections in 20 (8%). Regarding bacterial infection, other than SBP, the number of patients using or not using PPI was similar (Table 1). Twenty-five out of 289 patients with ascites without SBP had other bacterial infection: (urinary tract infection 12 patients, pneumonia seven patients, cellulitis four patients and cholangitis two patients).

In addition, 21 out of 289 patients with ascites without SBP had refractory ascites, many of them with type II hepatorenal syndrome.

SBP and PPI therapy

A total of 384 patients had ascites at admission, and 95 of those patients had a diagnosis of SBP. The clinical and demographic data at admission are shown in Table 2. In the univariate analysis peripheral leukocyte count (10,857 ± 5909 *vs.* 7925 ± 5020 cells/mm; $p = 0.001$) MELD score (21 ± 7 *vs.* 19 ± 7; $p = 0.01$),

Table 1. PPI use and bacterial infections other than SBP.

	PPI (n = 226)	No PPI (n = 295)
Urinary infection (n = 40)	19 (8.4%)	21 (7.1%)
Pneumonia (n = 39)	18 (7.9%)	21 (7.1%)
Cellulitis (n = 31)	13 (5.7%)	18 (6.1%)
Bacteremia (n = 30)	16 (7%)	14 (4.7%)
Others (n = 20)	8 (3.5%)	12 (4%)
Total	74 (32.7%)	86 (29.1%)

Data are n (%).

Table 2. Clinical and demographic characteristics at admission of patients with ascites with or without SBP.

	SBP (n = 95)	No SBP (n = 289)	*p* value
Age (years)	56 ± 13	58 ± 11	n.s.
Gender (male/female)	62/33	203/86	n.s.
MELD score (points)	21 ± 7	19 ± 7	0.01
Child-Pugh (points)	10.3 ± 2.1	11.8 ± 2	0.54
Child-Pugh B-C (%)	29/71	35/62	n.s.
Alcohol, n (%)	50 (53.7%)	135 (51.1%)	n.s.
Active consumption, n (%)	42 (84%)	108 (80%)	n.s.
Encephalopathy, n (%)	25 (26.3%)	60 (20.7%)	0.05
HBV, n (%)	15 (15.7%)	10 (3.4%)	0.0001
Nucleoside/nucleotide, n (%)	3 (20%)	4 (25%)	n.s.
HCV, n (%)	28 (29.4%)	72 (24.9%)	n.s.
Total bilirubin (mg/dl)	5.78 ± 6.78	5 ± 5.7	n.s.
Serum albumin (g/dl)	2.53 ± 0.54	2.5 ± 0.55	n.s.
Serum creatinine (mg/dl)	1.32 ± 0.85	1.12 ± 0.71	0.026
Serum sodium (mEq/L)	131 ± 6	132 ± 10	ns
INR	2 ± 0.78	1.8 ± 0.78	ns
Peripheral leukocytes (mm^3)	10,857 ± 5909	7925 ± 5020	0.001
Platelet count (mm^3)	83,050 ± 19,300	89,932 ± 12,459	n.s.
Protein in AF (g/dl)	1.03 ± 0.36	1.1 ± 0.5	n.s.
PPI consumption, n (%)	44 (46%)	121 (42%)	n.s.

$p < 0.05$ is considered not significant.

encephalopathy (25 out of 95 *vs.* 60 out of 289 patients; $p = 0.05$) and HBV infection (15 out of 95 *vs.* 10 out of 289; $p = 0.01$) were significantly different in the SBP patients compared with the patients with ascites without SBP. However, in the multivariate analysis only HBV infection ($p = 0.018$; OR 6.323; 95% CI 1.36–29.26), encephalopathy ($p = 0.023$; OR 1.973; 95% CI 1.09–3.54) and serum leukocyte count ($p = 0.02$; OR 1.000; 95% CI 1.01–1.09) were significantly associated to SBP.

Clinical and analytic data of patients with ascites receiving and not receiving PPI were compared and shown in Table 3. No significant differences were found between groups.

Moreover, SBP rate was similar among patients at high risk of developing the first episode of SBP (Child-Pugh C, low-protein ascites, platelet count <98,000/mm^3 and/or bilirubin levels >3.2 mg/dl), taking PPI 156 (79.5%) or not taking PPI 211 (78.7%), χ^2 0.036; $p = 0.85$.

In the patients without SBP, PPI consumption within the previous 3 months was 42% (121 out of 289 patients). In the patients with SBP, PPI intake within the previous 3 months was 46.3% (44 out of 95 patients). These values were not significantly different.

The incidence of PPI use at admission in the SBP patients was 33.6% (32 out of 95 patients), and the incidence of PPI use at admission in the patients with ascites but without SBP was 35.6% (103 out of 289). These values were not significantly different.

We investigated if the duration of PPI administration was associated with a different SBP rate in decompensated cirrhosis patients. The SBP rate in the patients with less than 2 weeks of PPI administration was 26.6%, and the SBP rate in patients with PPI intake lasting between 2 and 4 weeks was 22.8% and the SBP rate in patients with more than 4 weeks of PPI use was 23.1% (Table 3). There were no significant differences in these values.

In patients receiving PPI treatment, the origin of SBP was community acquired in 66% of cases and nosocomially acquired in 34% of cases. In the patients not taking a PPI, the origin of SBP was community acquired in 80.4% and nosocomially acquired in 19.6%. There were no significant differences in these values.

The percentage of positive cultures in SBP patients was 34.7% (33 out of 95 patients). These bacteria were Gram positive in 71% and Gram negative in 29% in the SBP patients taking a PPI. A small difference was found in the patients not taking a PPI: 58% of the bacteria were Gram positive and 42% were Gram negative. These values were not significantly different (Table 4).

We compared the incidence of SBP episodes caused by any GNB in PPI *vs.* non-PPI users: 4/14 (28.6%) of SBP episodes were caused by GNB in the PPI users, compared with 8/19 (42.1%) in the non-PPI users ($p = 0.66$) (Table 4).

In 42% of the patients receiving PPI, a clear indication for the use of these drugs was not identified.

Table 3. Clinical and demographic characteristics at admission of the patients receiving or not receiving PPI.

	PPI (n = 165)	No PPI (n = 219)	*p* value
Age (years)	56.7 ± 12	57.1 ± 11.5	n.s.
Gender (male/female)	105/50	165/49	n.s.
MELD score (points)	19.2 ± 7.1	19 ± 6.7	n.s.
Child-Pugh (points)	11.2 ± 1.8	10.5 ± 3.8	n.s.
Child-Pugh B-C (%)	45/55	42/58	n.s.
Alcohol, n (%)	(53.7%)	135 (51.1%)	n.s.
Active consumption (%)	84	80	n.s.
Encephalopathy (%)	43.5	56.5	n.s.
HBV, n (%)	14 (56)	11 (44)	n.s.
Nucleoside/nucleotide (%)	20	25	n.s.
HCV (%)	36.4	63.6	n.s.
Total bilirubin (mg/dl)	5.2 ± 6.5	5.4 ± 5.9	n.s.
Serum albumin (g/dl)	2.5 ± 0.5	2.5 ± 0.7	n.s.
Serum creatinine (mg/dl)	1.3 ± 0.94	1.8 ± 0.63	0.14
Serum sodium (mEq/L)	132 ± 6.1	131 ± 11	n.s.
INR	1.9 ± 0.7	1.8 ± 0.8	n.s.
Peripheral leukocytes (mm^3)	8324 ± 5047	8910 ± 5648	n.s.
Platelet count (mm^3)	79,789 ± 16,200	86,715 ± 11,443	n.s.
Protein in AF (g/dl)	1.02 ± 0.58	1.1 ± 0.4	n.s.
SBP, n (%)	44 (27%)	51 (31%)	n.s.

$p < 0.05$ is considered not significant.

Table 4. Type of bacteria in the SBP patients with or without PPI use.

	PPI (n = 14)	No PPI (n = 19)
Gram-positive cocci		
Staphylococcus aureus	4	4
Streptococcus pneumoniae	4	4
Enterococcus faecalis	2	2
Enterococcus faecium	0	1
Gram-negative bacilli		
Escherichia coli	1	3
Klebsiella pneumoniae	1	2
Pseudomonas aeruginosa	1	2
Acinetobacter	1	1

Data are n (%).

Discussion

The use of a PPI, which is a potent gastric acid suppressor, is widespread around the world, and these drugs represent a very important source of sales in the pharmaceutical markets. In many countries, including Argentina, PPIs do not require a prescription, and the majority of individuals taking a PPI do not have a clear indication for the drug.

Recent studies have introduced concerns regarding the increased risk of bacterial infections, typically SBP, in patients with cirrhosis [5–11].

This large, prospective, multicenter, nationwide study shows that PPI use does not increase the incidence of SBP in decompensated cirrhotic patients.

Six studies and one meta-analysis have been published investigating the risk of SBP in patients with cirrhosis taking PPIs, and the results of these studies are controversial. In four of the studies, an increase in the incidence of SBP in patients taking PPIs was shown [6–9]. This increase was not shown in one study [5] and in the sixth study SBP patients were more frequently treated with PPI but in the multivariate analysis PPI use did not emerge as a significant parameter associated with SBP [10].

The design of all these studies was identical and involved retrospectively reviewing the list of medications of cirrhotic patients hospitalized since 2001. The patients with at least one documented PPI use were considered PPI users, and the patients with an absence of data regarding PPI use were considered PPI non-users. The difficulty in the collection of data is shown by the large number of medical records invalidated for analysis in the different studies. In addition, the heterogeneity in the inclusion criteria of the previous studies is important. Because antibiotic therapy reduces intestinal bacterial overgrowth, patients receiving antibiotics were excluded in most of the studies, but they were not excluded in 1 study [8]. In this study, only the patients who had taken a PPI in the previous 7 days were at risk of developing SBP.

A recent meta-analysis including eight studies with 3815 patients was published. The conclusion of the authors was that pharmacologic acid suppression was associated with a greater risk of SBP [11]. However, the main criticism to the design of the meta-analysis is the fact that 3034 of these patients were reported only in abstract form.

A prospective cohort study of patients with cirrhosis and with infections was performed at eight North American tertiary-care liver centers. The rate of PPI intake was similar in patients who did or did not develop a second infection [12].

Low total protein in ascitic fluid, low platelet count and previous SBP have been suggested to be associated to an increased risk for the development of SBP. However, in our series, PPI intake had no significant impact on the incidence of SBP, neither in Child-Pugh C nor among patients with low-protein ascites. Patients with previous SBP were excluded since all were on quinolone prophylaxis.

Likewise, we did not find PPI to be a prognostic factor neither in the univariate nor in the multivariate analysis. On the contrary, encephalopathy, peripheral leukocyte count and, unexpectedly, HBV infection were significantly associated to SBP development.

The main hypothesis of PPIs increasing the SBP incidence in decompensated cirrhotic patients is itself controversial. Small intestinal bacterial overgrowth (SIBO) has been blamed as the principal side effect of PPIs and can lead to bacterial translocation and infections [13,14]. Nine studies using different tests for detecting SIBO have investigated the relationship between PPI use and SIBO in non-cirrhotic patients, and these studies had conflicting results [15–24]. The largest studies, using glucose hydrogen breath testing (GHBT) [18] or aspiration and culture of the small bowel contents [19], show that PPI use does not predispose patients to SIBO. In the recent largest retrospective study that included 1191 patients who underwent GHBT between 2004 and 2010, PPI use was not found to be significantly associated with the presence of SIBO.

Mechanisms other than SIBO have been mentioned as a risk factor for the development of bacterial infections in patients taking PPIs. Based on experimental data, it has been suggested, that acid-suppressive drugs may inhibit neutrophil function and natural killer cell activity [25]. The clinical significance of these findings is unknown.

We also investigated whether PPI use could be a factor increasing SBP caused by Gram negative bacteria by increasing bacterial translocation from the intestinal lumen to ascitic fluid. We were unable to confirm this hypothesis since, unexpectedly, the most frequently isolated bacteria in the present study were Gram positive cocci, mainly *Staphylococcus aureus*.

C. difficile infection was not reported in our series. Interestingly, the incidence of *C. difficile* in Argentina is very low, although definitive data are unknown. A recent study in one general hospital from Buenos Aires, Argentina, estimated the incidence as 40 per 10,000 admissions [26].

The current prospective multicenter study of a large number of patients with decompensated cirrhosis shows that PPI use does not increase the risk of SBP. Future large prospective multicenter studies are needed to assess the role of PPI in the development of bacterial infections in cirrhosis.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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