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BRIEF ARTICLE

PPIs are not associated with a lower incidence of portal-hypertension-related bleeding in cirrhosis

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Abstract

AIM: To determine if proton pump inhibitor use in cirrhotic patients with endoscopic findings of portal hypertension is associated with a lower frequency of gastrointestinal bleeding.

METHODS: Patients with cirrhosis and endoscopic findings related to portal hypertension, receiving or not receiving proton pump inhibitor (PPI) therapy, were included retrospectively. We assigned patients to two groups: group 1 patients underwent PPI therapy and group 2 patients did not undergo PPI therapy.

RESULTS: One hundred and five patients with a median age of 58 (26-87) years were included, 57 (54.3%) of which were women. Esophageal varices were found in 82 (78%) patients, portal hypertensive gastropathy in 72 (68.6%) patients, and gastric varices in 15 (14.3%) patients. PPI therapy was used in 45.5% of patients (n = 48). Seventeen (16.1%) patients presented with upper gastrointestinal bleeding; in 14/17 (82.3%) patients, bleeding was secondary to esophageal varices, and in 3/17 patients bleeding was attributed to portal hypertensive gastropathy. Bleeding related to portal hypertension according to PPI therapy occurred in 18.7% (n = 9) of group 1 and in 14% (n = 8) of group 2 (odds ratio: 0.83, 95% confidence interval: 0.5-1.3, P = 0.51).

CONCLUSION: Portal hypertension bleeding is not associated with PPI use. These findings do not support the prescription of PPIs in patients with chronic liver disease with no currently accepted indication.

Key words: Drug prescription; Liver cirrhosis; Portal hypertension; Proton pump inhibitors; Upper gastrointestinal bleeding

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INTRODUCTION

Since their first clinical use, proton pump inhibitors (PPIs)

have provided benefits in the management of gastrointestinal diseases. This class of drugs is clearly indicated for the treatment of peptic ulcer disease, gastroesophageal reflux disease (GERD), and nonvariceal upper gastrointestinal bleeding, and for prophylaxis in selected users of nonsteroidal anti-inflammatory drugs (NSAIDs)[1,2]. Unfortunately, the unnecessary prescription of PPIs has become an important problem, which increases economic costs in daily clinical practice[3,4]. According to previous studies in the clinical context, only 12.3% of cirrhotic patients have an appropriate indication for the prescription of these drugs[5]. Congestive gastropathy and esophageal and gastric varices are risk factors for the inappropriate use of PPIs[5].

Few studies, other than pharmacological studies, have investigated the safety and utility of PPIs in cirrhotic populations[6-9]. There are reports of possible hepatotoxicity associated with the use of PPIs in patients with chronic liver disease (CLD)[9], but there have been no clinical or experimental trials on the adverse effects of PPIs in the treatment of acute or chronic complications in patients with cirrhosis and portal hypertension (PH). Some data on the possible use of PPIs for the long-term prophylaxis of variceal bleeding exist[10], and a recent controlled trial by Zhoe *et al*[11] compared the efficacy of octreotide, vasopressin, and omeprazole for controlling acute bleeding associated with portal hypertension gastropathy. However, more clinical evidence is required. The use of this class of drugs in cirrhotic patients seems more habit-related than evidence-based, ultimately leading to an increase in health costs.

In patients with cirrhosis and PH, upper gastrointestinal bleeding has an annual frequency of 25%-35%, and 80%-90% is of variceal origin. The mortality related to variceal bleeding is about 30% per episode, and is recurrent in 70% of patients after the first year[12-15].

Considering the current paradigm of evidence-based medicine, the use of PPIs in patients with cirrhosis and endoscopic findings of PH is based only on expert opinion, with insufficient evidence to justify the use of these drugs as prophylaxis for variceal bleeding. The aim of this study was to determine whether the use of PPIs in patients with cirrhosis and endoscopic findings of PH (esophageal or gastric varices, or portal hypertensive gastropathy) is associated with a reduction in the frequency of gastrointestinal bleeding secondary to PH.

MATERIALS AND METHODS

We conducted a retrospective, observational, longitudinal, comparative study of outpatients with CLD and endoscopic evidence of PH, receiving or not receiving treatment with PPIs, between December 1, 2004 and January 1, 2006. The endoscopic data considered for PH were esophageal varices, gastric varices, and portal hypertensive gastropathy. The sample comprised a series of consecutive patients with clinical, biochemical, endoscopic, radiological, and/or histological signs of cirrhosis and PH who attended our gastroenterology and liver clinic. We included all patients over 18 years of age who had been reviewed on at least two visits over the course of one year during the period of the study. All patients with incomplete electronic or paper charts, with no confirmatory endoscopic study at the time of the bleeding episode, were excluded from the study. These patients formed a subset of patients included in our previous work[5]. Reasons for exclusion from the present study were absence of endoscopic evidence of PH (n = 80), and no previous endoscopy (n = 28).

The primary demographic and medical variables were age, sex, etiology of CLD, diagnosis of hepatocellular carcinoma, liver function tests, presence of ascites, encephalopathy, the model end-stage liver disease (MELD) score, and previous use of NSAIDs (at least five times per week during the last six months), cyclooxygenase-2 inhibitors, corticosteroids, anticoagulants, and aspirin. Any hospital stay associated with portal hypertensive bleeding was also recorded.

An endoscopic procedure was performed in all patients as an initial approach. Any patient with first endoscopy at the time of an episode of active bleeding was included. The primary endpoint of our study was the presence of portal hypertensive bleeding. We defined bleeding related to PH as any bleeding episode secondary to the rupture or erosion of esophageal or gastric varices and/or portal hypertensive gastropathy, manifested clinically as melena or hematemesis. All patients with suspected variceal bleeding during the period of the study were required to have an endoscopic procedure in the first 24 h after presentation. A regular diagnostic endoscope was initially used (GIF-100, GIF-130, GIF-140, or GIF-160; Olympus, Japan). The presence of esophageal or gastric varices, portal hypertensive gastropathy, red signs, and the size of the varices were recorded according to the Baveno Ⅳ consensus[16]. Other variables assessed included nonliver-related findings such as esophagitis, hiatal hernia, erosive gastritis, and duodenal or gastric ulcer.

The use of PPIs and other medical prescriptions within the six months preceding the study were identified in the patients' records. We defined PPI users as those patients with cirrhosis who had taken 20 mg of omeprazole (or an equivalent dose of any other PPI) for at least eight weeks before the episode of portal hypertensive bleeding or initial evaluation (first considered visit). Confirmation of the patients' compliance with the PPI treatment was based on chart records. A diagnosis of GERD was made according to the definition: "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications"[17]. Troublesome symptoms were defined by the patient as affecting his/her quality of life. The symptoms considered were heartburn, regurgitation, reflux-related chest pain, extraesophageal syndromes of GERD (laryngitis, cough, asthma) confirmed by their resolution with PPI therapy, pH monitoring, or endoscopic evidence of esophagitis, according to the Los Angeles classification (grades B, C, or D)[17].

Statistical analysis

The results are expressed as distributions, absolute frequencies, relative frequencies, medians and ranges, or

means ± SD. For comparison, patients were classified into two groups: patients who used PPIs and patients who did not use PPIs. The quantitative data were compared using the Student's *t*-test for variables with a normal distribution, and the Mann-Whitney *U* test for other variables. Differences between the proportions of categorical data were evaluated with Fisher's exact test when the number of expected subjects was less than five and otherwise with the χ^2 test. A multivariate logistic regression model was used to assess the independent association between PPI use and bleeding related to PH. A *P* value of < 0.05 was considered statistically significant.

Sample size calculation

According to data published by Hajime *et al*[10] the frequencies of variceal bleeding in patients with and without PPI use were 10% and 52.4%, respectively (a difference of 42%). According to these data, to detect a difference of at least 42%, we required at least 25 patients for each group (group 1, patients with cirrhosis and PPI use; and group 2, patients with cirrhosis and no PPI use). All statistical analyses were conducted with SPSS statistical software (v. 12.0; SPSS Inc., Chicago, IL, USA).

RESULTS

We initially evaluated 135 patients. Thirty patients were excluded because of incomplete data, therefore, a total of 105 patients were included in the study. The characteristics of the included patients are shown in Table 1. The most frequent endoscopic finding was esophageal varices in 82 (78%) patients, 16 (19.5%) of whom were recorded as having large varices and/or red signs. Portal hypertensive gastropathy was found in 72 patients (68.6%) and gastric varices in 15 patients (14.3%). Of those patients with gastric varices, 13/15 (86.6%) also had esophageal varices. Other findings not related to CLD were erosive gastropathy in 14 patients (13.3%), hiatal hernia in eight patients (7.6%), duodenal ulcer (Forrest Ⅲ) in three patients (2.9%), and gastric ulcer (Forrest Ⅲ) in three patients (2.9%). Other comorbidities are shown in Table 1. There was a tendency [odds ratio (OR): 1.3, 95% confidence interval (CI): 0.72-2.6, $P = 0.2$] to non-portal hypertension-related bleeding episodes ($n = 20$; erosive gastropathy, duodenal ulcer, and gastric ulcer) in patients not using PPIs.

Forty-eight (45.5%) patients underwent PPI therapy. Most of these patients used omeprazole, although 10 used pantoprazole. During the period of evaluation, 16.1% ($n = 17$) presented with upper gastrointestinal bleeding related to PH, and in 82.3% of these patients ($n = 14$), this bleeding was secondary to esophageal varices, whereas in three patients it was attributable to portal hypertensive gastropathy. We recorded no episodes of bleeding secondary to gastric varices. When we analyzed the presence of variceal bleeding in patients classified according to their pattern of PPI use (group 1, patients using PPI, $n = 48$; and group 2, patients not using PPI, $n = 57$), the frequency was 18.7% ($n = 9$) in group 1 and 14% ($n = 8$) in group 2 (OR: 0.83, 95% CI: 0.5-1.3, $P = 0.51$). When we evaluated only those patients with upper gastrointestinal bleeding secondary to esophageal varices, we observed frequencies of 12.5% in group 1 and 14% in group 2 (OR: 1.07, 95% CI: 0.56-2.0, $P = 0.81$). A comparison of the characteristics of patients using PPIs and those not using PPIs is shown in Table 1.

Table 1 Characteristics of the patients included in the study classified by proton pump inhibitor use (mean ± SD) *n* (%)

Variable	Patients using PPIs ($n = 48$)	Patients not using PPIs ($n = 57$)	*P* value
Age (yr)	56.1 ± 13.8	57 ± 12.4	0.71
MELD	12.8 ± 6.3	11.5 ± 5.4	0.25
CPT	8.3 ± 1.8	7.2 ± 2.2	0.55
Albumin (g/L)	28 ± 0.6	32 ± 1.5	0.16
Total bilirubin (mg/L)	27 ± 3.7	24 ± 3.3	0.62
ALT (UI/L)	47.2 ± 22.6	50 ± 40.5	0.66
Alkaline phosphatase (UI/L)	161.2 ± 92.2	132.9 ± 63.8	0.06
BMI	26.5 ± 4.4	25.9 ± 3.7	0.46
Sex, male	19 (40)	29 (51)	0.24
Etiology			
Viral hepatitis C	25 (52)	25 (44)	0.44
Alcohol	12 (25)	12 (21)	0.56
Cryptogenic	5 (10)	10 (18)	0.28
Autoimmune hepatitis	2 (4)	8 (14)	0.22
Other	4 (8)	2 (4)	0.26
Child-pugh-turcotte			
A	19 (40)	31 (54)	0.2
B	22 (46)	17 (30)	0.3
C	7 (15)	9 (16)	0.4
GERD	7 (15)	5 (9)	0.7
Gastric/esophageal varices	44 (92)	40 (70)	0.006
Large	6 (13)	3 (5)	0.1
Red signs	4 (8)	3 (5)	0.35
Responders to β-adrenergic blocker	13 (27)	11 (19)	0.34
NSAID	4 (8)	0 (0)	0.04
Antiplatelet agents use	7 (15)	5 (9)	0.1
Oral anticoagulation	1 (2)	1 (2)	0.9
Steroid use	3 (7)	2 (4)	0.37
Comorbidities			
Diabetes mellitus	19 (40)	28 (49)	0.43
Hypertension	9 (19)	14 (25)	0.63
High-level triglycerides	3 (6)	10 (18)	0.13

CPT: Child-pugh-turcotte class; GERD: Gastroesophageal reflux disease; MELD: Model for end stage liver disease; PPIs: Proton pump inhibitors; ALT: Alanine aminotransferase; NSAID: Non-Steroidal anti-inflammatory drugs; BMI: Body mass index (calculated as patient body weight divided by the square of their height expressed in kg/m^2).

The overall prevalence of GERD was 11.4% ($n = 12$), corresponding to 14.5% of group 1 ($n = 7/48$). Only seven (57.1%) patients with GERD received PPIs. Of the total number of patients with portal hypertensive bleeding, 11.7% ($n = 2/17$) had GERD. The presence of GERD was not statistically significantly associated with the presence of upper gastrointestinal bleeding (OR: 0.53, 95% CI: 0.15-1.8, $P = 0.31$). Univariate and multivariate analyses of the variables associated with gastrointestinal bleeding secondary to PH are shown in Table 2.

DISCUSSION

In this study, we observed that in patients with CLD and endoscopic evidence of PH, the presence of gastrointes-

Table 2 Univariate and multivariate analyses of risk factors associated with portal-hypertension related bleeding in cirrhotic patients

	B Coefficient	Standard error	Wald χ^2	OR (95% CI)	*P* value
Univariate					
Age ⩾ 60	-	-	-	1.1 (0.37-3.5)	1
Sex, male	-	-	-	1.7 (0.5-5.2)	0.39
CPT C	-	-	-	1.6 (0.40-6.6)	0.36
GERD	-	-	-	0.53 (0.15-1.8)	0.31
MELD > 15	-	-	-	1.2 (0.35-4.4)	0.47
PPI use	-	-	-	0.83 (0.5-1.3)	0.51
LEV	-	-	-	12 (3-123)	< 0.001
Red signs	-	-	-	10 (2-58)	< 0.001
NSAID	-	-	-	0.86	0.55
Multivariate					
LEV	23.7	15.1	0	10 (4-110)	< 0.001
Red signs	22.0	14.2	0	9 (4-102)	< 0.001

CPT C: Child-pugh-turcotte class C; GERD: Gastroesophageal reflux disease; MELD: Model for end stage liver disease; PPI: Proton pump inhibitor; LEV: Large Esophageal varices; NSAID: Non-steroidal anti-inflammatory drugs; OR: Odds ratio; CI: Confidence interval.

tinal bleeding secondary to variceal or portal hypertensive gastropathy was not associated with the use of PPIs. This is a very important finding because it has been reported that the presence of PH on endoscopy is associated with an unacceptable, and according to our data, unnecessary prescription of PPIs in patients with cirrhosis[5,18].

Soon after the introduction of PPIs into clinical practice, these drugs demonstrated their effectiveness in several gastrointestinal diseases. However, the overuse of this class of drugs has important economic implications. In patients with cirrhosis, many factors influence the appropriate prescription of PPIs[5,18]. It was observed in previous studies that patients in the early stages of Child-Pugh-Turcotte classification, and with a low MELD score, were more likely to be prescribed PPIs appropriately than those in the more advanced stages of the disease or with endoscopic findings of PH[5,18]. According to the scarce evidence available regarding the use of these drugs in the clinical context, it seems that physicians tend to consider the use of PPIs in cirrhotic patients as possibly beneficial for variceal bleeding. It has also been postulated in the past that gastroesophageal reflux may contribute to esophagitis and variceal bleeding in patients with CLD[19]. In fact, there are few data on the use of PPIs in these patients, and these data are predominantly related to the pharmacological properties of the drugs[20]. The findings of our study are consistent with those of other studies, which have reported that patients with PH, and especially those with portal hypertensive gastropathy, display increased bicarbonate production and an elevated gastric pH. The increased circulatory rate in these patients, the high gastric pH level, and the increased prevalence of hypochlorhydria are factors associated with lower pepsin activity[21-25].

The main limitation of our study is its retrospective design. However, data concerning the association of portal hypertensive bleeding with the use of PPIs are scarce and are based on only one study, published as an abstract[10]. There is an absence of data from randomized trials, thus, prospective studies are still required to develop more reliable recommendations regarding the use of PPIs in this context. The diagnosis of PH in this study was based on esophageal varices, gastric varices, and hypertensive gastropathy, therefore, it is possible that some patients with a hepatic venous pressure gradient above 12 mmHg were overlooked. However, our study focused on patients with endoscopic findings related to PH.

In conclusion, our data support the hypothesis that the use of PPIs is not associated with upper gastrointestinal bleeding related to PH in cirrhotic patients. Therefore, these findings do not support the use of PPIs in patients with CLD and endoscopic evidence of PH without a currently accepted indication.

COMMENTS

Background

Gastrointestinal bleeding secondary to portal hypertension is a major complication in patients with cirrhosis, and proton pump inhibitors are frequently used to prevent it. These drugs have provided benefits in the management of many gastrointestinal disorders; unfortunately, the unnecessary prescription of these drugs has become an important problem, which increases costs in daily practice. Considering the current paradigm of evidence-based medicine, their use in patients with cirrhosis and portal hypertension is based only on expert opinion, with insufficient evidence to justify the use of these drugs as prophylaxes.

Research frontiers

Proton pump inhibitors are widely used among patients with chronic liver disease and endoscopic findings of portal hypertension with the aim of preventing bleeding, however, there is no appropriate evidence to support their use for this condition. In this study, the authors demonstrate that the use of proton pump inhibitors is not associated with a lower frequency of gastrointestinal bleeding in cirrhotic patients.

Innovations and breakthroughs

In this study, the authors observed that in patients with chronic liver disease and endoscopic evidence of portal hypertension, the presence of gastrointestinal bleeding secondary to variceal or portal hypertensive gastropathy was not associated with the use of proton pump inhibitors. This is a very important finding because it has been reported that the presence of portal hypertension on endoscopy is associated with an unacceptable, and according to the data, unnecessary prescription of proton pump inhibitors in patients with cirrhosis.

Applications

This study provided evidence on the use of proton pump inhibitors in patients with chronic liver disease and endoscopic findings of portal hypertension, and does not support their use without a currently accepted indication for their prescription in this group of patients.

Terminology

Proton pump inhibitors are a class of drugs that reduce the secretion of HCl in the stomach, consequently increasing gastric pH. The current principal accepted indications for these drugs include peptic ulcer disease and gastroesophageal reflux disease. Esophageal varices and hypertensive gastropathy are referred to as endoscopic findings of portal hypertension. Portal hypertension is the main cause of gastrointestinal bleeding in patients with cirrhosis, and its prevention is very important in clinical practice.

Peer review

This is a clear cut-off of the question of non-steroidal anti-inflammatory drugs with/without proton-pump inhibitors administration dilemma. The clinical problem is well addressed and presented, and the authors provide a rationale for their conclusions.

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