European Journal of Internal Medicine 32 (2016) 91–95

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Impact of long-term gastric acid suppression on spontaneous bacterial peritonitis in patients with advanced decompensated liver cirrhosis

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ARTICLE INFO

Article history:
Received 5 February 2016
Received in revised form 25 March 2016
Accepted 15 April 2016
Available online 29 April 2016

Keywords:
Proton pump inhibitor (PPI)
Spontaneous bacterial peritonitis
Gastric acid suppression
National Health Insurance Research Database
Cirrhotic

ABSTRACT

Objective: Recent studies have presented conflicting results on the association between gastric acid suppression and spontaneous bacterial peritonitis (SBP). The long-term effects of gastric acid suppression on SBP in cirrhotic patients remain unclear. This study evaluated the risk of SBP in advanced decompensated cirrhotic patients with long-term gastric acid suppression.
Methods: Using the Taiwan National Health Insurance Research Database, we identified 4788 patients with decompensated cirrhosis from 1998 to 2011. The SBP incidence rate was compared among proton pump inhibitor (PPI), H2-receptor antagonist (H2RA), and control cohorts. Multivariate Cox proportional hazards regressions analysis was conducted to confirm the association between gastric acid suppression and SBP.
Results: Totally, 4788 patients were analyzed: 1870 in the PPI cohort, 1728 in the H2RA cohort, and 1190 in the control cohort. The overall incidences of SBP were 16.8, 11.9, and 9.80 per 1000 person-years in the PPI, H2RA, and control cohorts, respectively. The adjusted hazard ratio (aHR) of SBP during the follow-up period was 1.16-(95% confidence interval [CI], 0.72–1.86) and 1.00-fold (95% CI, 0.63–1.57) higher in the PPI and H2RA cohorts, respectively, than in the control cohort; the result was non-significant. Compared with the control cohort, patients with >180 days of PPI therapy had significantly higher risks of SBP, with an aHR of 2.28 (95% CI, 1.37–3.78).
Conclusions: Long-term PPI use is associated with a high risk of SBP in advanced decompensated cirrhotic patients. Well-designed prospective studies are necessary to evaluate the safety of long-term PPI use in such patients.

1. Introduction

Spontaneous bacterial peritonitis (SBP) is the most common and life-threatening bacterial infection in cirrhotic patients, accounting for 10%–30% of bacterial infections in hospitalized cirrhotic patients [1,2]. SBP occurrence markedly worsens the prognosis of cirrhotic patients and is associated with high morbidity and mortality [3,4]. Although the precise mechanism of SBP remains unclear, pathological bacterial translocation involving alterations in the gut microbiota, increased intestinal permeability, and impaired immunity may play a key role in the pathogenesis [1].

Proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) are the most widely prescribed classes of drugs for managing acid-related disorders including gastroesophageal reflux disease and peptic ulcer disease. However, acid-suppressive therapy may predispose patients to bacterial overgrowth and bacterial translocation. Several studies have indicated that long-term gastric acid suppression with PPIs is associated with possible adverse events including fractures [5], enteric infections [6], community-acquired and nosocomial pneumonia [7,8], and SBP [9].

The possible role of gastric acid suppression in the development of SBP in cirrhotic patients has recently drawn attention. However, case–control and cohort studies have provided conflicting results on the

Abbreviations: SBP, Spontaneous bacterial peritonitis; PPI, Proton pump inhibitor; H2RA, H2-receptor antagonist; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; HR, Hazard ratio; CI, Confidence interval.

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http://dx.doi.org/10.1016/j.ejim.2016.04.016
0953-6205/

increased risk of SBP in cirrhotic patients receiving acid-suppressive therapy [10–13]. Two meta-analyses have revealed controversial H2RA effects and that PPIs were associated with a high risk of SBP in cirrhotic patients [9,14], but a recent multicenter prospective study did not support this conclusion [13]. However, in that study, only 135 of 226 PPI users received acid-suppressive therapy for more than 2 weeks. Moreover, only one recent nested case–control study showed that more cumulative days of gastric acid suppression were associated with a higher risk of SBP [15]. Whether the duration of acid-suppressive therapy influences the risk of SBP in cirrhotic patients remains unclear. Therefore, in this nationwide population-based study, we investigated whether short-term and long-term gastric acid-suppressive therapy increases the risk of SBP in advanced decompensated liver cirrhotic patients, including those with cirrhosis with refractory ascites, gastric or esophageal varices with bleeding, or hepatic coma.

2. Patients and methods

2.1. Database

In Taiwan, the single-payer compulsory National Health Insurance (NHI) program was launched in 1995, covering more than 99% of the population of Taiwan (23.75 million people). The National Health Insurance Research Database (NHIRD) comprises claim data of beneficiaries from the NHI program and is maintained by the National Health Research Institutes. In this study, we used the Registry for Catastrophic Illness Patient Database (RCIPD), a subpart of the NHIRD. Patients in the RCIPD are exempt from copayments for medical services corresponding to catastrophic illnesses, and the registry for catastrophic illness dataset includes complicated cirrhotic patients. The details of the RCIPD have been adequately described in previous high-quality studies [16,17]. All data are anonymous and deidentified using encrypted and unique personal identification numbers to make the NHI reimbursement data suitable for public research. Disease diagnosis was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the institutional review board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement.

2.2. Study subjects

To increase the accuracy of liver cirrhosis diagnosis, we initially included patients who had advanced decompensated cirrhosis (ICD-9-CM 571.2, 571.5, and 571.6) from1998 to 2011. Decompensated cirrhosis was defined as the development of (1) cirrhosis with refractory ascites, (2) cirrhosis with hepatic coma, or (3) cirrhosis with esophageal or gastric varices with bleeding; the diagnoses were confirmed according to patients' inclusion in the RCIPD. Furthermore, the patients were divided into the following three cohorts: a PPI cohort, including the patients treated with only PPIs; an H2RA cohort, including those treated with only H2RAs; and a control cohort, including those who were not treated with either of the two drugs. The minimum duration of PPI or H2RA treatment was 28 days. The index date in the PPI and H2RA cohorts was the 28th day, and the index date in the control cohort was randomly selected as a month and day in the index year of the treated cases. Patients were excluded if they had SBP (ICD-9-CM567.23) or had undergone liver transplantation (ICD-9-CM V42.7 and 996.82) before the index date, were diagnosed with any gastrointestinal (GI) bleeding (ICD-9-CM530.7, 530.82, 531.0, 531.00, 531.01, 531.2, 531.2x, 531.4, 531.4x, 531.6, 531.6x, 532.0,532.00, 532.01, 532.2, 532.2x, 532.4, 532.4x, 532.6, 532.6x, 533.0, 533.00, 533.01, 533.2, 533.2x, 533.4, 533.4x, 533.6, 533.6x, 534.0, 534.00, 534.01, 534.2, 534.2x, 534.4, 534.4x, 534.6, 534.6x, 535.X1, 537.83,537.84, 578.0, 562.02, 562.03, 562.12, 562.13, 569.86, 569.3, 569.85, 578.1, and 578.9)within 2 weeks before SBP occurrence, or were younger than 20 years.

2.3. Outcomes and comorbidities

All the patients were followed up from the index date to SBP occurrence, death, withdrawal from the insurance program, or December 31, 2011. The examined comorbidities were coronary artery disease (ICD-9-CM 410–414), hypertension (ICD-9-CM 401–405), diabetes mellitus (ICD-9-CM 250), congestive heart failure (ICD-9-CM 428), chronic kidney disease (ICD-9-CM 585, 586, 588.8, 588.9, 250.4, 274.1, 403.x1, 404.x2, 404.x3, and 440.1), ascites (ICD-9-CM 789.5), hepatic encephalopathy (ICD-9-CM 572.2), and esophageal varices (ICD-9-CM 456.0–456.2) diagnosed before the index date.

2.4. Statistical analyses

The chi-square test was used to evaluate the differences in baseline characteristics and comorbidities among the three cohorts, except for mean age, which was examined through one-way ANOVA. Univariate and multivariate Cox proportional hazards regressions were performed to measure the risk of SBP. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox model. The multivariate models were simultaneously adjusted for age, sex, and comorbidities. All statistical analyses were performed using SAS software (Version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA), and two-tailed *P* values less than 0.05 were considered significant.

3. Results

3.1. Baseline characteristics

Table 1 presents a comparison of the baseline characteristics and comorbidities among the three cohorts. The mean ages of the PPI, H2RA, and control cohorts were 54.3, 54.6, and 53.1 years, respectively, and most of the patients were men. The patients in the PPI cohort had a lower proportion of comorbidities.

Table 1
Comparison of the demographics and comorbidities in the study population.

	Cirrhosis						
	PPI ($N = 1870$)		H2RA ($N = 1728$)		Control ($N = 1190$)		
	n	(%)	*n*	(%)	*n*	(%)	*P* value
Age, years							0.004
≤64	777	(41.6)	694	(40.2)	542	(45.6)	
65–74	649	(34.7)	619	(35.8)	424	(35.6)	
≥75	444	(23.7)	415	(24.0)	224	(18.8)	
Mean (SD)[a]	54.3	(12.7)	54.6	(12.6)	53.1	(11.9)	0.002
Sex							<0.001
Female	499	(26.7)	524	(30.3)	230	(19.3)	
Male	1371	(73.3)	1204	(69.7)	960	(80.7)	
Comorbidities							
Coronary artery disease	146	(7.81)	190	(11.0)	102	(8.57)	0.003
Congestive heart failure	67	(3.58)	75	(4.34)	44	(3.70)	0.47
Hypertension	410	(21.9)	498	(28.8)	312	(26.2)	<0.001
Diabetes mellitus	336	(18.0)	370	(21.4)	297	(25.0)	<0.001
Chronic kidney disease	232	(12.4)	276	(16.0)	156	(13.1)	0.006
Ascites	699	(37.4)	731	(42.3)	511	(42.9)	0.002
Hepatic encephalopathy	402	(21.5)	575	(33.3)	379	(31.9)	<0.001
Esophageal varices	512	(27.4)	962	(55.7)	749	(62.9)	<0.001

Chi-square test.
PPIs: proton pump inhibitors; H2RAs: H2-receptor antagonists.
[a] One-way ANOVA.