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Original Article

Association between use of proton pump inhibitors and occurrence of colon diverticulitis

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Abstract

Background: Some recent studies have described the adverse effects of proton pump inhibitors (PPIs). PPI use and colonic diverticulitis are both associated with bacterial enteric infection and translocation. The aim of this study was to assess the association between PPI use and colonic diverticulitis.

Methods: We conducted a population-based nested case-control study in part by use of data retrospectively collected from the National Health Insurance Research Database. Diverticulitis patients were identified using inpatient discharge records with International Classification of Diseases, Ninth Revision, Clinical Modification codes (562.11 and 562.13), and were recruited as the study cohort. The controls were matched to the study patients by age, sex, nonsteroidal anti-inflammatory drugs use, laxative use, and index date. The cumulative defined daily dose (DDD) was estimated as the sum of the dispensed DDD of any PPI. The adjusted odds ratio and 95% confidence interval (CI) were estimated using multiple logistic regression.

Results: We enrolled 690 patients with acute diverticulitis, along with 2760 patients who comprised the control group. The adjusted odds ratios for the study cohort compared with PPI nonusers, after adjusting for possible confounders (including sex, age, comorbidities, and medication), were 1.29 (95% CI = 0.70−2.36) and 1.02 (95% CI = 0.59−1.76) for the group with cumulative PPI use ≥42 and ≥55 DDDs over an exposure period of 90 and 180 days, respectively, prior to the claimed date of hospitalization for colonic diverticulitis.

Conclusion: The study showed that use of PPIs did not increase the risk of colon diverticulitis.

Keywords: defined daily doses; diverticulitis; nested case-control; nonsteroidal anti-inflammatory drugs; proton pump inhibitors

1. Introduction

The incidence of both asymptomatic and symptomatic colonic diverticulosis is increasing.[1] However, only 10−20% of patients with diverticulosis develop diverticulitis.[2] Factors such as physical inactivity, constipation, obesity, smoking, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of diverticular disease.[3]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Proton pump inhibitors (PPIs) are primary agents for the treatment of gastroduodenal ulcers and gatroesophageal reflux disease and are effective in preventing NSAID/aspirin-associated peptic ulcer and ulcer bleeding.[4] PPIs are among the most frequently prescribed classes of medications worldwide because of their high rate of efficacy and low toxicity.[5] However, PPIs have recently been reported to produce adverse effects.[6−8] PPIs can interact with targets other than the gastric H^+/K^+ ATPase. Colonic epithelial cells, which are involved in maintaining local electrolyte balance, express proton pumps in the colon.[9] PPIs also influence microbial growth by inhibiting the colonic H^+-K^+ ATPase.[10]

Bacterial colonization by exogenous enteric microbes is inhibited by host defense mechanisms such as gastric acid, host gut microflora, local gut immunity, intestinal motility, intestinal secretion, and the epithelial barrier.[11] PPI use[4,12] and colonic diverticulitis[13] are both associated with bacterial enteric infection and translocation. The relationship between PPI use and diverticulitis is not well documented. Therefore, we assessed the association between PPI use and colonic diverticulitis by conducting a nested case-control study based on the National Health Insurance Research Database (NHIRD) in Taiwan.

2. Methods

2.1. Ethics statement

All data that could be used to identify patients were encrypted in the National Health Insurance (NHI) files used in our study. The confidentiality of the data presented in our study, which was approved by the Taiwan's National Health Research Institute (NHRI), adheres to the regulations of the Bureau of National Health Insurance (BNHI), Taiwan. This study was also approved by the Institutional Review Board (IRB) of Taipei City Hospital (IRB No. TCHIRB-1021103-E). Written consent was waived by the IRB.

2.2. Data source

This nationwide cohort study was based on patient data obtained from the NHIRD, which is managed by the Taiwan NHRI. The NHIRD contains healthcare data for 99% of Taiwan's population (approximately 23 million).[14] The sample files of NHIRD contained comprehensive enrollment and drug-use information for a randomly selected sample of 1,000,000 NHI beneficiaries, representing approximately 5% of all enrollees in the year 2000. We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to define diseases.

2.3. Identification of cases and control

We conducted a population-based nested case-control study. Diverticulitis patients were identified from the NHIRD by using inpatient discharge records based on ICD-9-CM codes (562.11 and 562.13) following computed tomography, magnetic resonance imaging, colonoscopy, and barium radiological examination between January 1, 2000 and December 31, 2010. Patients under 20 years of age and patients with prior colonectomy, celiac disease, and inflammatory bowel disease were excluded. We also excluded patients diagnosed with colonic cancer between January 1, 1996 and the index date. Control group patients did not have the code ICD-9-CM: (562.xx) in their inpatient records or in the ambulatory-care claims. Four control patients were selected using data from inpatient medical databases to match each newly recorded colonic diverticulitis patient by conducting random sampling stratified by age, sex, NSAID use, and laxative use in the same observational period. Fig. 1 illustrates a flowchart of the patient selection process.

2.4. Determination of medication exposure for PPIs

2.4.1. Exposure assessment

Information on the prescribed drugs was extracted from the NHRI prescription database, and the defined daily doses (DDDs) recommended by the World Health Organization were used to quantify the use of PPIs.[15] The cumulative DDD was estimated as the sum of the dispensed DDD of any PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, or esomeprazole) with the final dose taken within the specified period prior to the index date. The gathered data comprised the date of prescription, daily dosage, and the number of days of drug use.

2.4.2. Drug exposure data

We defined current users as patients exposed to PPIs for 28 days prior to the claimed date of hospitalization for acute diverticulitis. We defined previous users as patients who experienced PPI exposure between January 1, 2000 and the

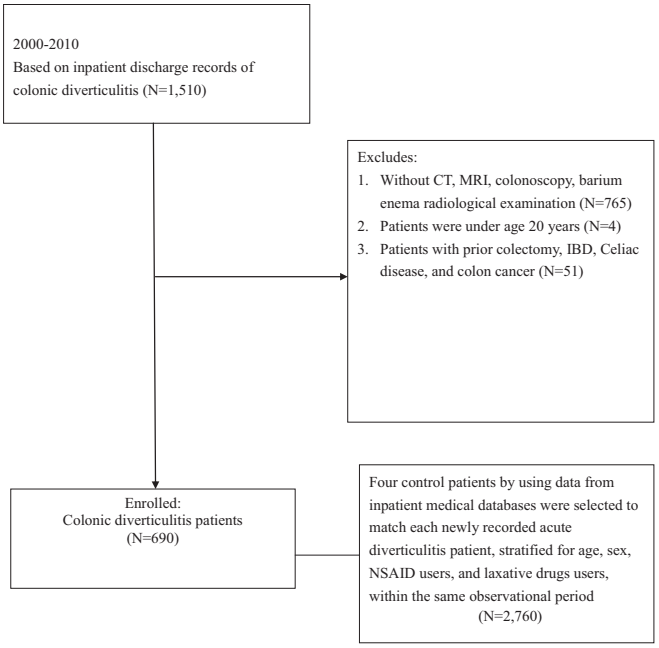

Fig. 1. Flowchart depicting the selection of participants.

claimed date of hospitalization for colonic diverticulitis, excluding the current users. Patients with no prescription for any PPIs at any time between January 1, 2000 and the claimed date of hospitalization for colonic diverticulitis were defined as nonusers.

2.5. Assessment of cofounders and covariates

2.5.1. Comorbid illness

Conditions that required inpatient care or three or more ambulatory-care visits between January 1, 1996 and the index date of the study were defined as comorbidities. The comorbidities identified in our cohort and their corresponding ICD-9-CM diagnosis codes are listed as follows: coronary artery disease (ICD-9-CM 410−414), cerebral vascular disease (ICD-9-CM 430−438), dyslipidemia (ICD: 272.xx), chronic obstructive pulmonary disease (ICD-9-CM 490−492, 494, and 496), diabetes mellitus (DM; ICD-9-CM 250), and peptic ulcers (ICD-9-CM 531, 532, and 533).

2.5.2. Use of other medications

Patients were defined as users of NSAIDs, laxatives, aspirin, cyclooxygenase-2-specific inhibitors, steroids, and antidiarrhea drugs based on whether they had consumed the prescribed medication within 28 days prior to the claimed date of hospitalization for colonic diverticulitis.

2.6. Statistical analysis

For comparing the proportions, chi-square statistics was used. A conditional logistic regression model was used to estimate the relative magnitude in relation to the use of PPIs. Exposure was defined as receiving PPIs between January 1, 2000 and the index date. Patients were categorized into one of the three PPIs exposure categories for analysis: nonusers, previous users, and current users. In the analysis, participants were categorized into PPI use below the median (<42 or <55 DDD) and PPI use equal or above the median (≥42 or ≥55 DDD) over an exposure period of 90 and 180 days, respectively, prior to the claimed date of hospitalization for colonic diverticulitis. Patients with no exposure were used as the reference for calculating odds ratios (ORs) and their 95% confidence intervals (CIs). Models with and without adjusted variables were presented. All statistical analyses were performed using the SAS System for Windows, version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

We enrolled 690 patients with acute diverticulitis, as well as 2760 patients who comprised the control group, based on NHIRD records from 2000 to 2010. Table 1 displays the demographic data including age, sex, comorbidities, and medications. Patients with colonic diverticulitis had a considerably low rate of dyslipidemia, but increased rates of peptic ulcer, aspirin use, cyclooxygenase-2 inhibitor use, and antidiarrhea drug use.

Table 1
Characteristics of participants admitted with acute diverticulitis and matched controls.

Variables	Control		Diverticulitis		*p*
	n = 2760	%	*n* = 690	%	
Sex					>0.99
Male	1492	54.06	373	54.06	
Female	1268	45.94	317	45.94	
Age (y)					>0.99
20−49	844	30.58	211	30.58	
50−69	944	34.20	236	34.20	
≥70	972	35.22	243	35.22	
Comorbidities					
CAD	1437	52.07	370	53.62	0.464
CVD	543	19.67	121	17.54	0.203
DM	570	20.65	161	23.33	0.145
COPD	656	23.77	162	23.48	0.873
Dyslipidemia	661	23.95	129	18.70	0.003
Peptic ulcer	476	17.25	156	22.61	0.001
Medication use					
NSAIDs	808	29.28	202	29.28	>0.99
Laxative drugs	1056	38.26	264	38.26	>0.99
Aspirin	333	12.07	243	35.22	<0.001
COX-2 inhibitors	322	11.67	278	40.29	<0.001
Antidiarrhea drugs	492	17.83	427	61.88	<0.001
Steroids	209	7.57	47	6.81	0.495
PPIs					0.025
Nonusers	2248	81.45	531	76.96	
Current users	75	2.72	21	3.04	
Previous users	437	15.83	138	20.00	

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; COX-2 inhibitors = cyclooxygenase-2 specific inhibitors; CVD = cerebral vascular disease; DM = diabetes mellitus; NSAIDs = nonsteroidal anti-inflammatory drugs; PPIs = proton pump inhibitors.

Compared with PPI nonusers, the crude ORs were 1.12 (95% CI = 0.69−1.84) and 1.34 (95% CI = 1.08−1.67) for current users and previous users, respectively. However, after adjusting for possible confounders (including sex, age, comorbidities, and medication), the adjusted ORs were 0.90 (95% CI = 0.48−1.72) and 1.01 (95% CI = 0.84−1.43) for the current users and previous users, respectively (Table 2). When PPI use was categorized by cumulative dosage, the crude ORs were 0.99 (95% CI = 0.60−1.62) and 1.10 (95% CI = 0.73−1.67) for the groups with cumulative PPI use of <42 and <55 DDDs, respectively, and 1.67 (95% CI = 1.04−2.68) and 1.40 (95% CI = 0.91−2.17) for the groups with cumulative PPI use of ≥42 and ≥55 DDDs over an exposure period of 90 and 180 days, respectively, prior to the claimed date of hospitalization for acute diverticulitis, compared with PPI nonusers. However, after adjusting for possible confounders (including sex, age, comorbidities, and medication), the adjusted ORs were 0.79 (95% CI = 0.44−1.42) and 0.93 (95% CI = 0.56−1.53) for the groups with cumulative PPI use of <42 and <55 DDDs, respectively, and 1.29 (95% CI = 0.70−2.36) and 1.02 (95% CI = 0.59−1.76) for the groups with cumulative PPI use of ≥42 and ≥55 DDDs over an exposure period of 90 and 180, days, respectively, prior to the claimed date of hospitalization for colonic diverticulitis (Table 2). In addition, values of 1.28

Table 2
Association between exposure to PPIs and acute diverticulitis.

Exposure	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Current use	21/669	75/2685	1.12 (0.69−1.84)	0.90 (0.48−1.72)
Previous use	141/528	451/2234	1.34 (1.08−1.67)	1.01 (0.84−1.43)
PPI use within 90 d preceding index date				
<42 DDDs	20/670	83/2677	0.99 (0.60−1.62)	0.79 (0.44−1.42)
≥42 DDDs	25/665	61/2699	1.67 (1.04−2.68)	1.29 (0.70−2.36)
PPI use within 180 d preceding index date				
<55 DDDs	30/660	111/2649	1.10 (0.73−1.67)	0.93 (0.56−1.53)
≥55 DDDs	28/662	81/2679	1.40 (0.91−2.17)	1.02 (0.59−1.76)

CAD = coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COX-2 inhibitors = cyclooxygenase-2 specific inhibitors; CVD = cerebral vascular disease; DM = diabetes mellitus; NSAIDS = nonsteroidal anti-inflammatory drugs; OR = odds ratio.
[a] Adjusted for matching variables such as comorbidities (including CAD, CVD, dyslipidemia, COPD, DM, and peptic ulcer) and medications (including NSAIDs, laxative drugs, aspirin, COX-2 inhibitors, antidiarrhea drugs, and steroids).

(95% CI = 1.01−1.61) and 1.27 (95% CI = 1.01−1.60) for DM patients, 1.30 (95% CI = 1.04−1.61) and 1.31 (95% CI = 1.05−1.63) for peptic ulcer patients, and 1.47 (95% CI = 1.22−1.77) and 1.47 (95% CI = 1.22−1.78) for antidiarrhea medication users, were recorded over an exposure period of 90 and 180 days, respectively, prior to the claimed date of hospitalization for colonic diverticulitis (Table 3).

4. Discussion

This clinical epidemiological study is the first of its kind that focuses exclusively on inpatients with colonic diverticulitis who receive PPIs. The nationwide population-based, nested case-control study did not reveal that use of PPI significantly increased the risk of colon diverticulitis after adjustment for possible confounding factors. Factors such as constipation and NSAIDs have been associated with an increased risk of colonic diverticulitis.[3] Therefore, four control patients were selected to match colonic diverticulitis case stratified by laxative drugs use and NSAID use.

Table 3
Independent predictors of acute diverticulitis among all the enrollees by conditioned logistic regression model.

Variables	PPI use within 90 d	PPI use within 180 d
	OR (95% CI)	OR (95% CI)
Comorbidities		
CAD	1.13 (0.90−1.42)	1.13 (0.90−1.42)
CVD	0.86 (0.66−1.10)	0.85 (0.66−1.10)
DM	1.28 (1.01−1.61)	1.27 (1.01−1.60)
COPD	0.93 (0.75−1.16)	0.93 (0.75−1.16)
Dyslipidemia	0.64 (0.51−0.81)	0.65 (0.51−0.82)
Peptic ulcer	1.30 (1.04−1.61)	1.31 (1.05−1.63)
Medication use		
Aspirin	0.89 (0.71−1.11)	0.89 (0.71−1.11)
COX-2 inhibitors	1.16 (0.94−1.42)	1.15 (0.94−1.41)
Antidiarrhea drugs	1.47 (1.22−1.77)	1.47 (1.22−1.78)
Steroids	0.86 (0.61−1.21)	0.86 (0.61−1.21)
PPIs use within 90 d preceding index date		
<42 DDD vs. nonusers	0.79 (0.44−1.42)	
≥42 DDD vs. nonusers	1.29 (0.70−2.36)	
PPIs use within 180 d preceding index date		
<55 DDD vs. nonusers		0.93 (0.56−1.53)
≥55 DDD vs. nonusers		1.02 (0.59−1.76)

CAD = coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COX-2 = cyclooxygenase-2; CVD = cerebral vascular disease; DM = diabetes mellitus; OR = odds ratio.

Current long-term PPI therapy has been associated with the induction of severe hypomagnesemia, iron and vitamin B_{12} deficiency, community-acquired pneumonia, hip fracture, and interstitial nephritis.[16] Elevation in gastric pH levels may exert deleterious effects on the gastrointestinal host defense including delayed gastric emptying, increased bacterial translocation, decreased gastric mucus viscosity, and changes in the normal microbial flora.[17] The pathogenesis of diverticulitis involves an altering of the gut flora[13] and a stasis or obstruction in the narrow-necked pseudodiverticulum leading to bacterial overgrowth.[18] Suppressing gastric acidity may therefore result in an increased load of pathogenic microbes in the gastrointestinal tract. However, our current study addresses the effect of PPIs on colonic diverticulitis and it remains a null association. PPIs have been implicated in the disruption of the ecology of the gut and changes in bacterial growth.[19] Janarthanan et al[20] conducted a meta-analysis and suggested that PPIs increase the incidence of *Clostridium difficile* infection. The case-control study conducted by Garcia Rodriguez et al[21] revealed an increased incidence of *Salmonella* and *Campylobacter jejuni* gastroenteritis in patients taking PPIs. People with comorbidities (especially elderly patients) are highly likely to be prescribed acid-suppressive therapy.[20] The role of PPI dosage and duration of use in immunocompetent and immunocompromised patients who have contracted varying levels of acute and recurrent diverticulitis requires investigation. Further study to evaluate whether use of PPI increased the risk of colon diverticulitis is warranted, especially in subgroup patients with risks or immune-compromised patients.

The clinical process of colonic diverticulitis varies in accordance with the extent of the disease's progress. Because only 10−20% of patients with diverticulosis develop diverticulitis, proving that these patients have recurrent asymptomatic diverticulitis might be difficult. Therefore, we adopted a strict definition of the control group, in which a patient cannot exhibit ICD-9-CM code 562.xx in their inpatient

records or in the ambulatory care claims between 2000 and 2010. To be included in the study group, patients were identified using ICD-9-CM codes following computed tomography, magnetic resonance imaging, colonoscopy, and barium radiological imaging (excluding 765 cases without image examination). Although imaging reports are unavailable in the NHIRD, the Bureau of the NHI randomly samples the claims data from every hospital and reviews charts to verify diagnostic validity. ICD-9-CM coding was strictly audited for the purpose of reimbursement.

Our observations are consistent with those of previous reports regarding the role of DM in diverticulitis, but no such association was observed for diverticulitis in steroid users. This study showed that DM is an independent risk factors of colonic diverticulitis, which is in agreement with Floch's[22] study. However, Humes et al[23] revealed that perforated diverticular disease is a severe surgical emergency, and oral corticosteroids (OR = 2.74; 95% CI = 1.63−4.61) are strongly associated with an increased risk of perforation. By contrast, our data suggested that steroid use did not increase the risk of acute diverticulitis, which is dissimilar to the result reported by Humes et al.[23] The primary discrepancy is the enrolled patient criteria. Further study is required to elucidate the role of corticosteroids, including duration and dose in immune-competent and immunocompromised patients, diagnosed with varying extents of diverticulitis.

This study had several limitations. First, factors such as patients' lifestyles, dietary habits (especially fiber intake), body mass indices, and smoking were not available for adjustment.[24−26] Second, certain data, such as the location of diverticulitis, are unavailable in the NHIRD. Left-sided diverticular disease is most common in Western societies, whereas right-sided diverticular disease is more prevalent in Asia. In addition, colonic diverticular disease is not as common in Asian societies as in Western societies, so the results cannot be applied to western societies. Third, the consumption of PPIs could not be confirmed in this study. However, the Bureau of the NHI has formed various audit committees that randomly sample claims data from every hospital and review charts on a regular basis to verify the diagnostic validity and quality of care. Fourth, the causality of this phenomenon has not been established by any randomized placebo-controlled clinical trials. Determining causality is difficult because neither withholding PPI therapy from those who require it, nor administering PPIs to those who do not require them are ethically feasible.[20] Therefore, we conducted a nested case-control study by using data from the Taiwan NHIRD. In Taiwan's NHI program, the use of PPIs is strictly limited to treating patients with reflex esophagitis or peptic ulcer disease for 4 months after gastroscopic confirmation.[27] Therefore, we analyzed the cumulative dose effect of PPIs on acute diverticulitis for an exposure period of 90 and 180 days prior to the claimed date of hospitalization for colonic diverticulitis. Fifth, hospitalization is indicated if the patient is unable to tolerate oral intake or if the patient has acute diverticulitis. Establishing a standard definition is crucial; therefore, we analyzed only the cases requiring hospitalization for colonic diverticulitis by using data from inpatient medical databases. The actual prevalence rate of diverticulosis is difficult to determine because most patients are asymptomatic. Therefore, we conducted the current study by using the nested case-control method instead of the cohort study method. Finally, use of over-the-counter oral PPI medications was not included in our database.

In conclusion, the study showed that use of PPIs did not increase the risk of colon diverticulitis. Prospective studies are necessary to confirm this association in the general population and explore whether this risk can be reversed by avoiding unnecessary PPI use and administering the optimal PPI DDD.

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