



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.

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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 gastroesophageal 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 diverticulitis¹³ 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 colectomy, 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

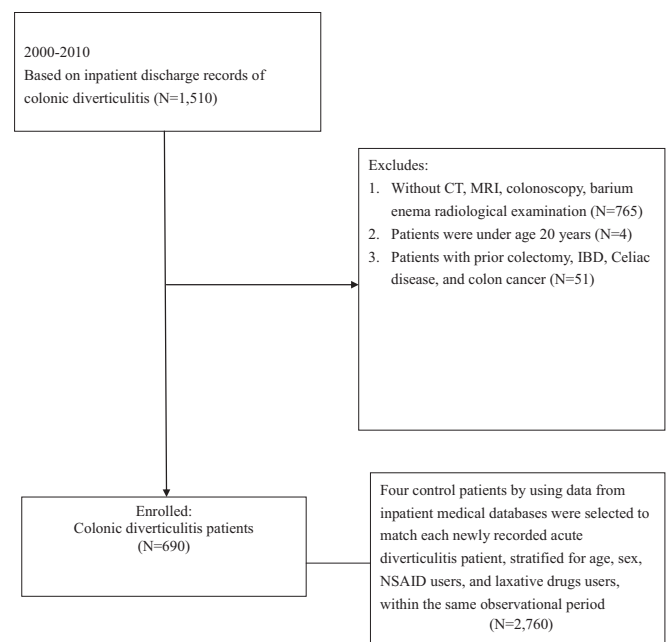


Fig. 1. Flowchart depicting the selection of participants.

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