Diagnostic and Interventional Endoscopy **Original Article**

Use of Proton Pump Inhibitors Increases the Number of Episodes of Inflammatory Bowel Disease

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Abstract

Objective: Proton pump inhibitors may alter intestinal microbiota, and changes in intestinal microbiota may lead to the activation of inflammatory bowel disease. In our study, we investigated the association between proton pump inhibitor use and inflammatory bowel disease activation.

Methods: A total of 67 inflammatory bowel disease patients were enrolled in this study. The number of inflammatory bowel disease episodes, medications used, and the use of proton pump inhibitors were evaluated retrospectively for all patients. We divided the patients into 2 groups as proton pump inhibitor users and non-proton pump inhibitor users, and the groups were compared.

Results: The median age of the 67 inflammatory bowel disease patients (41 male and 26 female) was 37 (18-70) years. The disease duration since diagnosis was 63.4 (10.2-223.6) months, and the total number of episodes was 3.0 (0-20). Crohn's disease was diagnosed in 23 patients (34.3%) and ulcerative colitis in 44 (65.7%) patients. Of the patients, 35 (52.2%) were on anti-tumor necrosis factor treatment and 41 (61.2%) had proton pump inhibitor usage history for a median of 40 (1-300) months. Among 41 proton pump inhibitor users, 34 (82.9%) had a history of inflammatory bowel disease activation during the course of treatment. When proton pump inhibitor users and non-proton pump inhibitor users were compared in terms of disease duration, there was no difference ($P = .65$); however, the number of inflammatory bowel disease episodes was significantly different (5.0 (0-20) episodes vs. 1.5 (0-17) episodes, respectively; $P < .0001$).

Conclusion: In patients with inflammatory bowel disease, proton pump inhibitor use may be associated with an increase in the incidence of disease episodes. Randomized, controlled studies involving more patients will guide to clarify the uncertain points of this finding.

Keywords: Crohn's disease, inflammatory bowel disease, proton pump inhibitors, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and in some cases life-threatening inflammatory disease of the gastrointestinal tract which is divided into Crohn's disease and ulcerative colitis.[1] In the pathogenesis of the disease, gut microbiota has also been accused in addition to genetic predisposition, environmental factors, and immunological abnormalities.[1] Intestinal microbiota is influenced by multiple factors such as diet, medication use, enzyme replacement, and fecal transplantation.[2,3] A large number of data strongly suggest that gut microbiota alteration plays an influential role in the pathogenesis of IBD.[4]

Proton pump inhibitors (PPIs) are used extensively in disorders that require gastric acid suppression, mainly for peptic ulcer and gastroesophageal reflux disease, due to their potent activity.[5] While acid suppression enables the healing of erosions and ulcers in the upper gastrointestinal tract, it may potentially lead to the occurrence of adverse effects. Among these, small intestinal bacterial overgrowth and alteration of gastrointestinal flora have been widely debated.[6] Changes in intestinal microbiota may also affect IBD activation. Our aim in this study was to assess the relationship between PPI use and IBD activation.

METHODS

We enrolled a total of 67 IBD patients followed at the Gastroenterology Outpatient Clinic of Ondokuz Mayıs University Faculty of Medicine. The study protocol was permitted by the ethics committee for clinical studies of Ondokuz Mayıs University Faculty of Medicine prior to initiation of the study (2022/271; June 7, 2022). The demographic characteristics, medication use, number of IBD episodes, and the use of PPIs were evaluated retrospectively. The definition of PPI users was as routinely defined as 2 times/wk and the IBD activation was diagnosed with clinical

Table 1. Demographic Characteristics of the Patients in This Study

	Numbers of Patients	Gender (Female/Male)	Age Year, Median (Min-Max)	Illness Duration Month, Median (Min-Max)	Numbers of Activation Median (Min-Max)
All participants	67	26/41	37 (18-70)	63.4 (10.2-223.6)	3.0 (0-20)
PPI users	41	15/26	44 (18-70)	65.3 (10.2-223.6)	5.0 (0-20)
Non-PPI users	26	11/15	30 (20-55)	48.9 (16.0-164.5)	1.5 (0-17)
P values[#]	-	NS	*P* = .003	NS	*P* < .0001

[#]PPI users vs. non-PPI users; NS, not significant; PPI, proton pump inhibitors.

and/or endoscopic examination. Values are presented as median (min-max). The data were analyzed with the Mann–Whitney *U* test according to the number of cases and abnormality of the distribution of the data. Values of $P < .05$ were considered statistically significant. Data were analyzed with Statistical Package for the Social Sciences 15.0 for windows.

RESULTS

The median age of the 67 IBD patients (41 male and 26 female) was 37 (18-70) years. The disease duration since diagnosis was 63.4 (10.2-223.6) months, and the total number of episodes was 3.0 (0-20). Crohn's disease was diagnosed in 23 patients (34.3%) and ulcerative colitis in 44 (65.7%) patients. Of the patients, 35 (52.2%) received anti-tumor necrosis factor (TNF) therapy and 41 (61.2%) had PPI usage history for a median of 40 (1-300) months. Among 41 patients with PPI use, 34 (82.9%) had a history of IBD activation during the course of treatment. The demographic data of the patients are given in Table 1.

When PPI users and non-PPI users were compared with regard to disease duration, there was no difference ($P = .65$). However, the number of IBD episodes was significantly different, with 5.0 (0-20) episodes in PPI users versus 1.5 (0-17) episodes in non-PPI users ($P < .0001$).

There was no significant difference between the 2 groups in terms of mesalazine use ($P = .93$), azathioprine use ($P = .29$), and anti-TNF use ($P = .84$).

DISCUSSION

The study was conducted with IBD patients to investigate the association between the use of PPIs and disease activation. In a retrospective study including 190 patients with ulcerative colitis in clinical remission, it has been revealed that the coadministration of PPIs may increase the relapse rate in patients treated with pH-dependent-released 5-aminosalicylic acid.[7] Similarly, Andrews et al[8] reported that treatment with mesalazine might cause a reduction in the fecal bacteria abundance.

It has been demonstrated that mucosal bacteria concentration increased by 1000-fold in IBD patients receiving azathioprine treatment in contrast with healthy controls.[9] In a study by Wills et al.[10] the use of thiopurine was shown to decrease the intestinal bacterial diversity in 19 IBD patients. Busquets et al[11] reported that the gut microbiota composition was altered in Crohn's disease patients treated with anti-TNF therapy. Collectively, these studies suggest that the currently used drugs in the treatment of IBD can influence the intestinal microbiota. However, it is uncertain whether alterations in gut microbiota in IBD patients receiving acute episodic treatment result from the drugs used or improvement of intestinal inflammation.[4] In our study, there was no significant difference between PPI users and non-PPI users in terms of the drugs used for the treatment of IBD. The lack of such a difference is important since it ensured that both groups had possibly similar effects of IBD drugs on gut microbiota, enabling better identification of the effect of PPI use.

The primary mechanism underlying the possible effect of PPI use on IBD activation involves the effects of PPIs on gastric acid secretion. We did not analyze the presence of *Helicobacter pylori* in our patients, and this may be considered as a limitation of our study. Considering previous studies reporting that *H. pylori* positivity may affect basal gastric acid secretion,[12] it is clear that it would have been more relevant if the study sample consisted of *H. pylori*-negative patients or patients with a similar prevalence of *H. pylori* positivity. However, as this was a retrospective study, it was not possible to evaluate the patients for the presence of *H. pylori*.

The use of drugs such as antibiotics, iron pills, and non-steroidal anti-inflammatory drugs could not be evaluated due to the fact that some of our patients included in the study were followed by more than one center, and their disease duration was long. It is known that these drugs may affect IBD activation, and this was considered as a limitation of our study.

In conclusion, it was found that the use of PPIs increased the incidence of IBD episodes. Another remarkable finding was the high rate and long-term use of PPIs among IBD patients. Thus, avoiding unnecessary use of PPIs may reduce the occurrence of known side effects of this drug class and may also help decrease the frequency of episodes in IBD patients. Future prospective studies involving more patients will guide to confirm these findings.

MAIN POINTS

- The patients were divided into 2 groups, who have the same demographic characteristics, as proton pump inhibitor (PPI) users and non-PPI users, and the groups were compared.
- The use of PPI in patients with inflammatory bowel disease (IBD) may be associated with an increase in the incidence of IBD episodes.
- Randomized, controlled studies with a larger sample size are required.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ondokuz Mayıs University (Date: June 7, 2022, Decision No: 2022/271).

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