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Proton pump inhibitor use is associated with an increased risk for microscopic colitis: a case-control study

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Abstract

Background: Microscopic colitis (MC) causes chronic watery diarrhea. Recent studies have suggested an etiological role for various medications, including proton pump inhibitors, in the pathogenesis of MC.

Aim: To determine whether an association exists between microscopic colitis and proton pump inhibitor use in patients with documented microscopic colitis versus age and sex-matched controls.

Methods: In this retrospective case-control study. Cases of microscopic colitis from a secondary and tertiary referral medical center diagnosed in the last 5 years were reviewed. Demographic characteristics, clinical, histological and endoscopic records, as well as exposure to PPIs and NSAIDs were assessed. Controls from the population were matched to cases by gender and by age.

Results: During the investigated period, 136 cases were identified in both hospitals. Of these, 95 cases of MC were retrieved for detailed analysis. Exposure to proton pump inhibitors at the time of the histological diagnosis was significantly higher in MC patients than in controls (38% vs 13%, $p < 0.001$; adjusted OR of 4.5 [95% CI 2.0-9.5]).

Conclusion: This observation confirms the presumed association between microscopic colitis and PPI use and supports the possible etiological role of PPI exposure in the development of microscopic colitis.

Keywords: microscopic colitis, proton pump inhibitors

Introduction

The term 'microscopic colitis' (MC) was introduced in 1980 to describe patients with chronic watery diarrhea characterized by normal radiological and endoscopic mucosal appearance but microscopic abnormalities in the colonic mucosa (1). Currently, 'microscopic colitis' is used as an umbrella term for two separate entities: collagenous colitis and lymphocytic colitis. The number of intraepithelial CD8+ T-lymphocytes is increased in both collagenous and lymphocytic colitis, exceeding 20% of the surface epithelial cells. This is accompanied by superficial epithelial damage and a variable inflammatory infiltrate in the lamina propria. In addition, collagenous colitis is also characterized by a thickened subepithelial collagen band, which exceeds 10 μm . These histological characteristics are not pathognomic as they may occur in various inflammatory conditions in the colon (2).

In the past, MC was thought to be a rare disorder. However, it has recently become apparent that MC accounts for up to 13% of patients investigated for chronic diarrhea, particularly in middle-aged and elderly patients (2, 3). Pardi *et al.* reported an increasing annual incidence rate of 7.1 for collagenous colitis and of 12.6 for lymphocytic colitis per 1000 000 in the period of 1998 to 2001 (3). The cause of MC remains unknown. One postulated hypothesis points to increased colonic permeability in MC patients, thereby allowing luminal antigens to enter the lamina propria and elicit an immune and inflammatory reaction. Environmental risk factors, such as drugs, have been suggested as causes or triggers of this process (4). These drugs include non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), biphosphonates, beta-blockers, statins and proton pump inhibitors (PPIs) (5).

Recently, several case reports have been published which further highlight the association between PPI use and development of MC (6-9). Initially, lansoprazole has been found to be associated with a high likelihood of inducing MC (10). A recent study also points to similar effects in case of exposure to omeprazole and esomeperazole (9). PPIs are one of the most frequently prescribed classes of medications worldwide because they combine a high level of efficacy with low toxicity. In 2006, expenditure on these drugs was 10 billion USD globally (11). In the five years since the introduction of esomeprazole in 2001, prescriptions for PPIs have doubled (11). A recent socio-demographic study from The Netherlands found that 11.8% of the population had at least one prescription for a PPI in the

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3 year 2006 (12). It is noteworthy, that the increasing incidence of MC (3) seems to parallel the rising
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5 use of PPIs. In this report, we analyze the possible association between MC and PPI use in patients
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7 with documented MC versus age and sex-matched controls.
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10 **Methods**

11 *Patients*

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13 We performed a retrospective, two-center, observational, case-control study. Patients with MC were
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15 identified by reviewing the pathology database and medical records at the Maastricht University
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17 Medical Center, The Netherlands, a tertiary medical center, and at Orbis Medical Center, Sittard, The
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19 Netherlands, a secondary medical center, from November 2005 to November 2009. Diagnosis was
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21 based on clinical symptoms, data from histology and endoscopy. Following identification, written
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23 informed consent was obtained from the patients to assess medical and pharmacy records.
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25 Information on prescribed medication for the period of two years prior to the histological diagnosis was
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27 obtained from the pharmacy database. All patients having had at least one prescription for a PPI
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29 (esomeprazole, omeprazole, lansoprazole, pantoprazole or rabeprazole) in 180 days prior to the time
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31 of histological diagnosis were considered exposed to PPIs. Similarly, we investigated exposure to
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33 NSAIDs, a known risk factor for MC, as well as exposure to benzodiazepines (BDZs), diuretics and
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35 ACE inhibitors, which have not been associated with MC, as control medication. Use of low-dose
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37 aspirin (up to 300 mg/day) was not considered as NSAID exposure. The reason for selecting a time
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39 window of 180 days between drug exposure and diagnosis of microscopic colitis was the considerable
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41 delay that can occur between initial symptom onset and eventual endoscopic examination with
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43 mucosal biopsy sampling. Also, comorbidity was also assessed by reviewing medical records.
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48 *Controls*

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50 The control group consisted of 355 individuals randomly selected from the general population in
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52 Maastricht, The Netherlands, derived from the municipal residential database. Controls received
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54 questionnaires regarding their current medical status and drug exposure. Ninety-five controls were
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56 matched randomly to cases by gender and by age (within 1 year). Also, comorbidity was assessed by
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58 reviewing medical records.
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Statistical analysis

Statistical analysis was done by performing χ^2 test and generalized linear model for binomial regression to calculate ORs and 95% CIs using SPSS, version 17.0 (Chicago, Illinois). Statistical significance was predetermined as $p < 0.05$.

Results

During the investigated period, 136 cases were identified in both hospitals. Of these, 95 cases of MC were retrieved for detailed analysis. No detailed pharmacy records were available for the remaining 41 cases. Mean age of MC patients was 58 ± 1 yrs, 66% were women. We observed a 1:1.07 ratio for lymphocytic vs collagenous colitis. Cases did not differ significantly in BMI from controls (25 ± 5 vs. 26 ± 4 kg/m^2 , mean \pm SD). Exposure to both PPIs and NSAIDs at the time of the histological diagnosis was significantly higher in patients than in controls (PPI 38% vs 13%, $p < 0.001$ and NSAIDs 20% vs 5%, $p = 0.002$ vs control, respectively). Co-exposure to both PPIs and NSAIDs was also significantly higher in MC patients compared to controls (8% vs 0%, $p = 0.007$). After adjustment for concomitant exposure to NSAIDs, BDZs, diuretics and ACE inhibitors as covariates, an adjusted OR of 4.5 [95% CI 2.0-9.5] was found for PPI exposure (see table 1). There were no differences observed in exposure to PPIs or NSAIDs with regard to the histological subtype (collagenous or lymphocytic). No significant association was found between gender and histological subtype or drug exposure.

Considering the fact that the pharmacy records were not available or obtainable in case of 41 patients, calculations have been done according to the 'worst-case scenario.' This would mean that of the 41 patients, from which no data on medication was obtainable or available, the assumption was made that none were taking PPIs prior to the histological diagnosis (0 out of 41, overall 36 out of 136). As for the control population for these additional 41 patients, we presumed that the consumption of PPIs would be equal to what we observed in the control population (13%, approximately 5 out of 41, overall 17 out of 136). Repeating the binary logistic regression analysis with these fictive numbers results in an OR of 2.5 [CI 1.3-4.7] for PPI exposure.

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5 Regarding the type of PPI patients were exposed to, we found the following distribution: 40%
6 omeprazole, 23% esomeprazole, 28% pantoprazole, 6% rabeprazole, 3% patients used lansoprazole
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8 (see table 3).
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10 Celiac disease and autoimmune diseases have been reported to be associated with MC (4). In our
11 patient population, celiac disease was diagnosed in 3% of patients with MC. This rate is comparable to
12 previous reports (3). Rheumatoid arthritis was found in 6%, hypothyroidism in 5% of MC patients (see
13 table 2). Multivariate logistic regression analyses with comorbidities as covariates resulted in an OR of
14 5.8 [2.5-13.5] for PPI exposure. This implies that patients with comorbidity have an even higher risk for
15 developing MC upon exposure to PPIs.
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25 Discussion

26 Recent studies have emphasized the association between exposure to PPIs and occurrence of MC.
27 Our findings confirm the importance of considering PPI use as a possible etiological factor for MC.
28 However, case-control studies generally do not allow interpretation with respect to a causal relation. It
29 should be noticed that our study has a number of limitations. First, the population in this study is
30 relatively small and pharmacy records were not available or obtainable in about 30% of the cases in
31 the period reviewed. Nevertheless, calculations according to a 'worst-case scenario' in which none of
32 the remaining 41 MC patients were exposed to PPIs in the studied period still show a significant risk
33 for developing MC. Second, use of over-the-counter medication could not be assessed. Third, the time
34 window between symptom onset and histological diagnosis may vary largely between MC patients,
35 which makes assessment of drug exposure more difficult. For that reason, we assessed drug intake
36 for a longer time window preceding the diagnosis. Fourth, for similar reasons, history of
37 gastrointestinal symptoms could neither be assessed in this time period. Further studies, when
38 possible on larger samples of patients, are needed to confirm our observations.
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54 The pathophysiological mechanisms underlying PPI-related induction of MC are poorly understood.
55 Proton pumps (H^+/K^+ ATPases) are present not only on gastric epithelium but also on colonic
56 epithelium where they contribute to whole body potassium homeostasis (13). Inhibition of the colonic
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3 proton pumps may therefore affect local electrolyte balance and compromise fluid acidification, which
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5 can possibly affect immune reactions in the colonic mucosa.
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9 Proteins other than H⁺/K⁺ ATPase have also been reported as targets for PPIs. Omeprazole and
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11 lansoprazole have been observed to induce smooth muscle relaxation and to inhibit contractile activity
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13 (13). This effect on contractile systems could also affect tight junction functionality since tight junction
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15 proteins are directly linked to the actinomyosin cytoskeleton. Therefore, conformational changes in the
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17 cytoskeleton of epithelial cells may result in alterations in the function of the tight junction, which leads
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19 to increased paracellular permeability. As a result, luminal contents can more easily penetrate the
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21 lamina propria causing an immune and/or inflammatory reaction. Esomeprazole has been shown to
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23 increase paracellular permeability in the upper gastrointestinal tract *in vitro* (14) and *in vivo* in humans
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25 (15). Increased paracellular permeability has been observed in MC and is considered a key
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27 component in the induction of diarrhea (16). Accordingly, expression of the tight junction proteins
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29 occludin, claudin-4 and zonuline-1 (ZO-1) was found to be decreased in mucosal biopsy specimens
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31 from MC patients (16, 17). We speculate that a direct or indirect effect of PPIs on colonic tight
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33 junctions and paracellular permeability may explain the association between PPI use and MC
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35 observed in this study.
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39 Although not directly linked to the pathogenesis of MC, recent case reports have related long-time PPI
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41 exposure to severe hypomagnesemia (18, 19). This effect has been described for omeprazole,
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43 esomeprazole, pantoprazole and lansoprazole as well (18). It has been proposed that PPIs induce a
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45 defect in the active absorption of magnesium in the intestine. This may result from an effect of PPIs on
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47 the tight junction proteins or on the TRPM6 and 7 channels (transient receptor potential melastin 6 and
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49 7). The latter are key molecules involved in active magnesium absorption. Either changes in intestinal
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51 pH induced by PPIs may affect channel functions, or subjects who are heterozygous carriers of
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53 TRPM6/7 mutations are more susceptible to developing adverse reactions to PPIs (19). Presently, we
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55 cannot exclude that effects of PPIs on magnesium absorption also play a role in the pathogenesis of
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57 MC.
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3 In addition, it has long been established that PPI therapy can alter intestinal microbial profiles (20).
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5 PPIs can directly affect intestinal microbiota through inhibition of the H⁺/K⁺ ATPase which can inhibit
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7 microbial growth. Several bacteria, including *H. pylori* and *S. pneumoniae*, as well as fungi such as *C.*
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9 *albicans*, contain H⁺/K⁺ ATPase in their plasma membranes which are highly homologous to their
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11 human counterparts (21). On the other hand, increase of intestinal pH can result in a diminished host
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13 defence against certain bacteria. Profound acid suppression increases the risk of enteric infections in
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15 susceptible individuals caused by *Shigella*, *Salmonella*, *Yersinia* or *Clostridium difficile* (22). The use
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17 of PPIs may also promote the expansion and colonization of *C. difficile* by its recognized potential to
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19 induce small bowel bacterial overgrowth with anaerobic colonic organisms (20). Many believe that PPI
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21 use may therefore directly contribute to *C. difficile* and other bacterial infections. Certainly, further
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23 research is needed to clarify the exact effects of PPIs on human intestinal microbiota. Nevertheless,
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25 alterations in intestinal microbiota should also be considered as a possible pathogenetic aspect in MC.
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29 In conclusion, the observations of our case-control study confirm the presumed association between
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31 MC and PPI use and support the possible etiological role of PPI exposure in the development of MC.
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33 When patients are prescribed PPIs to treat upper gastrointestinal disorders, it is important to recognize
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35 that PPIs are interacting at multiple targets. As a result, MC may occur as an adverse reaction of PPIs
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37 and PPIs should be considered as a possible cause of diarrhea in this population.
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Appendix 1. Table 1.

Drug	MC patients	Controls	OR [95% CI]
PPI	37.9%	12.6%	4.5 [2.0-9.5]
NSAID	20.4%	7.3%	2.3 [0.8-6.5]
BDZ	12.8%	8.4%	1.2 [0.4-3.7]
Diuretics	12.8%	8.4%	1.4 [0.5-4.4]
ACE-I	7.7%	5.3%	1.8 [0.5-4.4]
PPI+NSAID	8.0%	0%	N.A.

Table 1. Exposure to PPIs and NSAIDs in microscopic colitis (MC) patients and controls.

Appendix 2. Table 2.

	MC patients	Controls	p value (χ^2)
Celiac disease	3.2 %	0 %	0.25
Rheumatoid arthritis	6.3 %	0 %	0.03
Hypothyroidism	5.2 %	0 %	0.06
Irritable bowel syndrome	8.4 %	6.3 %	0.78

Table 2. Comorbidities among microscopic colitis (MC) patients and controls.

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Appendix 3. Table 3.

Type of PPI	MC patients	Controls
Omeprazole	40.0 %	50.0 %
Esomeprazole	22.8 %	30.0 %
Pantoprazole	28.6 %	20.0 %
Rabeprazole	5.7 %	0 %
Lansoprazole	2.8 %	0 %

Table 3. Types of PPIs used among microscopic (MC) patients and controls.

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