Case 1 -- A 48-year-old woman presented with watery diarrhea. She had been on chronic omeprazole therapy for gastroesophageal reflux disease (GERD), but had recently experienced worsening of her GERD and omeprazole was replaced with dexlansoprazole. She then developed diarrhea and was evaluated after 3 months of exposure to the dexlansoprazole. Stool testing for infectious etiologies (c. difficile toxin, ova and parasites, giardia antigen) was unremarkable. Colonoscopy revealed a grossly normal appearing colonic mucosa, and biopsies revealed changes consistent with collagenous colitis. The patient discontinued dexlansoprazole therapy and had prompt resolution of her diarrhea. Symptoms have not recurred over the following three years.

Case 2 -- A 67-year-old woman with a history of GERD treated with oral calcium carbonate developed progressive watery diarrhea. Stool testing for infection was unremarkable. She underwent colonoscopy revealing a normal appearing colon, and biopsies revealed lymphocytic colitis. She was treated with bismuth subsalicylate for 2 weeks with resolution of diarrhea. She remained asymptomatic with normal stools until three years later when she developed recurrent diarrhea two weeks after starting dexlansoprazole for persistent GERD. Testing for infectious etiologies was negative. Five weeks after initial exposure and three weeks after stopping the dexlansoprazole she underwent repeat colonoscopy which revealed hyper vascular colonic mucosa. Biopsies showed collagenous colitis. After discontinuing the dexlansoprazole she re-initiated bismuth subsalicylate with only modest improvement, eventually requiring therapy with budesonide. She ultimately required a three-month taper of budesonide. Over the next six years she has not had recurrence of diarrhea.

Case 3 -- An 85-year-old man with a history of chronic GERD treated with omeprazole developed C. difficile diarrhea after treatment with clindamycin. This was treated with oral metronidazole with resolution. Four years later he developed a second episode of C. difficile diarrhea. Colonoscopy confirmed acute colitis and he was treated with intravenous metronidazole and oral vancomycin with improvement in his symptoms. After completing the therapy for C. difficile he was asymptomatic. Two months later the patient started dexlansoprazole for worsening of GERD and within one month he developed diarrhea. Stool testing for infection was unremarkable. He continued to have mild diarrhea prompting repeat colonoscopy showing normal mucosa, but biopsy revealed collagenous colitis with neutrophilic and lymphocytic infiltration. Dexlansoprazole was discontinued and he was started on bismuth subsalicylate with improvement in his symptoms. He was then treated with budesonide which required tapering over months and stools returned to near normal. Follow-up colon biopsies 14 months later continued to show collagenous colitis with decreased lymphocytosis. Patient has had no persistent recurrence of diarrhea over five years of follow up.
Case 4 -- A 69-year-old male presented with acute diarrhea. The patient had a history of ulcerative colitis in remission for six years off treatment. A surveillance colonoscopy performed one-month prior showed normal mucosa and biopsies were negative for inflammation, dysplasia, or colitis. Two weeks prior to presentation, the patient had been switched from omeprazole to dexlansoprazole and after four days of therapy developed diarrhea. Stool testing for infection was unremarkable. Colonoscopy performed three weeks later revealed numerous regions of patchy erythema and loss of vascular pattern throughout the colon, but no areas of friability or acute colitis. Biopsies revealed collagenous colitis. Dexlansoprazole therapy was discontinued and within one week he was asymptomatic. Repeat colonoscopy five weeks after prior exam was unremarkable and mucosal biopsy was normal. Symptomatic remission has continued for 2.5 years.

Discussion

In this report we describe a series of patients who developed symptomatic collagenous colitis after exposure to dexlansoprazole suggesting an association with exposure to this PPI. Previous studies have shown that microscopic colitis is associated with multiple other drug exposures. This case series extends these observations and suggests dexlansoprazole can be the cause of some cases of collagenous colitis. An association is supported by the similarity of clinical events among the four cases. Symptoms began soon after exposure (2-12 weeks). All patients improved after drug withdrawal. No specific treatment was required in two of the cases. Finally, mucosal biopsies were similar in all cases, showing collagenous colitis and resolution or improvement was seen in the two patients who had follow-up biopsies.

There are some limitations to accepting causation as implied with our case series. First, three of our four patients had been chronically exposed to omeprazole, a potential cause of microscopic colitis [11]. The omeprazole had been well tolerated in all of these patients and had not resulted in diarrhea during therapy. While it is possible these patients may have had asymptomatic collagenous colitis from the prior PPI, the sudden onset of diarrhea associated with dexlansoprazole exposure suggests symptomatic colitis secondary to dexlansoprazole.

Next, the patient with ulcerative colitis in remission developed diarrhea following the initiation of dexlansoprazole. Inflammatory bowel disease has been possibly associated with the development of microscopic colitis and one may speculate that the dexlansoprazole therapy was only coincidental with the patient developing collagenous colitis [12,13]. However, the normal colon biopsies just before onset of symptoms and prompt histologic normalization after drug withdrawal argue against a relation to IBD.

Finally, one patient had a prior diagnosis of lymphocytic colitis, with interval resolution of symptoms before the development of dexlansoprazole-induced collagenous colitis. It may be argued that this patient had asymptomatic microscopic colitis prior to dexlansoprazole exposure.

In conclusion, we present a case series of four patients who developed diarrhea and histopathological changes of collagenous colitis when exposed to dexlansoprazole. Following discontinuation of dexlansoprazole all patients had improvement in their clinical symptoms and those later tested by biopsy demonstrated histopathologic improvement or resolution. Awareness of this association will be useful in the clinical use of proton pump inhibitors.

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Patient informed consent

Clinical details retrieved from data base on microscopic colitis approved by Institutional Review Board, Maine Medical Center, Portland, ME. In preparation of this manuscript, each patient was contacted about information in the existing medical record and involved in an informed consent process. This was conducted over the telephone by Dr. Wilcox and witnessed by an unbiased third party. All patients agreed to volunteer their medical information to be documented in the below format for intent of educational and scholarly purposes. There questions were answered, and follow-up information provided should they have additional questions for the authors in the future. Additional documentation available upon request.

Competing interests

None.

References


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