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Case Report

Lymphocytic Colitis Associated with Lansoprazole Treatment

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ABSTRACT

Introduction: There have been several reported cases of lansoprazole-associated collagenous colitis (CC) reported in the literature but only 1 reported case of lansoprazole-associated lymphocytic colitis (LC) in the literature. Both CC and LC are considered inflammatory bowel diseases, but they are distinctly classified based on the condition of the colon, which is typically confirmed through biopsy.

Case summaries: A 52-year-old white male (Patient 1), with a height of 178 cm and weight of 75 kg, presented to Gazi University Hospital, Ankara, Turkey, with a 3-month history of abdominal pain and nonbloody, watery diarrhea. The patient reported receiving PO lansoprazole 30 mg/d to treat heartburn ~1 week prior to the onset of diarrhea. The patient's medical history revealed that he did not have any preexisting conditions, other than gastroesophageal reflux disease (GERD) for which lansoprazole was prescribed. The medical history report also revealed that the patient was not receiving any concomitant medications or treatments at the time. A colon biopsy confirmed LC. Additionally, a 43-year-old white female (Patient 2), with a height of 168 cm and weight of 61 kg, presented to the same facility with a 6-month history of nonbloody, watery diarrhea and mild lower abdominal cramping. The patient reported that initial onset began ~2 months after receiving a 10-day *Helicobacter pylori* eradication combination treatment regimen that included lansoprazole, amoxicillin, and clarithromycin, followed by lansoprazole monotherapy to treat GERD. The patient's medical history revealed no other concomitant medications were being adminstered at the time. A colon biopsy confirmed LC.

Discussion: A search of the literature using the MEDLINE database and all relevant English-language articles with key words *lansoprazole* and *lymphocytic colitis*, found that there were several cases of lansoprazole-associated CC reported and 1 reported case of lansoprazole-associated LC. Histologic findings from labora-

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tory tests and colon biopsies confirmed diagnoses of LC in both patients in this case report. Patient 1 presented with diarrhea and cramping, which the patient reported had been ongoing for ~3 months, following lansoprazole administration. However, after lansoprazole was discontinued, the symptoms completely resolved within 7 days. Patient 2 presented with diarrhea and cramping, which had been occurring for ~6 months. That patient reported that initial onset commenced ~2 months after a 10-day *H pylori* eradication combination treatment regimen that included lansoprazole, amoxicillin, and clarithromycin, followed by lansoprazole monotherapy to treat GERD. However, after sulfasalazine (3 g/d) was prescribed for 2 months immediately upon diagnosis of LC, there was little improvement in the effort to control the diarrhea in this patient. After omeprazole 20 mg/d was substituted for lansoprazole, the patient's diarrhea ceased. Follow-up sigmoidoscopy 2 months later revealed normal mucosa and complete normalization of histologic findings. The patient remains diarrhea-free while on omeprazole. A causality assessment using the Naranjo adverse reaction algorithm produced scores of 6 for both patients, suggesting that LC was probably associated with lansoprazole treatment.

Conclusions: Here we report 2 cases of LC in patients probably associated with the administration of lansoprazole treatment. Complete remission occurred after lansoprazole was discontinued. (*Curr Ther Res Clin Exp.* 2007;68:360–366)

Key words: lansoprazole, microscopic colitis, gastroesophageal reflux disease.

INTRODUCTION

All proton-pump inhibitors bind to the parietal cell proton pump covalently at cysteine 813 or 822. Lansoprazole, however, binds at cysteine 321.[1,2] Binding of cysteine 321 inhibits colonic proton pumps, which might affect colonic secretion and pH, predisposing a patient to diarrhea and microscopic colitis (MC). Lansoprazole decreases gastric acid secretion by inhibiting the proton pump of gastric parietal cells.[1] The drug has been used as monotherapy for peptic ulcer disease, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome, and in combination therapy for *Helicobacter pylori* eradication.[1,2] Its acute and chronic use to treat these disorders has been well tolerated, with few serious adverse events (AEs).[2] The most common AEs reported are diarrhea (4.1%), headache (2.9%), and nausea (2.6%).[3] In long-term (>12 months) clinical trials.[3–5] monitoring lansoprazole in the treatment for GERD, diarrhea was the most commonly reported AE.

MC was first identified in 1980.[5] It is characterized by chronic watery, nonbloody diarrhea, abdominal pain or cramps, distention, nausea, fecal incontinence, and dehydration. MC includes collagenous colitis (CC) and lymphocytic colitis (LC).[6,7] Both CC and LC cause inflammation of the colon. Although inflammatory bowel disease is the general term used to refer to diseases that cause inflammation of the intestines (eg, Crohn's disease, ulcerative colitis), CC and

LC are classified separately based on the distinct condition of the colon (ie, the presence of collagen in the lining of the colon [CC] and the number of white blood cells found between the cells of the large intestine [LC]). Specifically, LC is characterized by increased lymphocytic infiltration of the colonic epithelium and lamina propria. CC is characterized by nearly identical clinical and histologic features, but it also presents with chronic mucosal inflammation and a thickened subepithelial collagen band.[5,6] Because the radiologic and endoscopic assessments of the colon appear normal, diagnoses of CC and LC are usually confirmed by colon biopsies, which reveal the presence of microscopic abnormalities.[8]

A study by Read et al[9] that included a group of patients with chronic diarrhea, found that the microscopic evaluation of biopsy material obtained from colonic mucosa had an increased number of intraepithelial lymphocytes.[7] While the etiology of MC is not known, it is thought to be associated with a poorly-regulated epithelial immune response to luminal or epithelial antigens, including bile acids, toxins, and infectious agents.[10] MC has been associated with autoimmune diseases and drug exposure, predominantly NSAIDs, but salicylates, simvastatin, ticlopidine, ranitidine, carbamazepine, flutamide, gold salts, and lansoprazole as well.[10] The use of these drugs might be associated with the pathogenesis of MC by acting as triggers of colonic inflammation in genetically predisposed individuals and as an aid in the development or exacerbation of diarrhea in a patient with underlying, undiagnosed MC. Therefore, in some patients, these drugs would be the most probable cause of diarrhea but not necessarily the probable cause of MC. In this case, these drugs might increase the possibility of early detection of MC.[11]

We present 2 cases of LC associated with lansoprazole. In both cases, histologic tests were performed, and colon biopsies confirmed MC diagnoses. After lansoprazole was discontinued, cessation of diarrhea occurred in both patients.

CASE SUMMARIES

Patient 1

A 52-year-old white male, with a height of 178 cm and weight of 75 kg, presented to Gazi University Hospital, Ankara, Turkey, with a 3-month history of abdominal pain and nonbloody, watery diarrhea. The patient had received PO lansoprazole* 30 mg/d to treat heartburn ~1 week prior to diarrhea onset. The patient's medical history did not reveal any preexisting conditions, other than GERD for which lansoprazole was prescribed. No concomitant medications or treatments were being administered at the time. Upon assessment, the patient reported having 6 to 7 bowel movements daily and intermittent lower abdominal cramping that was relieved with defecation. There was no associated weight loss. Stool studies were negative for leukocytes, culture, ova and

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parasites, and *Clostridium difficile* toxin. No occult blood was detected. Further diagnostic tests included a negative antiendomysial antibody test, normal iron studies (serum ferritin, serum iron, and serum-iron binding capacity), normal folate concentration, and normal thyroid-stimulating hormone concentration. Routine biochemistry parameters (blood-urea nitrogen, creatinine, glucose, alanine aminotransferase, aspartate aminotransferase, and electrolytes) were normal. A colonoscopy was performed and revealed normal mucosa.

Histopathologic findings of 2 random biopsies were obtained from each colon section. Tissue was fixed in 10% formalin, preserved in paraffin wax, and stained with hematoxylin–eosin. The colon biopsies confirmed diagnosis of LC (defined by the presence of >20 lymphocyte/100 epithelial cells). The subepithelial collagen plate was of normal thickness. There were no architectural distortions, crypt abscesses, or granulomas found or identified. There was no evidence of dysplasia or malignancy, and no microorganisms were identified. Discontinuation of lansoprazole corresponded with complete cessation of diarrhea and abdominal cramping within 7 days. After 2 months, a repeat colonoscopy with biopsies from each colon section found no evidence of LC.

Patient 2

A 43-year-old white female patient, with a height of 168 cm and weight of 61 kg, presented to Gazi University Hospital, Ankara, Turkey, with a 6-month history of nonbloody, watery diarrhea and mild lower abdominal cramping. The patient reported that the symptoms commenced ~2 months after receiving a 10-day *H pylori* eradication treatment regimen that included lansoprazole (30 mg BID), amoxicillin (1 mg BID), and clarithromycin (500 mg BID), followed by monotherapy with PO lansoprazole 30 mg/d to treat GERD. The patient's medical history did not reveal concomitant medications or treatments being administered at the time. The patient reported that the diarrhea and cramping had been ongoing for ~6 months. She was having 8 to 10 nonbloody, watery bowel movements daily, some of which interrupted sleeping patterns. The patient also reported an 8-kg weight loss. Routine blood tests included complete blood count (hemoglobin, hematocrit, platelet, white blood cell), complete metabolic profile, amylase and lipase activities, erythrocyte sedimentation rate, calcium concentration, and thyroid function tests (TSH, FT3, FT4). All laboratory findings were unremarkable or negative. Stool tests were negative for ova and parasites and for *C difficile* toxin. An upper endoscopy revealed GERD. Duodenal biopsy findings were unremarkable, and colonoscopy was grossly normal.

Two random biopsies were obtained from each colonic section. Tissue was fixed in 10% formalin, preserved in paraffin wax, and stained with hematoxylin–eosin. Histopathologic findings of the colon biopsies revealed a marked increase in the number of intraepithelial lymphocytes (defined by the presence of >20 lymphocytes/100 epithelial cells). The subepithelial collagen plate was of normal thickness. In addition, the lamina propria was infiltrated with lymphocytes and plasma cells, confirming a diagnosis of LC.

Sulfasalazine treatment was administered immediately upon LC diagnosis. After 2 months of treatment with sulfasalazine 3 g/d, there was little improvement in the effort to control the diarrhea in this patient. However, after PO omeprazole* 20 mg/d was substituted for lansoprazole, the diarrhea ceased within 5 days. Follow-up sigmoidoscopy 2 months later revealed normal mucosa and normal histologic findings. The patient remained free of diarrhea on omeprazole.

DISCUSSION

The etiology of MC (both CC and LC) is unknown but is suspected to be multifactorial. Several hypotheses have been suggested, including drug effect, immune dysfunction, autoimmunity, and infection. Among these, drug consumption has been suggested to play an important role. To date, ≥17 drugs have been reported to be associated with the onset of MC, including NSAIDs, and, rarely, salicylates, simvastatin, ticlopidine, ranitidine, and carbamazepine.[12–14] Drugs that can induce or exacerbate MC need to be identified because the condition impacts quality of life, can be life-threatening, and might require the use of expensive and potentially toxic treatments.[11]

There have been multiple reports of drug-associated MC, which include: LC secondary to ranitidine treatment implicating histamine$_2$-receptor blockers in persistent histologic features of both LC and CC[14,15]; an association between NSAID use and LC and CC[16,17]; a case of simvastatin-induced CC[18]; ticlopidine-induced colitis[19]; LC likely attributable to a vinca alkaloid[20]; chronic diarrhea consistent with LC in a patient who ingested tardyferon[21]; and 1 case report of CC associated with lansoprazole.[22] Once drug-induced diarrhea is suspected, diarrhea is typically treated by discontinuing the administration of the drug. Although the pathophysiology remains to be determined, possible mechanisms include bacterial overgrowth, alteration of intestinal pH, intestinal dysmotility, and bile salt abnormalities as a consequence of colonic proton-pump inhibition.[23]

The mechanism of lansoprazole-associated MC is unknown but might involve toxic or immunologic factors. Lansoprazole might have a direct toxic effect on colonocytes, or indirect toxic metabolites may be involved after the drug is hepatically biotransformed.[1,22,24] Alternatively, lansoprazole might stimulate an inappropriate immune reaction in certain predisposed individuals.[24]

All proton-pump inhibitors act on parietal cells by binding to cysteine residues 813 and 822 via 2 disulfhydryl bonds.[25] Lansoprazole, however, is unique in its ability to also inhibit colonic proton pumps by binding to cysteine residue 321 via 3 disulfhydryl bonds.[26] Inhibition of colonic proton pumps might have an effect on colonic secretion and pH, which could, in turn, affect bile salt solubility and action. These factors might explain the diarrheagenic potential of lansoprazole. Omeprazole, however, does not inhibit colonic proton pumps because it does not bind to cysteine 321. In Patient 2, substituting omeprazole

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for lansoprazole did not lead to recurrent diarrhea. In Patient 1, cessation of diarrhea and the absence of LC on a follow-up sigmoidoscopy after discontinuation of lansoprazole suggest an adverse drug reaction.

A causality assessment using the Naranjo adverse drug reaction algorithm[27] produced scores of 6 for both patients, suggesting that LC was probably associated with lansoprazole treatment.

CONCLUSIONS

Lansoprazole was probably associated with MC in these 2 patients. Discontinuing the drug reversed the abnormality in this difficult-to-treat condition. MC should be considered in patients who develop watery diarrhea while receiving lansoprazole.

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