Colonic Ulceration and Diclofenac/Misoprostol: A Case Report

Clinical awareness of esophageal, gastric, and duodenal lesions due to over-the-counter or prescribed nonsteroidal agents is prevalent in current medical practice and literature. Nonsteroidal agents have also been shown to cause inflammation and ulcers in the colon. Mechanism of injury to the colonic mucosa from NSAIDs is thought to be identical to that of the esophagus and small intestines. Incorporation of misoprostol with diclofenac has been shown to minimize the frequency and severity of upper gastrointestinal ulceration. Advantages of taking misoprostol are presumed to extend to the colon. We present a case of colonic ulceration secondary to daily ingestion of diclofenac/misoprostol for chronic pain.

INTRODUCTION
Nonsteroidal anti-inflammatory drugs are in high demand. These agents are readily purchased without a prescription for headaches, fever, pain, and other common physical symptoms and complaints. The management of osteoarthritis and other chronic pain disorders, more often than not, involves a prescribed regimen of nonsteroidals among other analgesic and anti-inflammatory drugs. The combination of diclofenac and misoprostol is unique in that it was developed to prevent or minimize the potential damage to intestinal mucosa, which is a common side effect of NSAIDs.

Diclofenac, as well as other nonsteroidal agents block the production of prostaglandins, which leaves

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the gastrointestinal mucosa vulnerable to inflammation and ulceration. Misoprostol protects the mucosa in that it is a prostaglandin E₁ analog. Furthermore, misoprostol reduces the secretion of some digestive enzymes. Research has shown that patients who take diclofenac with misoprostol have a reduced risk of esophageal, gastric, and upper intestinal lesions compared to patients who take NSAIDs only. The data reflecting the effectiveness of misoprostol in reducing the prevalence of colonic ulceration in patients taking combination medications such as diclofenac/misoprostol is scarce. We present a case of colonic ulceration as a result of the daily use of diclofenac/misoprostol for chronic pain.

CASE REPORT
An 84-year-old male presented to the emergency department with a history of shortness of breath, weakness, and tarry stools for several days. He denied nausea, vomiting, diarrhea, and rectal bleeding. Past medical history included congestive heart failure, hypertension, and osteoarthritis. Diclofenac 75mg/misoprostol 200 mg taken four times daily was prescribed for chronic back pain. He had been on diclofenac/misoprostol for several years. He was also taking a coated aspirin daily for cerebrovascular and cardiovascular prophylaxis. On physical examination, his blood pressure was 128/85, heart rate 101, respiratory rate 20, and 98% oxygen saturation on room air. Additional physical findings included pallor, a soft non-tender abdomen, and tarry hemocult positive stool.

Admission laboratory data revealed WBC of 12,500/cm³; hemoglobin and hematocrit were 6.6 gm/dL and 20.5%, respectively; reticulocyte count 2.1%; PT, INR, and PTT of 13.8, 1.32, and 21, respectively.

The patient was resuscitated and transfused three units of packed red blood cells, pantoprazole 40mg intravenously was initiated, and diclofenac/misoprostol and aspirin were held. Esophagastroduodenoscopy (EGD) revealed nodular gastric duodenitis and multiple antral erosions. Helicobacter rapid urea assay was negative.

Colonoscopy the following day revealed multiple large areas of ulceration, some with stricture formation. Inflammatory changes were seen at the ileocecal valve and at the hepatic flexure. Gross observation also revealed stricture formation at the hepatic flexure. Ulcerations were seen in the mid transverse colon, the splenic flexure, and the distal portion of the descending colon (Figure 1). Diverticular changes were seen in the sigmoid colon and the rectum was normal.

Differential diagnosis included ischemic colitis, inflammatory bowel disease, and NSAID-induced ulcerations. Histologic studies were key in making the correct diagnosis. There was an absence of surface epithelium in some of the biopsies. Mild cystic dilatation of some of the glands was also recognized. The lamina propria contained lymphocytes and plasma cells with rare eosinophils. Endoscopic and histologic findings were suggestive of NSAID colopathy.

DISCUSSION
Gastrointestinal ulceration with stricture formation, is a potential side effect of NSAIDs. NSAIDs have been associated with a five-fold increase risk of colonic perforation, ulcer formation, and hemorrhage (1). The exact etiology of NSAID-induced colonic ulcerations has not been determined.

Several hypotheses regarding the etiology of NSAID-induced lesions of the colon have been proposed and they are similar to those proposed for upper gastrointestinal lesions. Nonsteroidal drugs may cause occlusion of vessels in the mucosa secondary to their vasoconstrictive effects. An increase in free radical production due to NSAIDs has been suggested as a culprit in intestinal inflammation (2). Increased permeability of the mucosa after using NSAIDs potentially suppresses the immunologic defenses of the large intestines. In turn, the opportunity for inflammation to occur as a response to infection by gastrointestinal microorganisms is greater.

Reduction in prostaglandin synthesis is thought to be the most significant factor in gastrointestinal inflammatory changes due to nonsteroids. NSAIDs and aspirin inhibit prostaglandin synthesis by blocking cyclooxygenase production. Prostaglandins stimulate the secretion of bicarbonate and mucus, which protect the mucosa from inflammation and possible ulceration from digestive enzymes and other factors. Another hypothesis is the (continued on page 52)
inhibition of prostaglandin synthesis may induce an ischemic environment in the colon. Blood flow to the colonic mucosa decreases as the production of prostaglandin is decreased. Therefore, as NSAIDs reduce prostaglandin synthesis, blood flow may be restricted to areas of colon, diminishing the ability to heal minor insults to the mucosa and allowing progression to erosion, ulceration, and stricture formation (3).

Diclofenac/misoprostol is a unique formulation because the prostaglandin E₁ analog misoprostol compensates for the prostaglandin inhibition induced by diclofenac. Studies that evaluate the protective role of misoprostol in the colon in human participants have not been performed.

Püspök, et al retrospective study of eleven patients with NSAID-induced colitis revealed diclofenac was the most common NSAID used among the participants. A majority of patients experienced diarrhea, hematochezia, or abdominal pain. Many of the patients had anemia and required transfusions. Ulceration, granularity, diverticular changes, and other evidence of inflammation were found throughout the colon, with the right side of the colon bearing the brunt of the damage. Ring-shaped strictures, termed “diaphragm-like” strictures, with superficial erosions were also documented in four patients. Histologic examination of inflamed areas of the colon revealed findings similar to the inflammatory changes seen in our patient, such as an increase in lymphocytes in the lamina propria and granulation tissue. As biopsies of strictures generally only revealed fibrosis of the submucosa in a majority of the specimens collected, it has been postulated that stricture formation represents the progression of an ulcer. Researchers in this study also suggest that prostaglandin synthesis inhibition is the major cause of NSAID-induced damage in the large intestines.

It is highly probable that our patient’s daily aspirin regimen may have heightened his risk of colonic inflammation. Twenty percent of patients in the above study were taking a low-dose aspirin and NSAIDs. Research has shown that aspirin, like NSAIDs, may increase the development of erosions, ulcers, and strictures by making the mucosa of the colon more permeable. Again, no studies discuss the effectiveness of misoprostol against the additive inflammatory changes that result from a combination of nonsteroidals and aspirin and colonic injury.

A retrospective study of lower gastrointestinal bleeding in minority populations has been reported by Akhtar (4). Twelve percent of the African-American and Hispanic patients in this study, all with a history of NSAID and/or aspirin use, were reported to have inflammatory lesions of the colon. None of the patients were reported to have taken misoprostol or any mucosal protective medication.

Kurahara, et al published a retrospective study of 14 patients with NSAID-induced colonic ulceration. Of the 14 patients, two patients were taking oral diclofenac, one patient was taking diclofenac sustained-release, and three patients were using diclofenac suppositories. Endoscopic evaluation revealed round or semilunar ulcers with distinct margins in the ileocecal area. Diaphragm-like strictures were more prevalent in patients who had taken NSAIDs for greater than 12 months. This study emphasizes that the route of NSAID administration does not seem to influence the potential or rate of pro-

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progression of inflammatory changes. The route of administration does determine the location of ulcers and strictures. Stenotic lesions in or near the rectum and proctitis are generally associated with cases of diclofenac suppository (5). Repeat colonoscopy after discontinuation of nonsteroidals revealed overall healing of the lesions.

NSAIDs may exacerbate symptoms associated with existing pathologies of the colon such as Crohn’s disease, ulcerative colitis, and diverticular perforation or hemorrhage. Findings from gross and histologic examination aid the clinician in distinguishing the cause of inflammatory changes. Misoprostol’s ability to prevent the inflammatory side effects of NSAIDs, therefore reducing the risk of relapse of pre-existing disease is unknown.

NSAID-induced ulcers appear to have a predilection for the right side of the colon. Many NSAIDs, especially slow-release formulations, tend to be absorbed in the cecum. This may offer an explanation as to why a majority of lesions are found in the ileocecal area and the ascending and proximal transverse colon. Misoprostol is rapidly absorbed after oral ingestion, but the exact site of absorption in the intestinal tract has not been determined.

Discontinuation of NSAIDs is the first line of management in treating colonic ulcers. Information regarding the use of over-the-counter analgesic and anti-inflammatory products is essential in educating patients and increasing medical compliance. Most symptoms remit simply from stopping the inciting agent. Occasionally medications, such as metronidazole, sulfasalazine, or mesalamine are prescribed to treat NSAID-induced erosions and ulcers in the colon (6). Strictures appear to be unaffected by oral therapy. When there is evidence of obstruction, endoscopic dilatation or surgical intervention is required. Indicators predicting relapse have not been defined.

Medications such as nabumetone (a Pro-NSAID), cyclooxygenase-II (COX-II) inhibitors and 5-lipoxygenase inhibitors are popular alternatives in treating rheumatologic disorders and managing pain or inflammation, and they may reduce the risk of gastrointestinal lesions (7). It is important to remember that these medications are not entirely free from risk of gastrointestinal hemorrhage and ulceration.

CONCLUSION

Our case demonstrates that misoprostol may not provide sufficient defense against colonic injury due to NSAIDs. It further illustrates that the efficacy of misoprostol in the colon may be diminished in patients taking NSAIDs and aspirin. Compliance with an increased dosage of misoprostol may be problematic as doses above 200mg cause diarrhea. No studies on the benefits of misoprostol in the prevention of colonic injury have been reported. There are no concrete guidelines that predict susceptibility to NSAID toxicity. Prolonged use of NSAIDs and aspirin at least doubles the risk of NSAID-induced colonic ulceration. Diarrhea, dyspnea, weakness, abdominal pain, hemodynamic instability, anemia, and hemocult positive stool are commonly associated with inflammatory changes due to NSAIDs. Colonoscopy reveals progression of erosion to ulceration and diaphragm-like stricture. Histologic identification of inflammatory changes in the lamina propria is essential in distinguishing NSAID-induced colonic injury from other inflammatory bowel diseases. Immediate discontinuation of NSAIDs and aspirin is paramount in treating NSAID-induced colonic ulcers. A lower risk of colonic injury may be accomplished with the use of COX-II inhibitors and other anti-inflammatory medications.

References


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A CASE TO REMEMBER

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