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CASE REPORT

Mesalamine induced symptom exacerbation of ulcerative colitis: Case report and brief discussion

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Abstract

This paper describes a rare case in which the oral administration of mesalamine resulted in the exacerbation of ulcerative colitis (UC) in a patient who was previously responsive to mesalamine and whose colitis had been in remission for eight years. Mesalamine and other 5-aminosalicylic acid compounds are the mainstay of treatment for UC; however up to 8% of patients are unable to take the medications due to intolerance or hypersensitivity reactions. Common drug reactions are fever, nausea, diarrhea and abdominal pain; however, exacerbation of UC has rarely been reported. This study highlights the importance of ruling out mesalamine as the causative agent in cases of UC exacerbations.

Key words: Mesalamine; Exacerbation; Ulcerative colitis; Inflammation; Adverse drug reaction

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INTRODUCTION

This paper describes a 28-year old woman with a history of ulcerative colitis (UC) who developed worsening of her bloody diarrhea and abdominal pain after the reintroduction of mesalamine therapy. The patient developed inflammatory changes of her colon similar to that which is seen in typical UC exacerbation. After the discontinuation of mesalamine, the patient's symptoms quickly subsided. Mesalamine is chemically very similar to sulfasalazine, one of the mainstays of UC therapy. Unlike sulfasalazine, mesalamine lacks a sulphapyridine moiety that has been implicated in many of the adverse reactions associated with sulfasalazine. This paper describes the proposed mechanism by which mesalamine causes symptomatic exacerbation of UC in certain affected patients.

CASE REPORT

A 28-year old woman with a history of UC presented to her primary care physician with complaints of fatigue, crampy abdominal pain, bloating and 2-3 episodes of bloody diarrhea per day. She was initially diagnosed with UC at the age of 20 years and treated with mesalamine for several months with complete resolution of symptoms. She self-discontinued the mesalamine after approximately six months secondary to occasional episodes of nausea which she attributed to the medication and has since re-

ported good health until this presentation. Her primary care physician completed an extensive workup and treated her symptoms with a two week taper of oral steroids and resumption of mesalamine (800 mg by mouth three times a day). An outpatient sigmoidoscopy was obtained which revealed shallow ulcers and continuous areas of inflammation beyond the view of the scope. Despite this treatment, her symptoms persisted and worsened. She began to have an increase in frankly bloody bowel movements up to 12-15 per day and reported a 10-pound weight loss. She is a lifelong non-smoker, has no other history of medical illnesses or surgeries, denies recent medication or non-steroidal anti-inflammatory use and has had no known sick contacts or infectious exposures. She has no extraintestinal manifestations of her disease. Her primary care physician recommended that she be admitted to the hospital for intravenous steroids, fluids and further management.

On admission, physical examination, laboratory data and abdominal radiographs were only significant for an elevated C-reactive protein and a hemoglobin level of 10.9 g/dL. Despite an initial improvement in her diarrhea, the patient continued to complain of persistent nausea and crampy abdominal pain, particularly after mesalamine administration. A surgical consultation was obtained and a repeat sigmoidoscopy confirmed previous endoscopic findings. Histological evaluation revealed acute inflammation with crypt architectural distortion diffusely consistent with inflammatory bowel disease, favoring UC. Stool studies were negative for infection. A computed tomography scan was obtained which suggested significant symmetrical bowel wall thickening with adjacent mesenteric inflammatory changes extending from the ascending colon to the rectum. After seven days of hospitalization, she continued to complain of nausea, abdominal pain and 4-6 bloody bowel movements per day. Over the course of the admission she became increasingly irritable and anxious. The correlation between the mesalamine administration and the nausea prompted a withdrawal of the mesalamine drug. Her bowel symptoms then improved significantly on the steroid monotherapy and after an additional three days of inpatient care, she was well enough to be discharged home on an oral steroid taper.

DISCUSSION

Sulfasalazine and other 5-aminosalicylic acid (5-ASA) compounds are used as mainstay drugs for the treatment of UC. Sulfasalazine was devised in the early 1940s by Dr. Nanna Svartz and consists of a 5-ASA molecule linked to a sulphapyridine moiety by an azo bond. Sulfasalazine is relatively safe and effective in inducing and maintaining remission from UC symptoms; however, up to 30% of patients cannot take it due to intolerance or hypersensitivity reactions which are often attributed to the sulphapyridine moiety[1]. Mesalamine, which is simply 5-ASA, lacks the sulphapyridine moiety and is better tolerated with fewer adverse reactions[2]. In 1977, Azad Khan *et al*[3] showed that mesalamine is as efficacious as sulfasalazine when used topically and several topical and delayed release oral compounds were subsequently developed. This case describes one of the few reported incidences of severe exacerbations of UC after administration of mesalamine, for which the pathogenesis is largely still unknown[3].

Most patients with intolerance to 5-ASA compounds experience systemic manifestations such as fever, nausea, vomiting, diarrhea and rashes, thought to be allergic drug reactions[4]. These reactions are rare, affecting only 8% of patients. Severe reactions include bone marrow suppression, arthritis, pneumonitis, pericarditis and pancreatitis[5]. Diarrhea is seen more commonly with olsalazine (13%), composed of two 5-ASA molecules linked by an azo bond, than with mesalamine (5%) and is attributed to a secretory mechanism secondary to the inhibition of ileal and colonic Na^+ K^+ ATPase which leads to malabsorption of sodium and water. This mechanism, however, does not explain the bloody diarrhea or the endoscopic and histological evidence of inflammation seen in this case[4,6].

Mesalamine, unlike sulfasalazine and non steroidal anti-inflammatory drugs (NSAIDs), is an uncommon cause of UC exacerbation. In order to confirm mesalamine as the causative agent, a mesalamine challenge can be performed. Two such challenges have been reported in patients who previously demonstrated mesalamine intolerance but were in remission at the time of the study. In 1995, Kapur *et al*[4] administered a mesalazine suppository to such a patient and subsequently induced bloody diarrhea within four hours. Prior to the challenge, biopsies taken from three sample sites showed typical chronic UC in remission with chronic inflammatory cells in the lamina propria but no evidence of a neutrophilic infiltrate or mucus depletion. After the challenge, biopsies demonstrated a diffuse neutrophilic infiltrate from the lamina propria to the crypt epithelium along with mucus depletion. Additionally, there was no evidence of any increased eosinophilia nor was there any evidence that pointed to a drug reaction rather than a relapse. Sturgeon *et al*[1] performed a similar rectal challenge in a patient with UC in remission. Biopsies taken before the challenge showed chronic UC and those taken after the challenge showed a neutrophilic and eosinophilic infiltrate of the lamina propria as well as crypt destruction. In both studies, there was endoscopic evidence of edema, erythema and punctate mucosal exudates, similar to that which was found in our patient[1,4]. In all of the reported cases of mesalamine exacerbated UC, there is no consistent pattern in the alteration of lab values. Some patients have lab values that remain unchanged whereas others, such as our patient, demonstrate increased inflammatory markers and/or leukocytosis. The means by which mesalamine causes these changes remains unknown as it lacks the sulphapyridine moiety implicated in sulfasalazine exacerbations[5].

Alteration of arachidonic acid metabolism is one proposed mechanism for mesalamine induced exacerbation of UC. In 1998, Fine *et al*[6] proposed that 5-ASA compounds might exacerbate colitis in patients with inflammatory bowel disease (IBD) by a mechanism similar to acetylsalicylic acid and NSAIDs due to their similar

structure[6]. In the rectal dialysates of patients with active IBD there are elevated levels of prostaglandins and leukotrienes[5]. NSAIDs alter arachidonic acid metabolism by inhibiting cyclooxygenase which causes a decrease in prostaglandin synthesis. However, there is a paradoxical increase in leukotriene synthesis as arachidonic acid is shunted into the lipoxygenase pathway, leading to intestinal inflammation and diarrhea. While *in vitro* studies demonstrate that mesalamine inhibits both the cyclooxygenase and the lipoxygenase pathways, Fine *et al*[6] analyzed the fecal eicosanoids of a patient with mesalamine exacerbated IBD and showed a 45% decrease in prostaglandin E_2 but a 500% increase in leukotriene B_4, similar to what would be expected with NSAID exacerbated colitis. Evaluation of fecal dialysates was not performed on the patient in this case. Furthermore, steroids, often used concomitantly in patients with UC exacerbations, inhibit phospholipase activity which causes a decrease in leukotrienes and can mask mesalamine intolerance until they are stopped[5].

Mesalamine intolerance does not indicate a global intolerance to all 5-ASA compounds. In a comparative study in which patients with UC intolerant to sulfasalazine were administered three 5-ASA compounds, mesalamine, olsalazine and balsalazide, 91% of patients were able to tolerate at least one of the three compounds. This study shows that even in patients intolerant to mesalamine, a trial of another 5-ASA compound may still be indicated[7].

Mesalamine is an efficacious and relatively safe drug that is widely used to treat UC. More research must be done to understand the mechanism by which mesalamine causes exacerbations of UC in certain patients. Physicians must remember to keep mesalamine on the differential for UC exacerbations, especially in patients who are recently started on the drug or those whose symptoms appear after withdrawal of steroids.

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