



Letter

Mesalamine desensitization in a patient with treatment refractory ulcerative colitis and aspirin and nonsteroidal anti-inflammatory drug hypersensitivity

Inflammatory bowel disease is an increasingly prevalent problem worldwide.^{1–3} Ulcerative colitis (UC) can present with inflammation throughout the colon, always involving the rectum.^{2,3} The disease is characterized by relapsing and remitting flares that require lifelong maintenance therapy once remission is achieved. Common symptoms experienced by patients include abdominal pain, rectal urgency, bloody diarrhea, and tenesmus, and the diagnosis should be suspected clinically and confirmed with colonoscopy and biopsy.^{1–3} When possible, treatment of these patients should begin with oral and rectally administered medications, saving surgical resection for severe refractory colitis.^{1–4}

The initial choice for treatment of mild to moderate UC includes mesalamine, orally or rectally, in combination with other medications.^{2–4} It is similar in structure to acetylsalicylic acid or aspirin.⁵ Aspirin functions as an anti-inflammatory by inhibiting cyclooxygenase (COX) enzymes (COX-1 and COX-2). Mesalamine also inhibits COX enzymes, thus affecting the production of prostaglandins and decreasing inflammation of the colon. Despite the fact that the drug targets colonic inflammation, significant systemic absorption occurs with all mesalamine products and is relevant to issues of drug toxicity or adverse reactions, including drug allergy.

The clinician occasionally encounters patients with UC who require mesalamine therapy with history of adverse reactions to aspirin, which complicates the decision to prescribe mesalamine given the similar chemical structure.

We describe a 33-year-old woman with history of chronic UC who was referred to the University of Arkansas for Medical Sciences gastroenterology and allergy/immunology clinics for management and for a reported aspirin and nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity, respectively. She had active moderate colitis that involved the entire colon and had predominant rectal symptoms. Infectious causes were excluded, and histopathologic samples obtained at colonoscopy were consistent with a diagnosis of chronic UC. Initial therapy with oral and rectal mesalamine was indicated; however, there was concern regarding the safety of this therapy given the patient's prior reactions to multiple NSAIDs, including aspirin, naproxen, and ibuprofen.

Therapy was initiated with azathioprine and prednisone with minimal improvement in symptoms. Her diarrhea and abdominal pain worsened after 3 months, and the azathioprine dosage was increased. Symptoms continued to worsen, unalleviated by the addition of hydrocortisone enemas. Infectious causes, such as cytomegalovirus and *Clostridium difficile*, were excluded. Because the patient was poorly responsive to progressively increasing doses of azathioprine and prednisone, therapy was escalated to

infliximab. Because of persistent diarrhea and severe abdominal pain after induction therapy with infliximab at 5mg/kg per infusion, colonoscopy was repeated, which revealed backwash ileitis, cecal patch inflammation, and mucosal healing of midportions of the colon but with a dominant residual proctosigmoiditis. Oral enteric-coated budesonide was added to the treatment regimen with concomitant increase of azathioprine and infliximab. Rectal symptoms persisted, and she was believed to be receiving maximal medical treatment with the exception of not having tried oral or rectal mesalamine. The patient did not wish to pursue surgery, however, so she was referred to the allergy clinic for consideration of desensitization to aspirin.

On initial evaluation in the allergy and immunology clinic, she reported reactions to aspirin, naproxen, and ibuprofen. As a child, she had urticaria and laryngeal angioedema after ingestion of aspirin that required intubation to maintain her airway. She had not been exposed to aspirin again since this severe reaction. More recently, ibuprofen and naproxen had caused diffuse pruritus in the absence of rash with subsequent development of edema of her trunk. These symptoms were accompanied by a feeling of confusion, reportedly alleviated with diphenhydramine. Importantly, she did not have any history of asthma or chronic sinus disease.

Little is known regarding the cross-reactivity between aspirin and mesalamine with regard to allergic reactions. One case report suggests that a patient with aspirin allergy developed urticaria after challenge dosing of mesalamine.⁵ Others have found that there is no cross-reactivity between mesalamine and aspirin.⁶ In fact, the literature supports a test dose before initiation of mesalamine treatment in patients with aspirin hypersensitivity regardless of the type of reaction rather than complete desensitization.^{6–8} The information concerning need for desensitization, possibility of test dosing, and lack of literature supporting cross-reactivity between NSAIDs and mesalamine should all be important in the clinical considerations of patients with NSAID hypersensitivity that requires mesalamine therapy.

However, a clinician must also weigh the risk of anaphylaxis and even patient preference regarding the appropriate therapy interventions. Given the severity of her reaction to aspirin (laryngeal angioedema), the patient's anxiety, and the need to pursue alternative medical treatment for UC, we decided that the patient would undergo desensitization to oral mesalamine as an inpatient in the medical intensive care unit. Aspirin and mesalamine challenge was not pursued secondary to the severity of her aspirin reaction.

The patient was admitted to the medical intensive care unit and started on a 3-day mesalamine desensitization protocol (Table 1). The dosing for the desensitization protocol was taken from the study by Paraskevopoulos et al.⁵ Unlike other desensitization

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Table 1
Three-Day Desensitization Protocol in Ulcerative Colitis⁵

Day and Time	Dose, mg	Formulation
Day 1		
1100	Placebo	
1120	1	Solution
1140	2	Solution
1200	4	Solution
1220	8	Solution
1240	15	Solution
1300	30	Solution
1320	60	Solution
1410	100	Solution
1540	150	Solution
1710	200	Solution
Total	570	
Day 2		
0910	Placebo	
0930	200	Solution
1030	300	Solution
1200	500	Capsule
Total	1,000	
Day 3		
0600	Placebo	
0620	500	Capsule
0640	500	Capsule
1000	1,000	Capsule
1600	1,000	Capsule
Total	3,000	

protocols that have been reported for this medication, liquid and capsule formulations of mesalamine were used. After each dose, we measured arterial pressure and the peak expiratory flow rate. All signs and measurements were found to be normal. She reported pain behind her right eye and drowsiness after receiving the placebo dose on day 2. She also had nausea and 1 episode of emesis after the first mesalamine dose on day 2. She was monitored overnight after the desensitization was complete and reported mild pruritus on postdesensitization day 1. Otherwise, she tolerated desensitization well with no ill effects. She was discharged from the hospital with oral and rectal mesalamine for treatment of UC.

We describe a patient with multiple reported severe reactions to aspirin and other NSAIDs who received oral desensitization to mesalamine in a single-blind, placebo-controlled procedure with minimal adverse effects. Because of the high risk of a reaction with the patient's reported history of angioedema requiring intubation, confirmation with oral challenge with aspirin and NSAIDs was not attempted, which is a limitation of our report. To our knowledge, this is the first desensitization protocol for mesalamine to use liquid and capsule formulations, allowing for easy titration of the mesalamine dose. Ultimately, on discharge, she was taking rectal

and oral mesalamine, tolerating both formulations well. This case suggests that reactions to multiple NSAIDs do not preclude use of mesalamine for patients who require this treatment in the correct setting, which is consistent with the current experience and literature.^{6–8} Careful consideration for and trials of alternative therapies should be attempted; then, in the absence of improvement, one could consider test dose or desensitization to mesalamine.

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