Mesalamine-induced Pneumonitis and Serum Sickness–like Reaction

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Sulfasalazine and 5-aminosalicylic acid (5-ASA) analogues are used as mainstays for treatment of Crohn's disease (CD) and mild or moderately active ulcerative colitis (UC) and to maintain remission in these disease entities.[1] Although these drugs are effective in treating CD and UC,[2,3] sulfasalazine has been associated with complications, including pancreatitis, hepatitis, skin abnormalities, and hematologic consequences.[4] In fact, up to 30% of patients taking 4 g of sulfasalazine daily are intolerant, experiencing side effects such as nausea or myalgias. Sulfasalazine, the archetypal azo-bonded 5-ASA drug, is engineered to release free 5-ASA (mesalamine) in the colon, after bacterial azoreductase cleavage of the 5-ASA sulfapyridine diazo bond. Dose escalation is limited by intolerance and hypersensitivity to the sulfapyridine moiety, resulting in bone-marrow suppression, folic-acid deficiency, anemia, pancreatitis, headaches, and gastrointestinal intolerance. Like sulfasalazine, the conjugated 5-ASA preparations with azo-bonds release active 5-ASA in the colon. Unlike sulfasalazine, dose escalation is allowed because there is no sulfapyridine-associated toxicity. Oral mesalamine preparations—unconjugated, free 5-ASA—have been formulated as either delayed-release preparations (Asacol, Procter & Gamble) with a resin (Eudragit) coating that is degraded at pH 6 or 7 (the approximate pH of the ileum and proximal colon) or as sustained-release preparations (Pentasa, Shire) that are encapsulated in ethyl cellulose microgranules and released in solution throughout the entire small bowel and proximal colon.[5] The novel 5-ASA 1.2 g delayed- and sustained-release MMX mesalamine formulation (Lialda, Shire) has recently been studied and found to be well tolerated.[6,7] Topicalized mesalamine (Canasa suppositories, Axcan; Rowasa enemas, Alaven) deliver 5-ASA directly to the distal rectum and sigmoid colon.

Although the preparations of newer oral mesalamine products allow for dose escalation, these medications are still associated with intolerance and problematic allergic reactions. Reports in the literature have cited side effects, including nephritis,[8] pancreatitis,[9] pericarditis,[10] and even Kawasaki-like syndrome.[11] Several case reports have also been published regarding pulmonary complications in response to mesalamine.[12-14] We present our experience with a case of pneumonitis and a serum sickness–like reaction to sustained-release mesalamine.

Case Report

A 31-year-old woman diagnosed with irritable bowel syndrome at 12 years of age but in relatively good health until the age of 23 presented with cramping abdominal pain, constipation, and bloody diarrhea. Colonoscopy revealed moderate-to-severe chronic active colitis of the cecum and mild chronic active colitis in the ascending colon. The terminal ileum was deemed to be normal. The patient was started on delayed-release mesalamine at this time but experienced worsening bowel habits. She was switched to sustained-release mesalamine but continued to worsen. During this time interval, the patient denied coughing or having a fever, chest pain, or shortness of breath. Small-bowel series and colonoscopy performed in the following months reportedly tested negative. The patient discontinued sustained-release mesalamine due to her worsening abdominal pain and diarrhea and was started on colestipol (Colestid, Pharmacia and Upjohn), to which she ultimately responded.

The patient presented again 8 years later on no medication with cramping abdominal pain, constipation, and bouts of bloody, loose bowel movements. Work-up included stool studies that were negative and computed tomography (CT) scan of the abdomen and pelvis that

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was significant for a slightly thick-walled 7–8 cm segment of the terminal ileum, which was suspicious for ileitis. A subsequent small-bowel series showed the distal 12–13 cm of the terminal ileum to have ulcerations, erosions, and irritability consistent with CD. Esophagogastroduodenoscopy (EGD) and colonoscopy were subsequently ordered. EGD revealed mild antral gastritis (*Helicobacter pylori*-negative) and a small hiatal hernia. Colonoscopy was significant for mild inflammation with atrophic and friable mucosa in the cecum; however, biopsies of the cecum, colon, and rectum were normal. Biopsies of the ileum showed superficial active inflammation and architectural distortion without granulomas. Given these findings and the patient's continuing complaints, a diagnosis of CD was made and the patient was again started on sustained-release mesalamine 4 g daily.

Almost immediately after starting the medication, the patient began to worsen and continued complaints of abdominal pain and diarrhea. Five days later, she presented to the emergency room with fevers up to 105° F, myalgias, and arthralgias. She also complained of an "exploding" headache, a stiff neck, pain radiating to her shoulders, and intermittent pleuritic chest pain along with shortness of breath. She denied having a cough, hemoptysis, rash, drug use, or recent travel.

Upon presentation to the emergency room, her physical examination was remarkable for fever up to 102.2° F, tachycardia, absence of meningeal signs, clear lungs, soft abdomen, guaiac-negative brown stool, and no rash, clubbing, cyanosis, or edema of the extremities. Her admission chest radiograph was clear, and initial laboratory examinations were significant for baseline anemia (hemoglobin of 10.6 g/dL) and a white blood cell count of 7,300, with 59% neutrophils and 16% bands. Liver function tests were unremarkable, and lactate dehydrogenase was within normal limits.

During her course, the patient was continuously febrile, to a maximum of 103.9° F, and was persistently tachycardic. Her room air saturation ranged from 94% to 98% but decreased with exercise to 90%. She continued to complain of diffuse abdominal pain, arthralgias, myalgias, and shortness of breath. Blood cultures and urine cultures were negative. Repeat chest radiograph showed bibasilar pleural effusions with questionable superimposed atelectasis/infiltrate. CT scan of the chest was significant for bilateral pleural effusions with bibasilar patchy parenchymal disease. Subsequent CT scan of the abdomen was significant for no intestinal abnormality, inflammatory bowel process, or abscess. Doppler of the lower extremities was negative for deep vein thrombosis, and ultrasound of the abdomen was negative for gallstones. Her electrocardiogram showed no sign of ischemia or pericarditis, and her echocardiogram demonstrated normal ejection fraction, mild mitral regurgitation, and trace pericardial effusion. Her thallium stress test was negative for ischemia.

The patient became more anemic, to a nadir hemoglobin of 8.8 g/dL, and she also became thrombocytopenic, with a platelet count of 102,000 per cubic millimeter. Her erythrocyte sedimentation rate (ESR) peaked at 95 mm/hr. Her fibrinogen, amylase, lipase, renal function, electrolytes, liver function tests, and troponins were all within normal limits, and a rheumatologic work-up during her stay was similarly negative.

Given the patient's fever, myalgias, arthralgias, diffuse abdominal pain, anemia, thrombocytopenia, and pneumonitis, sustained-release mesalamine was discontinued and treatment with intravenous methylprednisolone was started. Improvement began immediately, and the patient was converted to an oral steroid taper. Her abdominal pain, arthralgias, and myalgias resolved, and her shortness of breath abated. Consequently, she was discharged from the hospital.

Upon follow-up after her discharge, the patient was breathing comfortably without chest discomfort. Her anemia had resolved (hemoglobin of 11.3 g/dL), and her platelet count had risen to 431,000 per cubic millimeter. Her ESR had decreased to 39 mm/hr, and repeat chest radiograph demonstrated resolution of the pleural effusions.

Discussion

It is well known that inflammatory bowel disease has a constellation of extraintestinal manifestations, including oral aphthae, rash, and arthralgias[15]; however, lung involvement is rarely recognized as an inherent complication of inflammatory bowel disease. Several studies have attempted to elucidate the incidence of pulmonary involvement as a manifestation of inflammatory bowel disease, though it is difficult to determine when lung involvement in the inflammatory bowel disease patient is due to the disease itself or the consequence of a treatment modality.[16] Although lung injury due to mesalamine use is thought to be a rare occurrence,[17] case reports have been published in the literature showing that it may be more frequent than commonly believed.[18] Mesalamine has been cited in case reports as a precipitant of lung inflammation manifested as interstitial lung disease, alveolitis, eosinophilic pneumonia, or bronchiolitis obliterans with organizing pneumonia.[19] Mesalamine-induced lung disease is usually insidious and characterized by progressive symptoms; pulmonary function tests (PFTs) usually show a restrictive pattern, though a combination of restrictive and obstructive patterns can be seen. Bronchial alveolar lavage may show fibrosing alveolitis or acute interstitial pneumonitis.[20]

Patients who have pulmonary decompensation associated with mesalamine have varied courses and histories with the drug. For example, Muzzi and colleagues[21] noted a case in which a patient was treated with and tolerated mesalamine for 10 years before the patient began to experience shortness of breath with adverse pulmonary function, as evidenced by PFTs. The mesalamine was stopped with the subsequent resolution of the symptoms but was then restarted 1 week later without recurrence of the pulmonary symptoms. Alternately, some case reports include patients who have lung injury upon initial exposure to mesalamine. Varela and colleagues[22] described a case in which a patient had been taking oral 5-ASA (Claversal, SmithKline) for 3 years before having a hypersensitivity reaction to it (which included facial swelling, angioedema, and pruritis). This finding was proven when it occurred during an observed 1:1 blinded trial and the patient was successfully desensitized to oral 5-ASA. Other oral desensitizations have been noted as well.[23]

Whether or not mesalamine-induced lung injury is dose-related has also been questioned. However, a review of case reports in the literature showed that the dosage of mesalamine ranges from 750 mg daily to 4 grams daily and adverse findings have not been deemed to be dose-responsive, which suggests an idiosyncratic reaction.[24]

Our patient had an initial adverse reaction to mesalamine 8 years prior to her second presentation with significant side effects of worsening abdominal symptoms, causing her to stop the medicine after several months. Initially, she exhibited signs of mesalamine intolerance, an indication that she should not have been rechallenged with any 5-ASA product, conjugated or unconjugated. Upon rechallenge, she developed a classic severe allergic reaction with high fever and then respiratory compromise.

In reassessing the patient, the symptoms of myalgias, arthralgias, high-spiking fevers, pleuritic chest pain, and shortness of breath were related to a serum sickness–like disease in response to the sustained-release mesalamine. Although the patient did not have a rash or peripheral eosinophilia, she did exhibit new thrombocytopenia and anemia while in the hospital. Her symptoms were classic for allergy to mesalamine and may have resolved with immediate discontinuation of the drug. However, the mesalamine was initially continued in the hospital, and the symptoms did not resolve until the medication was discontinued and steroids were administered. In this case, a careful history reveals the correct diagnosis of mesalamine pneumonitis. Immunoglobulins, lung biopsy, and PFTs were not useful in establishing the diagnosis. Prompt early withdrawal of sustained-release mesalamine would have most likely reversed the hypersensitivity reaction immediately; instead, delayed withdrawal required treatment with steroids.

Although mesalamine is a safe drug that is effective in treating inflammatory bowel disease, it is important to recognize early signs of allergic reactions: high fevers, worsening diarrhea, myalgias, and, in select patients, nephritis, pneumonitis, and pericarditis. It is additionally important to understand that prompt withdrawal of the mesalamine preparation (in this case, sustained-release mesalamine) is critical and that rechallenge with a 5-ASA derivative in such patients is contraindicated.

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Review

Is Mesalamine Safe?

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The aminosalicylates currently available for treating inflammatory bowel disease share a common ancestry with the development of sulfasalazine by Nana Svartz in the late 1930s and 1940s. This drug was the fortuitous result of the diazo bonding of an antibacterial agent, the sulfa moiety sulfapyridine, and a salicylate, 5-aminosalicylic acid, also known as mesalamine. Although the goal for this drug was treatment of inflammatory arthritis, subsequent clinical observations suggested that it provided particular benefit to patients with both arthritis and colitis.[1] Clinical trials in the 1960s showed clear benefit for treatment of mildly-to-moderately active ulcerative colitis as well as for maintenance of remission in these patients.[2-5] Although widely used for treatment of patients with Crohn's disease, it was less certain that the drug was effective when studied in controlled trials. For years, the relative anti-inflammatory role of the parent molecule as compared to the sulfa moiety or the salicylate was unknown. Enema studies by Khan in the 1970s found that the benefit of sulfasalazine could be reproduced by 5-aminosalicylic acid, but not by sulfapyridine, in treating distal colitis.[6] This led to the conclusion that the active ingredient in sulfasalazine was the 5-aminosalicylic acid and that sulfasalazine is a prodrug: this molecule passes unaffected through the gastrointestinal tract until reaching the colon, where bacterial diazo reductase cleaves the diazo bond, releasing the two moieties. Much of the sulfa is absorbed in the colon and is responsible for many of the adverse effects associated with the parent molecule, whereas the 5-aminosalicylic acid appears to be the active agent and free of most of the adverse effects previously found with sulfasalazine.[7] Many formulations, including delayed-release, sustained-release, and alternative prodrugs, have been developed to deliver the 5-ASA or mesalamine to the distal bowel, with the hope that most adverse effects of sulfasalazine can be avoided. Trials of mesalamine in the treatment of ulcerative colitis have shown efficacy in treating mildly-to-moderately active disease and in maintenance of remission.[8,9] Studies in Crohn's disease have shown less impressive benefit in treating mildly-to-moderately active disease and in maintenance trials.[10]

The mechanism of action of mesalamine preparations is attributed to modulation of the arachidonic acid metabolism with inhibition of the cyclooxygenase and lipoxygenase pathways. Additionally, mesalamine inhibits inflammatory cell functions, natural killer cell activity, plasma cell antibody production, and tumor necrosis factor activity, decreases interleukin-1 production from macrophages, and acts as a free oxygen radical scavenger.[11] Some of these mechanisms, though not all, are shared by sulfasalazine.

Types of adverse effects to sulfasalazine can be divided into those that are dose-related intolerance versus those that are non–dose-related idiosyncratic reactions. Dose-related problems include nausea, vomiting, headaches, malaise, and nonspecific abdominal pain, and may be related to the patient's acetylator status, with regard to the sulfapyridine.[12] Idiosyncratic reactions that are not dose-related are common as well and include hypersensitivity rash, male infertility, agranulocytosis, aplastic anemia, hemolytic anemia, hepatic dysfunction, pulmonary dysfunction, and worsening bowel symptoms. Up to 30% of patients are intolerant to sulfasalazine at doses of 4 g daily, and few patients are able to tolerate more than this daily dose,[13] which is equivalent to 1.6 g daily of mesalamine. Some of these adverse effects can be alleviated by dosage reduction or gradual dose escalation. At least 80% of patients intolerant of sulfasalazine are able to tolerate mesalamine preparations.[14] These sulfa-free preparations have been used in doses of mesalamine up to 4.8 g daily for treatment of gastrointestinal inflammation, usually with excellent tolerance and with a frequency of adverse events no more common than with placebo.[15]

Although mesalamine preparations are generally well tolerated, adverse reactions have been described with their usage.[16] These include worsening colitis; renal toxicity such as interstitial nephritis and nephrotic syndrome; pulmonary toxicity such as interstitial lung disease and fibrosis, bronchiolitis obliterans, pulmonary granulomatosis, and eosinophilic pleural effusion; pericarditis, pancreatitis, hair loss, and Stevens-Johnson syndrome. These reactions appear to be idiosyncratic in onset, though the mechanism remains unclear. It is possible that some of these effects are seen primarily with mesalamine as a result of the larger doses associated with this drug than with sulfasalazine. Generally, these adverse effects will occur in affected patients with any oral or topical preparations of delayed-release mesalamine or prodrug

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preparations, though there are a few reports suggesting a lack of cross-reactivity among various preparations.[17] Another lack of cross-reactivity involves patients sensitive to sulfites, where an adverse effect may develop from the sulfites in enema preparations used to stabilize the chemical solution. Patients with this problem may not tolerate the enema preparation but experience no difficulty with oral preparations or suppositories. In addition, the prodrug olsalazine has uniquely been associated with secretory diarrhea, which has not been associated with balsalazide, another prodrug. This suggests that the diazo bond itself is not the source of adverse effects.

In the well-documented case of ileocolonic Crohn's disease reported by Harris and associates,[18] the patient had experienced an apparent adverse reaction to delayed-release (Asacol, Procter & Gamble) and sustained-release (Pentasa, Shire) mesalamines administered after her initial diagnosis years earlier. This was not identified 8 years later when she presented with recurrent gastrointestinal symptoms and findings consistent with active Crohn's ileocolitis. When re-treated with mesalamine, she developed significant symptoms involving the pulmonary, hematologic, and gastrointestinal systems. Her problems continued to progress in severity until it was recognized that mesalamine may be the underlying problem. The rapid resolution of adverse effects after discontinuing the sustained-release mesalamine strongly suggests that this was a drug-related adverse event.

This patient also experienced significant pulmonary toxicity. Such effects have been described upon onset as early as after a few days to as late as after several years of treatment. Symptoms may be characterized by insidious onset of dyspnea on exertion, dry cough, fever, or pleural effusion. Some cases seem to be dose-related, whereas others behave more like idiosyncratic reactions. As in this patient, cessation of the drug will usually allow rapid resolution of the pulmonary abnormalities.[19-22] The serum sickness symptoms also began and resolved parallel to the pulmonary symptoms, suggesting a common mechanism.

This case illustrates the importance of reviewing the history of possible adverse drug events in patients with inflammatory bowel disease who are being considered for therapy with a mesalamine preparation. A history of poor response or worsening symptoms with prior use of sulfasalazine or any delayed- or sustained-release mesalamine drug, prodrug, or topical preparation should alert the clinician to the possibility of an idiosyncratic reaction. When such a mesalamine adverse effect is suspected, it is reasonable to consider starting therapy with a single tablet or capsule of the mesalamine preparation and observing the response for a day or so before advancing the dosage further. If well tolerated, a slow increase in dosage over several days to the desired level may allow the clinician and patient to identify a tolerable dose. Trying an alternative mesalamine preparation should also be considered. When patients who have tolerated mesalamine therapy for long periods of time develop new symptoms, the possibility of drug-related adverse effects should be considered and the drug may be stopped temporarily to see whether adverse symptoms improve. With these precautions in mind, mesalamine can be used safely with excellent benefit in many patients with inflammatory bowel disease.

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