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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