
Case report

Lack of cross-reactivity between 5-aminosalicylic acid–based drugs: a case report and review of the literature

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Background: 5-Aminosalicylic acid (5-ASA)–containing drugs are the mainstay of therapy in inflammatory bowel disease, but adverse reactions to these medications are relatively common. Because there may be a lack of cross-reactivity among the various 5-ASA formulations, treatment with alternative preparations is sometimes possible even after an apparent allergic reaction to a 5-ASA product.

Objective: To describe a patient with a possible allergy to 2 different 5-ASA drugs who tolerated a third.

Methods: A 27-year-old man with Crohn disease developed a rash while taking mesalamine (Pentasa and Asacol). Treatment with 5-ASA products was discontinued, and 6-mercaptopurine and prednisone were prescribed. He then experienced multiorgan failure secondary to herpes simplex infection, which required discontinuation of the immunosuppressive therapy. After recovery from the acute infection, he underwent successful graded challenge with balsalazide.

Results: The patient continued treatment with balsalazide for 9 months, with good control of his inflammatory bowel disease and no adverse effects.

Conclusions: Adverse reactions to 1 or more 5-ASA medications do not necessarily preclude the use of others in the same class. A treatment algorithm for patients with adverse reactions to 5-ASA is outlined based on the case report and review of the literature.

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INTRODUCTION

Drugs that incorporate the 5-aminosalicylic acid (5-ASA) moiety are commonly used to treat inflammatory bowel disease. In recent years, several different formulations of 5-ASA products have been developed to improve tolerability and facilitate adherence to the regimen. Hypersensitivity to these products has been described, including rash, fever, pneumonitis, interstitial nephritis, and gastrointestinal symptoms. A previous article¹ suggests that the various derivatives of 5-ASA do not necessarily cross-react as antigens and that patients who exhibit allergy to one drug may be safely treated with another. Herein we describe a patient who seemed to display allergic symptoms on treatment with coated 5-ASA (mesalamine [Asacol; Procter & Gamble Pharmaceuticals, Cincinnati, OH, and Pentasa; Shire US Inc, Wayne, PA]) but tolerated 5-ASA linked to an inert carrier with an azo bond

(balsalazide disodium [Colazal; Salix Pharmaceuticals Inc, Morrisville, NC]).

CASE REPORT

A 27-year-old man had poorly controlled Crohn disease for 4 years with no other significant medical or surgical history. Family history was noncontributory. He denied tobacco, alcohol, or illicit drug use. He tolerated aspirin therapy, but he had a rash after penicillin VK exposure as a child. He was initially treated with balsalazide, but he had frequent exacerbations of Crohn disease, thought possibly to be related to nonadherence to the prescribed regimen. Balsalazide therapy was discontinued, and Pentasa was prescribed. After a few weeks of therapy with Pentasa, he developed a generalized, nonpruritic, papular rash without systemic symptoms that resolved after discontinuation of Pentasa therapy. He was then treated with an alternative 5-ASA drug, Asacol. However, a similar generalized, nonpruritic, papular rash associated with lip and pedal swelling occurred on the first day of therapy. The rash and edema resolved after discontinuation of Asacol therapy and use of antihistamines. Subsequently, the use of all 5-ASA preparations was discontinued, and for the next 10 months, therapy consisted of 6-mercaptopurine (50 mg daily) and prednisone (50 mg daily). The patient was then hospitalized with a 7-day history of rash, fever, abdominal pain, anorexia, odynophagia, nausea, and vomiting.

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On examination, he was a cachectic young man who appeared pale and acutely ill. Vital signs were significant for an oral temperature of 103°F and tachycardia. Physical examination revealed dry mucous membranes without oral lesions. There was a crusted, vesicular rash on the neck anteriorly. His abdomen was soft but diffusely tender, with palpable hepatosplenomegaly. The remainder of the physical examination findings were unremarkable.

Laboratory investigations during the hospital stay revealed pancytopenia (white blood cell count, 800 cells/mm³; hemoglobin level, 11 g/dL; platelets, 56,000 cells/mm³). Disseminated intravascular coagulopathy, acute renal failure, and acute hepatitis were confirmed by laboratory testing. Hepatitis A, B, and C serologic findings were negative. Upper gastrointestinal endoscopy showed ulcerated lesions. Herpes simplex viral infection was diagnosed based on positive cultures from skin and esophageal lesions. The skin culture was also positive for *Staphylococcus aureus*. Computed tomography of the abdomen demonstrated colonic wall thickening with hepatosplenomegaly.

Prednisone and 6-mercaptopurine treatments were discontinued, and the patient was given vancomycin hydrochloride and valacyclovir hydrochloride for the disseminated herpetic infection. After 3 weeks, pancytopenia, renal insufficiency, hepatitis, and esophagitis had resolved. However, abdominal pain and diarrhea from the underlying Crohn disease persisted. After considering the patient's difficult history and all available therapeutic options, he underwent a graded challenge with balsalazide consisting of incremental doses beginning with 2.5 mg, followed by 25, 750, and 1,500 mg given at 8 hourly intervals. No adverse effects were noted, and the patient was discharged from the hospital taking balsalazide, 1,500 mg twice daily. He continued to do well with this regimen 9 months later.

DISCUSSION

Sulfasalazine has been the first-line therapy for inflammatory bowel disease for several decades.² However, 20% to 30% of patients treated with sulfasalazine exhibit adverse events, including dose-related adverse effects and allergic or idiosyncratic reactions.^{2,3} Recognition that the benefits of sulfasalazine were due to the 5-ASA moiety, whereas most adverse effects were related to the sulfapyridine component,⁴ resulted

in the development of a variety of alternative 5-ASA medications without sulfapyridine that used different delivery systems⁵ designed to provide similar efficacy with fewer adverse reactions.

Orally administered 5-ASA is rapidly absorbed from the upper gastrointestinal tract⁶; therefore, modifications were made to delay absorption and thus facilitate its transport to the inflamed intestine, where the desired action is to occur. These alterations can be divided into 3 categories (Table 1)⁷:

1. Forming a prodrug of 5-ASA by binding to a carrier (4-aminobenzoyl-L-alanine or 5-ASA) via an azo bond that is cleaved by colonic bacterial reductases. The drugs formed are balsalazide (Colazal) and olsalazine sodium (Dipentum; Pfizer Inc, La Jolla, CA), respectively.

2. Coating 5-ASA with a pH-sensitive acrylic resin that dissolves once the pH is greater than 7, usually in the distal ileum or proximal colon (Asacol).

3. Ethylcellulose encasement coating of 5-ASA that is moisture sensitive and releases 5-ASA on contact with moisture throughout the gastrointestinal tract (Pentasa).

5-Aminosalicylic acid without modification (mesalamine) can also be used directly as a suppository (Canasa; Axcan Pharma Inc, Mont-Saint-Hilaire, Quebec) or an enema (Rowasa; Solvay Pharmaceuticals Inc, Marietta, GA) for rectal inflammation.

Eighty to ninety percent of sulfasalazine-intolerant patients tolerate one of the other forms of 5-ASA without sulfapyridine.^{1,8-10} The other 10% to 20% of patients are reported to have a similar adverse reaction to all 5-ASA products. Most of these residual reactions are medication-related adverse effects, such as gastrointestinal complaints, headache, and malaise, which are unlikely to be allergic.^{1,8-10} Fewer 5-ASA-reactive patients have symptoms that may be construed as allergic. Idiosyncratic reactions are rare.

There are currently no standardized in vivo or in vitro tests for 5-ASA allergy. The history, physical examination findings, and response to drug challenge are the only means to determine whether 5-ASA allergy, as opposed to intolerance, is present. There is variability among individual patients suspected of being allergic to the various formulations of 5-ASA, as illustrated by our patient, who tolerated balsalazide but not Pentasa or Asacol. In a series of 43 patients with sulfasalazine intolerance, 10 had a rash that may have been

Table 1. Formulations of 5-ASA Products Currently Available in the United States

Category	Medication	Site of delivery	Formulation
5-ASA prodrug (azo bond cleaved by colonic bacteria)	Sulfasalazine (Azulfidine)	Colon	Sulfapyridine linked to 5-ASA
	Olsalazine (Dipentum)	Colon	5-ASA dimer
	Balsalazide (Colazal)	Colon	Inert carrier linked to 5-ASA
Coated 5-ASA	Mesalamine (Asacol)	Distal ileum/colon	5-ASA coated with pH-sensitive acrylic resin
Unmodified 5-ASA	Mesalamine (Pentasa)	Stomach to colon	Ethylcellulose-coated 5-ASA
	Mesalamine (Canasa)	Rectum	5-ASA suppository
	Mesalamine (Rowasa)	Rectum to splenic flexure	5-ASA enema

Abbreviation: 5-ASA, 5-aminosalicylic acid.

Table 2. Types of Reactions to 5-ASA Drugs and Proposed Management

Type of reaction	Signs and symptoms	Suggested management
Adverse effect	Nausea, vomiting, diarrhea, headache, fever	a) Lower dose of medication; if still present, proceed to (b); b) Change to another 5-ASA product
Allergy	Sudden onset of pruritic rash after drug ingestion, urticaria, angioedema, joint swelling, fever	a) Change to another 5-ASA product; if reaction recurs, proceed to (b) if not severe. If life-threatening with no other treatment options, proceed to (d); b) Try another 5-ASA product; if reaction recurs, proceed to (c); c) Graded challenge with a third 5-ASA product; if it fails, proceed to (d); d) Desensitize to sulfasalazine or 5-ASA depending on the clinical indication
Idiosyncratic reaction	Stevens-Johnson syndrome, pneumonitis, blood dyscrasias, pancreatitis, hepatitis, interstitial nephritis, pericarditis, oligospermia	a) Avoid drug; if no other treatment options, proceed to (b); b) Change to another 5-ASA product with close monitoring; c) If reaction occurs, avoid all 5-ASA products

Abbreviation: 5-ASA, 5-aminosalicylic acid.

allergic in origin. Of these patients, 1 had a similar reaction as to Asacol but tolerated balsalazide and olsalazine. The other 9 patients were tolerant of all 3 of the 5-ASA products.¹ Rao et al⁸ used Asacol and olsalazine to challenge 47 sulfasalazine-intolerant patients with ulcerative colitis, 4 of whom initially developed a rash. Three of these 4 patients had a similar rash with sulfasalazine and Asacol, and, subsequently, olsalazine was not administered. Conversely, 1 patient had rash, joint pain, and swelling with olsalazine but tolerated Asacol.

Other studies have suggested that some patients may be allergic to the 5-ASA moiety itself. One patient developed a pruritic rash to sulfasalazine Asacol and Pentasa.¹¹ Another 2 patients had a similar reaction to sulfasalazine and either olsalazine or Asacol.^{11,12} The lack of reproducibility of reactions to varying formulations of 5-ASA suggests that the inciting allergen may be the modified drug and more rarely the 5-ASA moiety or breakdown products thereof. The occurrence of adverse reactions may also be related to individual differences in metabolism and absorption. In a study comparing Asacol and balsalazide, Sandborn et al¹³ demonstrated that mean absorption in healthy individuals was similar between the drugs, but some patients showed as much as a several-fold difference in how they absorbed the 2 products. When equivalent doses of olsalazine, Asacol, and Pentasa were administered to patients with ulcerative colitis, serum concentrations of 5-ASA in olsalazine and Pentasa were 2 $\mu\text{mol/L}$ compared with 6 $\mu\text{mol/L}$ in Asacol.¹⁴ The urinary excretion of 5-ASA was significantly lower with olsalazine compared with Asacol and Pentasa.¹⁴

Idiosyncratic reactions to sulfasalazine and 5-ASA drugs resolve after discontinued use of the medication (Table 2). Although these reactions are usually drug specific, there are rare reports of recurrence after changing from sulfasalazine to

another 5-ASA drug.^{9,15–19} For patients with rash and fever associated with sulfasalazine therapy, several oral desensitization protocols have proved successful.^{20–23} Furthermore, successful desensitization to other 5-ASA products has been reported using protocols ranging from 3 to 32 days that used either oral or rectal administration of the same drug to which the patient previously reacted.^{12,24–26}

CONCLUSION

Adverse reactions to 5-ASA-containing medications, particularly those also containing sulfapyridine, are not uncommon and may lead to abandonment of the drug class. We suggest the following treatment algorithm in patients who develop adverse reactions to a 5-ASA-containing drug. Based on the history, physical examination findings, and laboratory testing, determine whether the reaction is most likely an adverse effect or an allergic or idiosyncratic reaction (Table 2). An adverse effect may respond to lowering the dose of the medication. If this fails, or if the patient has what seems to be an allergic reaction, change to another 5-ASA product. Many patients can be successfully challenged with an alternative drug, but there are insufficient data to quantitate the risk of a life-threatening reaction with that course. A graded administration protocol can be considered. It seems prudent to suggest that the initial dose of an alternative product be given in an office setting where diphenhydramine and epinephrine are available. If the patient does not tolerate any 5-ASA drug, proceed with oral desensitization to sulfasalazine or 5-ASA, depending on the clinical indication. However, if the sulfasalazine reaction was idiosyncratic, one may consider a change to another 5-ASA agent. Desensitization is not advocated for patients in this category.

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