Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease

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INTRODUCTION

Salicylazosulfapyridine (sulfasalazine) was originally proposed as a treatment for rheumatoid arthritis. It was subsequently discovered that sulfasalazine was also efficacious in treating inflammatory bowel disease, particularly ulcerative colitis. The 5-aminosalicylic acid (5-ASA) medications were developed because many patients were intolerant of or allergic to sulfasalazine.

This topic will review the pharmacology of sulfasalazine and 5-ASAs, mechanism of action in inflammatory bowel disease, and side effects. The role of sulfasalazine and 5-ASAs in the treatment of inflammatory bowel disease and rheumatoid arthritis are discussed in detail separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults" and "Medical management of low-risk adult patients with mild to moderate ulcerative colitis" and "Management of the hospitalized adult patient with severe ulcerative colitis" and "Sulfasalazine: Pharmacology, administration, and adverse effects in the treatment of rheumatoid arthritis".)

PHARMACOLOGY

Sulfasalazine is a prodrug composed of 5-aminosalicylic acid (5-ASA) linked to sulfapyridine through an azo bond (figure 1). Sulfasalazine is partially absorbed in the jejunum after oral

ingestion. The remainder passes into the colon, where it is reduced by coliform bacterial enzyme, azoreductase, to sulfapyridine and 5-ASA [1].

The majority of absorbed sulfasalazine is excreted into bile; only a small fraction is excreted in the urine. 5-ASA is poorly absorbed from the colon and is largely excreted in the stool. Sulfapyridine is rapidly absorbed from the colon, metabolized by the liver, and excreted in the urine with only small amounts remaining in the stool.

5-ASA is primarily responsible for the efficacy of sulfasalazine, while sulfapyridine accounts for many of its side effects. Unconjugated 5-ASA (mesalamine) does not have the side effects associated with sulfapyridine, but is rapidly absorbed in the jejunum, allowing only 20 percent to reach the terminal ileum and colon. Therefore, a number of 5-ASA compounds have been developed to prevent absorption of 5-ASA in the proximal gastrointestinal tract, and thereby increase delivery to the colon (table 1).

5-ASA formulations — Oral 5-ASA formulations differ in their mode of delivery of the active drug to the colon (table 1) [2]. The systemic absorption and efficacy are comparable to sulfasalazine, and 5-ASAs are better tolerated [3,4]. There does not appear to be any difference in efficacy or safety between the various formulations of oral 5-ASAs [5]. Therefore, the choice of oral 5-ASA for treatment of inflammatory bowel disease should be based on the indication (eg, induction or maintenance of remission in ulcerative colitis), disease location, patient preference, ability to comply with the prescribed dosing regimen, cost, and availability of the drug. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Left-sided or extensive colitis'.)

The following oral 5-ASA formulations have been developed:

- Dimerization of 5-ASA has been used to develop prodrug formulations olsalazine and balsalazide. Olsalazine consists of two 5-ASAs joined together with an azo bond, while balsalazide consists of one 5-ASA linked to an inert unabsorbed carrier molecule. As colonic bacteria are required to cleave the azo bond and release the 5-ASA moiety, these formulations are active only in the colon. Olsalazine is administered orally twice daily. Balsalazide is available in two formulations, which are administered orally usually two to three times a day.

- Delayed- and controlled-release mesalamine formulations consist of single 5-ASA molecules enclosed within an enteric coat or a semipermeable membrane that resists gastric breakdown.

In delayed-release formulations, the release of 5-ASA is pH-dependent. The acrylic-base resin dissolves at a pH ≥7, delivering 10 to 15 percent of 5-ASA to the terminal ileum and remainder in the colon. In controlled-release formulations, the release of 5-ASA is time-dependent and independent of pH. The ethylcellulose coating serves as a semipermeable membrane that releases 30 to 40 percent of 5-ASA in the duodenum and continues release throughout the small intestine and colon. Delayed-release mesalamine can be administered orally one to three times daily and controlled-release mesalamine is typically administered orally four times daily. However, studies suggest that some formulations can be taken once daily [5-8].

- Extended-release forms of mesalamine contain mesalamine granules encased in microcrystalline cellulose that delivers mesalamine to the colon via a proprietary extended-release mechanism. The outer coating dissolves at a pH ≥6 in the distal ileum. Upon release, the granules swell to delay transit through the colon and provide gradual, extended release of 5-ASA throughout the colon, allowing for once daily dosing.

- Mesalamine pellets consist of 5-ASA microgranules with acrylic resin or ethylcellulose. Pellets pass unaltered to the distal small bowel, where they begin to release 5-ASA at pH >6.0 and then continue to release 5-ASA throughout the colon. Mesalamine micropellets are administered orally once to four times daily and have the advantage that they can be sprinkled on food.

- The Multi-Matrix System (MMX) mesalamine formulation consists of a pH-dependent coating to delay drug release until the terminal ileum and lipophilic and hydrophilic matrix. The outer coating dissolves at pH 7 in the distal ileum, exposing the matrix. The matrix expands when exposed to luminal fluid to form a gel that gradually releases 5-ASA in the ileum and colon. MMX-mesalamine has a comparable efficacy and safety profile to other 5-ASA formulations, and has the advantage of once daily dosing and possibly improved compliance [9-13].

A number of topical formulations of 5-ASA are also available and are discussed in detail separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)

MECHANISM OF ACTION

Although the precise mechanism responsible for the clinical efficacy of 5-aminosalicylic acid (5-ASA) compounds is not known, they are thought to act topically. In vitro investigations have

identified many antiinflammatory and immunosuppressive properties of 5-ASA, suggesting a multifactorial basis of therapeutic action. The following mechanisms have been proposed.

Inhibition of cytokine synthesis — Downregulation of peroxisome proliferator activated receptor-gamma (PPAR-gamma) has been shown to be involved in inflammation in patients with inflammatory bowel disease [14,15]. Enhanced mucosal production of proinflammatory cytokines has also been correlated with active inflammatory bowel disease [16]. 5-ASA medications may exert their anti-inflammatory effect by inducing PPAR-gamma gene expression and that of its target genes and suppressing the activation of cytokine NFκB and toll-like receptors (TLRs) [17]. 5-ASAs, and to some extent sulfasalazine, also inhibit the biologic functions of the proinflammatory cytokines interleukin 1 (IL-1), tumor necrosis factor alpha (TNFa), IL-2, IL-8, and NF kB [18-20]. (See "Toll-like receptors: Roles in disease and therapy".)

Inhibition of prostaglandin and leukotriene synthesis — Sulfasalazine and 5-ASA inhibit cyclooxygenase and lipoxygenase enzymes in arachidonic acid metabolism, thereby preventing formation of proinflammatory prostaglandins and leukotrienes (eg, LTB4) [21-25]. Support for this proposed mechanism of action in inflammatory bowel disease was derived from preliminary trials with lipoxygenase inhibitors [26,27]. Although subsequent randomized trials have not demonstrated a clinical benefit in patients with inflammatory bowel disease, it is unclear if this lack of efficacy was due to incomplete enzyme inhibition [28].

Free radical scavenging — Reactive metabolites of oxygen and nitrogen mediate tissue injury via oxidation of cellular proteins. 5-ASA is a potent free radical scavenger and antioxidant at the concentrations achieved within the intestinal mucosa [29-31]. The enhanced production of oxidized 5-ASA metabolites in the mucosa and stool of patients treated with sulfasalazine lends support to free radical scavenging activity as a mechanism of action [30].

5-ASA may also exhibit antioxidant activity by another mechanism. In one study, for example, it augmented the thermal induction of intestinal epithelial heat shock protein (hsp72) expression, an effect that was accompanied by increased cellular protection against oxidant injury [32].

Immunosuppressive activity — Sulfasalazine and 5-ASA possess immunosuppressive activity. They block lymphocyte DNA synthesis and cell cycle progression in vitro, thereby preventing clonal expansion of potential pathogenic T-cell and B-cell populations [33,34]. In addition, 5-ASA prevents the accumulation of the early T-cell activation gene for IL-2 [33]. Thus, 5-ASA inhibits both T-cell proliferation and subsequent activation and differentiation.

Impairment of white cell adhesion and function — Polymorphonuclear leukocyte and macrophage functions, including chemotaxis, phagocytosis, and adhesion, which are crucial to acute inflammatory processes, are also markedly inhibited by sulfasalazine and 5-ASA in vitro

[35-37]. The reduction in leukocyte adhesion appears to be mediated via inhibition of the enzyme amino-imidazolecarboxamidoribonucleotide (AICAR) transformylase. This leads to the accumulation of AICAR, which results in an increase in adenosine release at inflamed sites [38]. Adenosine reduces local inflammation by inhibiting leukocyte adhesion to endothelial cells.

SIDE EFFECTS

Side effects can occur with both sulfasalazine and 5-ASA (table 2), but are more common with sulfasalazine.

Sulfasalazine — Approximately 20 to 25 percent of patients discontinue sulfasalazine due to side effects [39]. The side effects associated with sulfasalazine are either idiosyncratic (eg, hypersensitivity or immune-related) or dose-related [40]:

- Idiosyncratic effects include skin rash that may be severe (eg, exfoliative dermatitis), hepatitis, pancreatitis, pneumonitis, agranulocytosis, and aplastic anemia [41]. When such reactions occur, the drug should be immediately stopped, and the patient should not be rechallenged with sulfasalazine.

- Dose-related side effects include gastrointestinal, central nervous system, and mild hematologic toxicities. Symptoms and laboratory findings of such involvement include anorexia, headache, nausea, vomiting, dyspepsia, diarrhea, leukopenia, hemolytic anemia, and a megaloblastic anemia. These side effects may resolve with dose reduction.

The most common side effects of sulfasalazine include nausea, headache, fever, and rash (table 2). Male patients treated with sulfasalazine may experience oligospermia and infertility that are reversible with drug discontinuation [42].

Although most episodes of leukopenia are mild and transient, life-threatening agranulocytosis is a rare side effect of sulfasalazine [43,44]. Agranulocytosis typically occurs within the first three months of therapy and is almost invariably accompanied by fever and rash. Agranulocytosis may be fatal, although bone marrow recovery occurs in the majority of patients within one to two weeks of drug discontinuation. (See "Drug-induced neutropenia and agranulocytosis", section on 'Sulfasalazine'.)

Complete blood count, renal function tests, and liver biochemical tests should be performed at the initiation of therapy. Subsequent monitoring should be performed every one to two weeks during the first month, then monthly for the next three months, and every three months thereafter [42].

Sulfasalazine inhibits transport of reduced folic acid across cell membranes in an in vitro model [45]. This effect could cause intracellular folate deficiency and contribute to the megaloblastic anemia associated with sulfasalazine therapy. Folic acid supplementation at a dose of 1 mg daily should therefore be recommended in all patients on sulfasalazine. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Left-sided or extensive colitis'.)

5-aminosalicylic acid (5-ASA) — The 5-ASA compounds are generally better tolerated than sulfasalazine. Headache, nausea, and abdominal pain are the common side effects with 5-ASA medications (table 2) [46]. Although most patients who are intolerant of sulfasalazine will tolerate 5-ASA, approximately 10 percent of patients will experience similar side effects and are unable to tolerate oral 5-ASAs [47].

Mild watery diarrhea can occur in up to 8 percent of patients on oral 5-ASA preparations. Diarrhea occurs at the initiation of therapy and usually resolves in four to eight weeks due to the ability of the colon to adapt to an elevated fluid load secondary to increased absorption. However, olsalazine and balsalazide can cause persistent watery diarrhea in up to 15 percent of patients by promoting ileal secretion of water and electrolytes. In such cases, olsalazine or balsalazide should be switched to another 5-ASA preparation [48].

Approximately 3 percent of patients on oral 5-ASAs have a paradoxical worsening of their colitis symptoms with diarrhea, bleeding, acute abdominal pain, and in some cases fever, headache, and rash. These patients should be considered allergic to 5-ASAs, and 5-ASAs should no longer be used.

Pancreatitis, pericarditis, skin rash that may be severe (eg, toxic epidermal necrolysis), and pneumonitis have been reported due to hypersensitivity reactions to 5-ASAs. In such cases, the drug should be discontinued and should not be resumed as these side effects are likely to recur [49-52].

Nephrotoxicity is rare in patients on 5-ASA medications with a mean incidence of 0.3 percent per person-year [53]. In most cases, renal failure is caused by an acute or chronic interstitial nephritis, which is idiosyncratic and unrelated to the 5-ASA formulation and dose [54]. Renal function should be monitored, though there is no consensus on how frequently this needs to occur. We recommend serum blood urea nitrogen and creatinine be measured at six weeks, six months, and 12 months after initiation of 5-ASA therapy and then annually [53]. These drugs should be used cautiously in patients with underlying renal insufficiency with careful monitoring of renal function [55]. (See "Medical management of low-risk adult patients with

mild to moderate ulcerative colitis", section on 'Laboratory monitoring' and "Clinical manifestations and diagnosis of acute interstitial nephritis".) .

SPECIAL POPULATIONS

Pregnancy — Sulfasalazine can be continued safely throughout pregnancy and nursing. Folic acid 2 mg daily is recommended in pregnant women due to the effect of sulfasalazine on folate metabolism. Non-enteric coated 5-aminosalicylic acid (5-ASA) and topical 5-ASAs also appear to be safe in pregnancy (table 1) [56,57]. The use of sulfasalazine and 5-ASAs in pregnancy and nursing is discussed in detail separately. (See "Fertility, pregnancy, and nursing in inflammatory bowel disease".)

Patients with COVID-19 — Issues related to SARS-CoV-2 infection in patients with IBD, including medication adjustments in the setting of COVID-19, are discussed separately. (See "COVID-19: Issues related to gastrointestinal disease in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ulcerative colitis in adults" and "Society guideline links: Crohn disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Ulcerative colitis in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Ulcerative colitis (Beyond the Basics)" and "Patient education: Sulfasalazine and the 5-aminosalicylates (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pharmacology** – Sulfasalazine is a prodrug composed of 5-aminosalicylic acid (5-ASA) linked to sulfapyridine through an azo bond. 5-ASA is primarily responsible for the efficacy of sulfasalazine, while sulfapyridine accounts for many of its side effects. (See 'Pharmacology' above.)
- **5-ASA formulations** – Since orally ingested unconjugated 5-ASA (mesalamine) undergoes rapid absorption in the jejunum, various formulations have been developed to prevent proximal absorption of 5-ASA and increase bioavailability in the distal small bowel and colon (table 1). (See '5-ASA formulations' above.)

  5-ASA preparations are as effective as sulfasalazine in the treatment of inflammatory bowel disease and are better tolerated. Therefore, initial treatment choice should be based on the indication (eg, induction or maintenance of remission in ulcerative colitis), disease location, patient preference, ability to comply with the prescribed dosing regimen, cost, and availability of the drug.
- **Mechanism of action** – 5-ASAs have antiinflammatory properties and are thought to act topically. Several different mechanisms of action have been proposed, including inhibition of cytokine, prostaglandin, and leukotriene synthesis, free radical scavenging, immunosuppressive activity, and impairment of white cell adhesion and function. (See 'Mechanism of action' above.)
- **Adverse effects** – The 5-ASA compounds are generally better tolerated than sulfasalazine. Common side effects of sulfasalazine and 5-ASAs include nausea and headache. Sulfasalazine has been associated with reversible male infertility and, rarely, agranulocytosis. Transient mild watery diarrhea can occur in patients on all oral 5-ASA preparations. However, olsalazine and balsalazide can cause persistent watery diarrhea. Approximately 3 percent of patients on oral 5-ASA have a paradoxical worsening of their colitis symptoms with diarrhea, bleeding, and acute abdominal pain (table 2). These patients should be considered allergic to 5-ASAs, and 5-ASAs should no longer be used. (See 'Side effects' above.)

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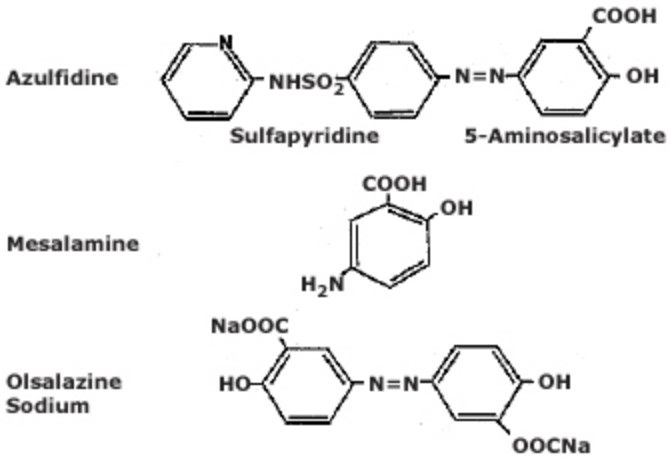
GRAPHICS

Structures of sulfasalazine, mesalamine, and olsalazine



Sulfasalazine is a composite molecule composed of 5-ASA linked by an azo bond to sulfapyridine. Mesalamine is the 5-ASA moiety alone, while olsalazine consists of two 5-ASA molecules joined by an azo bond.

5-ASA: 5-aminosalicylic acid.

Graphic 76617 Version 2.0

Sulfasalazine and 5-aminosalicylic acid (5-ASA) formulations

Medication	Trade name (US or as noted)	Strength of commonly available oral preparations (mg)
Oral 5-aminosalycylic acid (5-ASA) derivatives		
Sulfasalazine		
Non enteric-coated tablet (scored)	Azulfidine, Sulfazine, Salazopyrin*	500
Suspension	Salazopyrin*	250 per 5 mL*
Enteric-coated tablet (not scored)	Azulfidine EC, Sulfazine EC, Salazopyrin EN-tabs*	500
Mesalamine[¶]		
Delayed release enteric-coated tablet	Asacol[Δ ◇], Asacol HD[◇]	400[Δ], 800
Capsule containing delayed release tablet	Delzicol	400
Delayed and extended release tablet, multimatrix	Lialda, Mezavant*	1200
Capsule containing delayed release enteric-coated granules	Apriso	375
Controlled release capsule	Pentasa[§]	250, 500, 1000*
Enteric-coated delayed release granules (packet, sachet)	Salofalk*, Pentasa Sachet*	500, 1000, 1500, 2000 sachet*
Olsalazine capsule	Dipentum	250, 500*
Balsalazide		
Capsule	Colazal, Colazide*	750
Tablet	Giazo[¥]	1100

US: United States.

* Not available in US. Trade names shown are for products commonly available elsewhere (eg, Canada, United Kingdom, and Europe).

¶ Mesalamine is US generic name. Mesalazine is an international generic name.

Δ Asacol 400 mg tablets are no longer marketed in US. Asacol 400 mg delayed-release tablets and generic versions are available widely elsewhere.

§ According to US prescribing information, Pentasa capsules can be swallowed whole or opened and contents sprinkled over spoonful of applesauce or yogurt and swallowed immediately; capsule contents should not be crushed or chewed.

¥ US approval is limited to treatment of ulcerative colitis in male patients; failed to demonstrate efficacy in female patients.

Data courtesy of authors with additional data from: Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012; 380:1606.

Graphic 86818 Version 14.0

Side effects of sulfasalazine and aminosalicylates

	Common (>10%)	Uncommon (1 to 10%)	Rare (<1%)
Sulfasalazine	Nausea/headache Rash Male infertility Headache	Abdominal pain Hemolytic anemia Leukopenia Thrombocytopenia	Hepatitis Pneumonitis Neutropenia Pancreatitis Agranulocytosis Otalgia Severe cutaneous adverse reaction
Aminosalicylates	Watery diarrhea Abdominal pain Headache Nausea	Pancreatitis Colitis exacerbation Fever/rash Rash	Pneumonitis Pericarditis Nephritis Thrombocytopenia Photosensitivity Nephrolithiasis* Severe cutaneous adverse reaction

* Nephrolithiasis has been reported with mesalamine use; it is unknown whether other aminosalicylate formulations (eg, balsalazide, olsalazine) pose a similar risk.

Graphic 64059 Version 4.0

Contributor Disclosures

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Conflict of interest policy

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