Serious Complications of Sulfasalazine

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Whereas minor side effects of sulfasalazine are common, serious adverse reactions to this drug generally are considered rare. However, this report discusses three major complications of sulfasalazine that occurred within the past three years, one resulting in the death of a patient. As more patients with inflammatory bowel disease are being managed by physicians of various disciplines, it is important to become familiar with the potentially dangerous side effects of all medications prescribed. For this reason, a brief review of the pharmacology, clinical use, and toxicity of sulfasalazine is presented. [Key words: Sulfasalazine; Complications]

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SULFASALAZINE has been the most widely used medication for the management of inflammatory bowel disease since its introduction over 40 years ago. Side effects of sulfasalazine occur in about 20 percent of patients.[1] The most common but least severe adverse reactions, such as nausea, vomiting, malaise, headache, and hemolysis, appear to be dose-related. Rarer, more serious side effects have been noted that can involve almost every organ system. These include a spectrum of skin rashes, fever, arthralgias, blood dyscrasias, hepatitis, pneumonitis, and male infertility.[2]

This report discusses three serious complications of sulfasalazine that occurred within the past three years, one of which resulted in the death of a patient.

Report of Cases

Patient 1: A 63-year-old black man was admitted to the colorectal surgery service for evaluation of intermittent diarrhea and rectal bleeding that had been increasing in frequency and severity over the past 20 years. A diagnosis of chronic ulcerative colitis was made on the basis of colonoscopic examination and multiple mucosal biopsies. The patient was started on 2 gm of sulfasalazine daily, and with resolution of the diarrhea and bleeding was discharged. He continued to take the medication uneventfully for the next three weeks at home, and then began to complain of headache, malaise, and a maculopapular skin rash on his face, chest, and abdomen. The dose of sulfasalazine was reduced to 1 gm daily, and the patient was instructed to notify his physician if symptoms did not abate on this regimen. Three days later, he presented to the emergency room with anorexia, nausea, a fever of 102° F, and bullous vesicles distributed diffusely over his entire body. His white blood cell count was 4600, with a differential count that included 62 neutrophils, ten stabs, 13 lymphocytes, eight monocytes, and seven eosinophils. A presumptive diagnosis of erythema multiforme bullosae secondary to sulfasalazine was made, and the patient was started on intravenous fluids, 100 mg of hydrocortisone intravenously every 6 hours, and 25 mg of Benadryl® intramuscularly every 8 hours.

Over the next 48 hours, he began to slough large areas of skin and became hemodynamically unstable. Multiple cultures of blood, urine, sputum, and fluid from the vesicles were obtained, and he was transferred to the intensive care section of the burn unit with a diagnosis of toxic epidermal necrolysis. Soon after admission to the intensive care unit, the patient had a cardiopulmonary arrest during insertion of a Swan-Ganz catheter and could not be resuscitated.

Patient 2: A 56-year-old white woman with a 15-year history of chronic ulcerative colitis presented with an episode of rectal bleeding and diarrhea of two months' duration. She had been treated previously with varying doses of oral or rectal steroids for intermittent episodes of rectal bleeding. Proctosigmoidoscopic examination revealed acute ulcerative colitis up to and beyond the 25-cm level.

The patient had not been treated with sulfasalazine previously and, on questioning, no history of allergy to sulfa medication could be elicited. She was placed on a low dose of sulfasalazine (250 mg bid), which was to be gradually increased to 4 gm/day during the ensuing week.

Four days later, the patient was seen in the emergency room with a severe allergic reaction manifested by a maculopapular pruritic rash typical of the Stevens-Johnson syndrome. Bullous eruptions covered her palms and soles. In addition to the skin lesions, she had oral mucosal eruptions, edema of the tongue, and difficulty swallowing, along with fever and chills. She was admitted to the hospital, sulfasalazine was discontinued, and she was started on intravenous fluids, steroids, epinephrine, and antihistamines. She made a slow, progressive recovery, and was discharged ten days later, when most of the skin and mucosal lesions cleared. She had no further rectal bleeding and has remained in remission.

Patient 3: A 33-year-old black woman was well until July 1983, when she had a cesarean section at the end of a normal pregnancy. She suffered an ileofemoral arterial thrombosis immediately postoperatively that required urgent thrombectomy and ultimately a right below-knee amputation. The source of the occlusion was diligently sought but no specific factor identified. The presumed diagnosis was aortic trauma during cesarean section. She was anticoagulated with Coumadin® and did well for the next six months. In January 1984, she was admitted to the hospital with a one-week history of bright red rectal bleeding. She had diarrhea but no nausea or vomiting. She had experienced no previous gastrointestinal symptoms. The Coumadin® had been stopped in the outpatient clinic, but the bleeding persisted. Her hematocrit was 40 percent on admission, and she had no coagulopathy. Proctosigmoidoscopy demonstrated diffuse inflammation and ulceration, and barium enema showed ulceration and pseudopolyposis of the entire colon. Enteric pathogens were sought but not found, and liver function was normal. She continued to bleed for the first week, her hematocrit dropped to 31 percent and she was intermittently febrile to a maximum of 101° F.

Oral sulfasalazine, 4 gm daily, was started and she had rapid resolu-

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tion of symptoms, with cessation of bleeding and diarrhea over the ensuing four days. Her diet was advanced and well tolerated. One week later, total colonoscopy showed diffuse severe ulcerative colitis with ulceration and pseudopolyposis. The vascular surgery service believed that continued anticoagulation was still necessary; therefore Coumadin® was restarted without further rectal bleeding. She was discharged feeling well three weeks after admission, taking only Coumadin® and sulfasalazine, 4 gm/day.

Two weeks after discharge she was examined in clinic, she was feeling lethargic and had a temperature of 103° F. She was admitted to the hospital immediately. On examination she was obese and in moderate distress with tachypnea and diaphoresis. She had no pain and no recent diarrhea or rectal bleeding. She had mild postural hypotension, a pulse of 130 and a temperature of 105° F. Her head, eyes, ears, nose, and throat showed mild erythema of the mucous membranes and a supple neck. Her lungs were clear, there was a systolic ejection murmur, and no flank tenderness. Examination of the abdomen showed hyperactive bowel sounds but no tenderness, palpable masses, or organomegaly. The remainder of the examination was unchanged from the earlier admission.

Cultures were obtained repeatedly and were consistently negative. Her white blood cell count rose progressively during the admission to a high of 40,000, with a predominance of atypical lymphocytes. An ultrasound examination of the liver was normal, with no evidence of ductal obstruction. Hepatitis antigens and antibodies were negative. Liver function tests showed a progressive rise in the bilirubin to a maximum of 2.4, 1.4 direct, LDH to 2660 IU with fractionation showing liver damage, SGOT to 1062 IU, SGPT to 1223 IU and alkaline pohosphatase to 286 IU. Her hematocrit was stable.

Sulfasalazine was discontinued on admission, and prednisone was started. She had rapid resolution of her lethargy and anorexia, and gradual lysis of her fever. One week after admission she was well. Despite the chemical abnormalities, she was discharged and seen weekly in clinic, taking only prednisone and Coumadin®. Over the next six weeks all blood studies returned to normal and her ulcerative colitis remained asymptomatic. The prednisone was tapered and discontinued over the following six weeks.

In the year and one half since this episode, she has remained generally well, requiring two short courses of prednisone for recurrent rectal bleeding and diarrhea. Repeated colonoscopic examinations continue to show diffuse pseudopolyposis but less ulceration and no dysplasia on biopsies. She is currently taking no medication, and is having one formed stool per day.

Discussion

Although serious adverse reactions to sulfasalazine involving almost every organ system have been reported, they generally are considered rare. However, the occurrence of three major complications in such a short period of time warrants a brief review of the pharmacology, clinical use, and toxicity of sulfasalazine.

Only about 10 to 15 percent of an ingested dose of the drug is absorbed from the small bowel as sulfasalazine. The remainder reaches the colon, where it is split by the action of enteric bacteria into sulfapyridine and 5-aminosalicylic acid. In the colon, most of the sulfapyridine is absorbed and acetylated or otherwise metabolized by the liver, and then excreted in the urine. The demonstration that sulfapyridine is the principal portion of the drug found in the serum suggests that this component of sulfasalazine may be responsible for most of the drug's toxicity. In contrast, about 80 percent of the 5-aminosalicylic acid, which is thought to be the active moiety of the drug, is excreted unchanged in the stool.[3]

The mechanism of action of sulfasalazine is not clear. Possible modes of action include a particular affinity of the drug for colonic connective tissue, and an antibacterial effect on the colonic flora resulting in a reduction of clostridia and *Escherichia coli* in the feces.[2]

In patients with mild to moderate ulcerative colitis, sulfasalazine (2-4 gm/day) has proven useful in controlling symptoms and improving the endoscopic appearance of the colonic mucosa.[4] Furthermore, sulfasalazine has been shown to have an important role in maintaining remissions of ulcerative colitis when lower doses (2 gm/day) have been continued for one year or longer.[5]

Sulfasalazine seems to be effective in patients with Crohn's colitis or ileocolitis, but not in patients with ileitis alone, where steroids generally are considered to be more effective.[6] It is doubtful that prophylactic administration of sulfasalazine in patients with Crohn's disease will prevent recurrences.

Side effects may accompany the clinical use of sulfasalazine. Dose-related toxicity may cause nausea, vomiting, headache, fever, a bluish discoloration of the skin, and arthralgias, whereas sensitivity reactions include urticaria, maculopapular skin rashes, bronchospasm, blood dyscrasias, hepatotoxicity, and peripheral neuropathy.[2] Most of these side effects occur in the first eight to twelve weeks of therapy, and are more likely to occur in patients who acetylate the drug slowly.[1]

Desensitization of patients to sulfasalazine can be accomplished by careful adjustment of the dosage.[1] The drug should be withdrawn if any side effects are noted and, then reintroduced gradually in increasing doses. However, a history of agranulocytosis or frank hemolysis during sulfasalazine therapy is a contraindication to renewing the drug.[3]

As more patients with inflammatory bowel disease are being managed by physicians of various disciplines, it is important to remember that every drug has potentially dangerous side effects. The occurrence of three serious complications of sulfasalazine in such a short time, including one death, reinforces the concept of sulfasalazine as a double-edged sword.

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