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Sulfasalazine

Updated: September 25, 2017.

OVERVIEW

Introduction

Sulfasalazine is an antiinflammatory agent used extensively in chronic, long term therapy of inflammatory bowel disease. Sulfasalazine is structurally composed of a sulfonamide (sulfapyridine) and 5-aminosalacyclic acid (5-ASA) joined by an azo bond. Sulfasalazine is a rare, but well known cause of idiosyncratic liver injury.

Background

Sulfasalazine is a modified sulfonamide composed of sulfapyridine that is covalently linked to 5-aminosalacyclic acid (5-ASA). Sulfasalazine is poorly absorbed, but its azo bond is broken by bacteria in the bowel lumen releasing sulfapyridine that is absorbed and 5-ASA, which reaches high levels and acts locally decreasing inflammation. Sulfasalazine was approved for clinical use in the United States in 1950 and is still commonly used. Current indications are for treatment of active ulcerative colitis and prevention of relapses in disease, both in adults and children. Sulfasalazine is also used for juvenile or adult rheumatoid arthritis. Sulfasalazine is available in generic forms in 500 mg tablets and under the commercial name Azulfidine. Extended release forms are also available. The usual dose in adults is 3 to 4 grams daily initially, with maintenance dosage of 2 grams daily (4 divided doses). Common side effects include anorexia, headache, nausea, gastrointestinal upset, fever, arthralgias and rash.

Hepatotoxicity

Sulfasalazine, like other sulfonamides, causes a characteristic idiosyncratic liver injury that has features of drug-allergy or hypersensitivity. The typical onset is sudden development of fever and rash followed by jaundice within a few days or weeks of starting the medication. Eosinophilia or atypical lymphocytosis are also common. The pattern of injury is typically mixed but can be cholestatic or hepatocellular, and can be complicated and prolonged. Sulfasalazine has been linked to cases of acute liver failure, particularly with hepatocellular patterns of injury. Most cases, however resolve rapidly once the mediation is withdrawn, usually within 2 to 4 weeks unless cholestasis is severe. Because sulfasalazine is given chronically, rare instances of late onset of drug induced liver disease have been reported, but the characteristic signature and pattern of injury is different and the role of other medications and perhaps 5-ASA in these late onset cases has yet to be resolved. Chronic therapy may also be associated with mild and transient ALT elevations either alone or as a part of a generalized hypersensitivity reaction; these elevations can be accompanied by hepatic granulomas.

Mechanism of Injury

The clinical pattern of injury with the sulfasalazine suggests a drug-allergy or hypersensitivity mechanism, perhaps through the metabolism of the sulfonamide component to a toxic, reactive or antigenic metabolite. There may be a higher rate of hepatotoxicity in persons of African extraction.

Outcome and Management

Sulfasalazine induced liver injury can result in minor ALT and alkaline phosphatase elevations (sometimes with other signs of hypersensitivity and with hepatic granulomas), acute self-limited hepatitis and even acute liver failure. Most cases resolve rapidly with discontinuation of drug, and full recovery is expected within 2 to 8 weeks. Severe cholestatic injury may be prolonged, and rare cases of chronic liver injury with vanishing bile duct syndrome have been reported. Hepatic injury is usually a part of a systemic hypersensitivity reaction and may be referred to as DRESS syndrome (drug rash with eosinophilia and systemic symptoms). Sulfasalazine, like other sulfonamides, can also cause Stevens Johnson syndrome that can be accompanied by hepatic injury. Rechallenge should not be done, and patients should be told that they are allergic to sulfonamides ("sulfa-drugs") and not receive other drugs in this class. The other component of sulfasalazine is 5-aminosalicyclic acid (5-ASA) with can also cause idiosyncratic liver injury. Prednisone has been used with variable success, but may be particularly helpful in patients with prominent allergic features with systemic features and fever, severe rash, arthralgias, lymphoadenopathy, facial edema, and eosinophilia or atypical lymphocytosis.

References to the safety and potential hepatotoxicity of sulfasalazine are given in the Overview on Sulfonamides.

Drug Class: Antiinfective Agents, Sulfonamides

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sulfasalazine – Generic, Azulfidine®

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Sulfasalazine	599-79-1	C18-H14-N4-O5-S