U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Sulfadoxine-Pyrimethamine. [Updated 2017 Dec 5].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Sulfadoxine-Pyrimethamine

Updated: December 5, 2017.

OVERVIEW

Introduction

The combination of sulfadoxine and pyrimethamine is used in the treatment and prophylaxis of chloroquine resistant strains of malaria and the treatment of toxoplasmosis. Sulfadoxine-pyrimethamine has been linked with rare cases of idiosyncratic liver injury which resembles the hepatotoxicity associated with sulfonamides.

Background

Pyrimethamine (pir" i meth' a meen) is a diamino-pyrimidine and anti-folate, similar in structure and activity to proguanil, which has potent inibitory activity against malaria parasites as well as Toxoplasma gondii. Pyrimethamine has profound antimalarial synergy with sulfonamides and has been widely used in combination with sulfadoxine (sul" fa dox' een) as prophylaxis and treatment of chloroquine-resistant malaria. In recent years, this combination has been replaced by other approaches, partially because of the frequency of hypersensitivity reactions including hepatotoxicity. However, it is still used for treatment of malaria (particularly in Africa) and for prophylaxis against chloroquine-resistant malaria in patients with contraindications to other agents. This combination is available under the brand name of Fansidar in tablets that combine 25 mg of pyrimethamine with 500 mg of sulfadoxine. Pyrimethamine is also available separately as 25 mg tables in generic forms and under the commerical name Daraprim for use in therapy of toxoplasmosis in combination with a sulfonamide. Pyrimethamine should not be used alone, either for treatment of toxoplasmosis or malaria.

Hepatotoxicity

Sulfadoxine-pyrimethamine can cause clinically apparent, idiosyncratic liver injury with prominet features of drug-allergy or hypersensitivity, as is typical of sulfonamide hepatotoxicity. The typical onset is sudden development of fever and rash followed by jaundice within a few days or weeks of starting the medication. The pattern of injury is typically cholestatic or mixed and can be complicated and prolonged. This combination has also been linked to cases of acute liver failure with marked hepatocellular injury. However, most cases resolve rapidly, usually within 2 to 4 weeks unless cholestasis is severe. Mild ALT elevations without jaundice can accompany hypersensitivity reactions to the sulfonamides and may be accompanied by hepatic granulomas. Reexposure leads to a more rapid onset of injury and should be avoided (as should use of other sulfonamides). It is not clear whether pyrimethamine is capable of causing liver injury on its own, largely because it is used only in combination with a sulfonamide.

Likelihood score: C (probable cause of clinically apparent liver injury).

Mechanism of Injury

The clinical pattern of injury with sulfadoxine suggests a drug-allergy or hypersensitivity mechanism, perhaps through its metabolism to a toxic, reactive or antigenic metabolite.

Outcome and Management

Sulfadoxine-pyrimethamine induced liver injury can result in acute liver failure, but most cases resolve rapidly with discontinuation of drug, and full recovery is expected within 2 to 8 weeks. Cases in which granulomatous hepatitis was identified on liver biopsy have been described, but the clinical course is not distinctive. Liver injury is usually a part of a systemic hypersensitivity reaction, and some cases can be categorized as DRESS syndome (drug rash with eosinophilia and systemic symptoms). 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. 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, lymphadenopathy and eosinophilia or atypical lymphocytosis.

References to sulfadoxine-pyrimethamine induced liver injury are given in the Overview section on Sulfonamides.

Drug Class: Antiinfective Agents, Sulfonamides; Antimalarial Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sulfadoxine-Pyrimethamine – Fansidar®

DRUG CLASS

Antiinfective Agents; Antimalarial Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Pyrimethamine-Sulfadoxine	37338-39-9	C12-H14-N4-O4-S. C12-H13-Cl-N4