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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-. Carbonic Anhydrase Inhibitors. [Updated 2017 Oct 2].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Carbonic Anhydrase Inhibitors

Updated: October 2, 2017.

OVERVIEW

Introduction

Acetazolamide and methazolamide are carbonic anhydrase inhibitors used as diuretics and in the therapy of glaucoma. Both acetazolamide and methazolamide have been linked to rare cases of clinically apparent drug induced liver disease.

Background

Acetazolamide (a seet" a zol' a mide) and methazolamide (meth" a zol' a mide) are inhibitors of carbonic anhydrase, an enzyme that converts carbon dioxide and water to carbonic acid. Inhibition of this enzyme in the kidney causes an alkalization of the urine and diuresis. In the eye, inhibition of carbonic anhydrase causes a decrease in intraocular pressure making these agents valuable in the treatment of glaucoma. The effects of acetazolamide on acid-base status (causing a mild metabolic acidosis) are also of potential value in managing other conditions including epilepsy, sleep apnea, and acute mountain sickness. Acetazolamide was approved for use in the United States in 1986 for treatment of glaucoma and as a diuretic. Acetazolamide is available in 125 and 250 mg tablets in generic forms and under the brand name of Diamox. Acetazolamide is also available in extended release forms (capsules of 500 mg) and as powder for injection. The recommended dose and regimen of acetazolamide varies by indication, but for chronic use in adults the typical dose is 250 to 1,000 mg daily in divided doses. Methazolamide was approved for use in the United States in 1959 for the treatment of glaucoma. Methazolamide is available as tablets of 25 and 50 mg in generic forms and under the trade name Neptazane. Typical doses of methazolamide in adults with glaucoma are 50 to 100 mg two to three times daily. The common side effects of acetazolamide and methazolamide are change in taste, numbness and tingling in fingers and toes, blurred vision, tinnitus, dizziness, decrease in hearing, polyuria, nausea, diarrhea, fatigue, and headache. Methazolamide and acetazolamide have similar chemical structures and are related to the sulfonamides and can cause allergic reactions including anaphylaxis, rash, erythema multiforme, and Stevens Johnson Syndrome.

Hepatotoxicity

Idiosyncratic, clinically apparent liver injury from acetazolamide and methazolamide is rare, but several instances have been reported as isolated case reports. Acetazolamide is a sulfonamide and cross reactivity to sulfonamide reactions have been reported. The liver injury typically arises after a few days to weeks of therapy and the pattern of serum enzyme elevations is usually hepatocellular or mixed. Immunoallergic features (rash, fever, eosinophilia) are common, but autoantibody formation is not. Both acetazolamide and methazolamide have been linked to Stevens Johnson Syndrome and a genetic association has been made with HLA-B*5901. Hepatic involvement and jaundice can occur in some cases of Stevens Johnson Syndrome.

Likehood score: D (possible but rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of acetazolamide hepatic injury is believed to be due to hypersensitivity with shared pathogenesis with the sulfonamides.

Outcome and Management

Severity ranges from mild, asymptomatic elevations in serum enzymes, to clinically apparent acute hepatitis to severe injury with acute liver failure or prolonged jaundice. Corticosteroids are often used in patients with other features of hypersensitivity, but their role in altering the ultimate outcome of the injury is unproven. Rechallenge should be avoided and patients should be warned to avoid sulfa-containing drugs in the future.

References to the safety and potential hepatotoxicity of the carbonic anhydrase inhibitors are provided in the overview section on diuretics.

Drug Class: Diuretics

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Acetazolamide – Generic, Diamox®

Methazolamide – Generic, Neptazane®

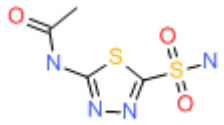
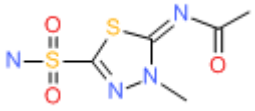
DRUG CLASS

Diuretics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Acetazolamide	59-66-5	C4-H6-N4-O3-S2	
Methazolamide	554-57-4	C5-H8-N4-O3-S2	

Both acetazolamide and methazolamide have a sulfonamide like structure which may account for the similarity of the hypersensitivity reactions that occur with both.