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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-. Amiloride. [Updated 2017 Oct 5].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Amiloride

Updated: October 5, 2017.

OVERVIEW

Introduction

Amiloride is a potassium-sparing diuretic used in the therapy of edema often in combination with thiazide diuretics. Amiloride has been linked to rare cases of clinically apparent drug induced liver disease.

Background

Amiloride (a mil' oh ride) is a pyrazinoylguanidine derivative that acts on the sodium channels of renal epithelial cells causing an increase in sodium excretion with little or no effect on potassium excretion, thus accounting for its potassium-sparing characteristics. Amiloride is similar in action to triamterene, but differs in chemical structure. Amiloride was approved for use in the United States in 1986, but is not widely used. Amiloride is available in 5 mg tablets in generic forms and under the brand name of Midamor. The typical dose of amiloride is 5 to 20 mg in one or two doses daily. Amiloride causes only a modest diuresis and it is often used in combination with a thiazide diuretic (such as hydrochlorothiazide: Moduretic), which takes advantage of it potassium-sparing characteristics to offset the potassium-wasting characteristics of the thiazides. The major side effects of amiloride include hyperkalemia, headache, dizziness, gastrointestinal upset and rash.

Hepatotoxicity

Amiloride therapy has not been associated with serum aminotransferase elevations. Idiosyncratic, clinically apparent liver injury from amiloride is rare, but several instances have been reported as isolated case reports in which the combination of amiloride with hydrochlorothiazide was used (Case 1). The numbers of cases have been too few to characterize the clinical features, but the latency to onset was ranged from 2 to 12 months and the pattern of injury either hepatocellular or mixed. Immunoallergic features and autoantibodies have not been associated with the liver injury from amiloride.

Likelihood score: D (possible rare cause of liver injury).

Mechanism of Injury

The mechanism of amiloride hepatic injury is unknown, but is likely due to metabolic idiosyncrasy.

Outcome and Management

The rare instances of clinically apparent liver injury due to amiloride/hydrochlorothiazide combinations have been associated with jaundice and at least one case resulted in cirrhosis and ultimately death from liver disease.

There is unlikely to be cross reactivity to the liver injury with other potassium-sparing diuretics, which have quite different chemical structures.

References to the safety and potential hepatotoxicity of amiloride are provided in the overview section on Diuretics (updated October 2017).

Drug Class: Diuretics, Potassium-Sparing Diuretics

Other Drugs in the Subclass: Eplerenone, Spironolactone, Triamterene

CASE REPORT

Case 1. Amiloride/hydrochlorothiazide induced acute liver injury.

[Modified from: Valhovd M, Kildahl-Andersen O. [Drug-induced severe jaundice]. Tidsskr Nor Laegeforen 2003; 123: 1202-3. Norwegian. PubMed Citation]

A 37 year old man with hypertension developed jaundice and hepatitis 2 months after starting the combination of amiloride (2.5 mg) and hydrochlorothiazide (25 mg). On examination, he was jaundiced and had mild fever (37.6^{o} C), but no rash or organomegaly. Laboratory testing showed serum bilirubin of 5.8 mg/dL with marked elevations in serum aminotransferase levels (Table). White blood cell counts, eosinophil counts, prothrombin time, and serum albumin were normal. Tests for hepatitis B and for autoantibodies were negative. Magnetic resonance imaging of the liver and biliary system were normal. The diuretics were stopped, but liver tests worsened for the next three weeks, serum bilirubin rising to as high as 28.3 mg/dL. A liver biopsy showed an intrahepatic cholestasis typical of drug induced hepatic injury with some degree of bile duct injury. Prednisolone (60 mg daily) was initiated, and he improved slowly. Four months later and 6 weeks after stopping prednisolone therapy, he was asymptomatic, but serum enzyme levels were still mildly elevated. A note in follow up mentioned that he developed pancytopenia and was retreated with corticosteroids, but that serum bilirubin and aminotransferase levels were normal.

Key Points

Medication:	Amiloride (2.5 mg) and hydrochlorothiazide (25 mg daily)
Pattern:	Hepatocellular (R=32.5)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 months
Recovery:	Incomplete at 4 months
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin* (mg/dL)	Other
8 weeks	0	2930	494	11.1	Diuretics stopped
9 weeks	1 week	1466	351	18.5	Liver biopsy
11 weeks	3 weeks	697	309	28.3	Prednisolone started
5 months	3 months	29	176	1.5	Prednisolone stopped
6 months	4 months	196	225	1.5	
Normal Values		**<50**	**<275**	**<1.2**	

* Converted from µmol/L to mg/dL.

Comment

This patient developed an acute hepatitis-like illness followed by deep jaundice 2 months after starting a combination of amiloride and a thiazide diuretic for hypertension. The course was complicated by the development of pancytopenia during recovery. It is not clear whether the amiloride or the hydrochlorothiazide was responsible for the hepatic injury (and the bone marrow failure). Certainly, other cases of thiazide diuretic induced liver injury have been quite different with a shorter latency and more benign course. No other similar cases of liver injury implicating amiloride have been reported.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Amiloride – Generic, Midamor®

DRUG CLASS

Diuretics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Amiloride	2609-46-3	C6-H8-Cl-N7-O