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Thiazide Diuretics

Updated: October 2, 2017.

OVERVIEW

Introduction

The thiazides are the most commonly used oral diuretics and are widely used in the therapy of hypertension and congestive heart failure, as well as the treatment of edema due to local, renal and hepatic causes. Only rare instances of clinically apparent liver injury have been linked to use of thiazide diuretics.

Background

The benzothiazide diuretics are structurally related drugs that act by inhibition of sodium (and chloride) transport in the distal convoluted tubule by binding to and inhibiting the Na+-Cl- symporter. As a result, there is increased excretion of sodium and water and an associated loss of potassium. Chronic therapy may also result in increase calcium and magnesium loss. The thiazide diuretics are grouped together based upon shared chemical, sulfonamide-like, structure. More recently non-benzothiazide drugs with a similar mechanism of action have been developed (metolazone, indapamide), which are referred to as thiazide-like diuretics. The thiazide and thiazide-like diuretics are all available generically and differ largely in their pharmacokinetic properties of oral availability, relative potency, serum and effective half-life and route of elimination. The general indications for the thiazide diuretics are treatment of hypertension and edema.

Thiazide diuretics are available in multiple forms and all are available generically. Bendroflumethiazide (ben' droe floo" me thye' a zide) is available in tablets of 2.5 mg in generic forms; recommended oral doses in adults are 2.5 to 10 mg in two divided doses. It is also available in a fixed dose with nadolol generically and under the brand name Corzide.

Chlorothiazide (klor" oh thye' a zide) is available in tablets of 250 and 500 mg generically and under the trade name of Diuril; recommended oral doses in adults are 500 to 1000 mg once or twice daily.

Chlorthalidone (klor thal' i done) is available in tablets of 25 and 50 mg generically and under the brand name of Thalitone; recommended oral doses in adults are 25 to 100 mg once daily or 100 mg every other day.

Hydrochlorothiazide (hye' droe klor" oh thye' a zide) is available in tablets of 25 and 50 mg and as capsules of 12.5 mg generically and under the trade names of Hydrodiuril, Microzide and Esidrix; recommended oral doses in adults are 12.5 to 50 mg daily given in one or two divided doses.

Methyclothiazide (meth" i kloe thye' a zide) is available in tablets of 2.5 and 5 mg generically and under the trade name of Enduron; recommended oral doses in adults are 2.5 to 5 mg once daily.

Polythiazide (pol" ee thye' a zide) is available in tablets of 1, 2 and 4 mg generically and under the trade name of Renese; typical oral doses in adults are 2 to 4 mg in one or two divided doses daily.

Metolazone (me tol' a zone) is a thiazide-like diuretic that is available as tablets of 2.5 and 5 mg generically and under the trade name of Zaroxolyn; recommended oral doses in adults are 2.5 to 20 mg once daily.

Indapamide (in dap' a mide) is a thiazide-like diuretic that is available as tablets of 1.25 and 2.5 mg generically and under the trade name of Lozol; recommended oral doses in adults are 1.25 to 5 mg once daily.

Common side effects of the thiazide and thiazide-like diuretics include nausea, dizziness, headache, polyuria, dehydration, hyponatremia, hypokalemia and hypomagnesia. Chronic therapy may be associated with hyperuricemia and gout, and possibly an increased risk of cholecystitis. Many of the thiazide diuretics are also available in fixed dose combination with other antihypertensive medications or with potassium-sparing diuretics.

Hepatotoxicity

The thiazide diuretics have not been shown to cause serum aminotransferase elevations to an appreciable extent, and are often used as a control group in assessing adverse events including serum aminotransferase elevations of newer antihypertensive medications. Despite their widespread use, the thiazide diuretics have only rarely been implicated in cases of clinically apparent acute liver injury. No clear signature or clinical pattern has been demonstrated in the rare case reports and in some instances other potentially hepatotoxic medications were being used and other possible diagnoses were present. The usual latency period to onset has been short (few days to several weeks) and the pattern of serum enzyme elevations has been either hepatocellular or mixed (Cases 1 and 2). Immunoallergic features are uncommon as is autoantibody formation. Recovery is usually rapid upon stopping. Thus, only hydrochlorothiazide has been implicated in causing drug induced liver injury. However, it is also the most commonly used thiazide diuretic. The similarity in chemical structure among the thiazide diuretics suggests that liver injury might be a class effect.

Hydrochlorothiazide likelihood score: D (possible rare cause of clinically apparent liver injury).

Other thiazide diuretics likelihood score: E (unlikely causes of clinically apparent liver injury).

Mechanism of Injury

Some instances of hepatic injury attributed to the thiazide diuretics have appeared to be due to metabolic idiosyncrasy.

Outcome and Management

The few instances of hepatic injury attributed to thiazide diuretics have been self-limited and rapidly reversed upon stopping the medication. There have been no convincing instances of acute liver failure or prolonged jaundice or vanishing bile duct syndrome associated with the thiazide diuretics. There have been no reports of cross challenges among the different thiazide and thiazide-like diuretics.

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

Drug Class: Diuretics, Thiazide Diuretics

CASE REPORTS

Case 1. Acute anicteric liver injury due to hydrochlorothiazide.

[Modified from: Arinzon Z, Alexander P, Berner Y. Hydrochlorothiazide induced hepato-cholestatic liver injury. Age Ageing 2004; 33: 509-10. PubMed Citation]

A 72 year old woman with hypertension developed anorexia, nausea and right upper quadrant abdominal pain 6 days after starting hydrochlorothiazide. She had no history of liver disease and had normal liver tests shortly before starting therapy. She took no other medications except for calcium and did not drink alcohol or have risk factors for viral hepatitis. Physical examination demonstrated tenderness over the liver, but no jaundice. Laboratory tests showed elevations in serum aminotransferase levels, alkaline phosphatase and gamma glutamyl transpeptidase (GGT) (Table). White blood cell counts were normal. Tests for hepatitis A, B and C were negative as were autoantibodies. Liver ultrasound was normal. Hydrochlorothiazide was stopped and symptoms resolved within days. Serum aminotransferase levels were normal within two weeks and alkaline phosphatase and GGT within three weeks of stopping treatment.

Key Points

Medication:	Hydrochlorothiazide (25 mg daily)
Pattern:	Mixed (R=3.4)
Severity:	1+ (enzyme elevations and symptoms)
Latency:	6 days to onset of symptoms
Recovery:	2-3 weeks
Other medications:	Calcium

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	GGT* (U/L)	Other
Pre	Pre	18	72	24	
0	Hydrochlorothiazide (25 mg daily) given for 6 days				
1 week	0	236	150	363	
3 weeks	2 weeks	30	120	186	
4 weeks	3 weeks	20	78	36	
5 weeks	4 weeks	20	75	30	
Normal Values		**<41**	**<140**	**<60**	

* Values estimated from Figure 1.

Comment

The acute liver injury was mild, but associated with symptoms arising within days of starting a low dose of hydrochlorothiazide. While the rapidly of onset suggests a hypersensitivity reaction, there were no other manifestations of an immunoallergic reaction (fever, rash, eosinophilia). Hydrochlorothiazide is one of the most frequently used medications in the world, but has only rarely been implicated in acute liver injury.

Case 2. Recurrent acute liver injury due to hydrochlorothiazide.

[Modified from: Anez MS, Dickson G, Zabala R, Zabaleta P, Pacheco A, Briceno D. [Acute hepatitis due to hydrochlorothiazide: report of a case]. Gastroenterol Hepatol 1981; 4: 476-8. (Not in PubMed)]

A 47 year old man developed jaundice 20 days after starting hydrochlorothiazide (50 mg daily) for hypertension. He had no history of liver disease, jaundice, alcohol abuse or risk factors for viral hepatitis. He was taking no other medications. He complained of change in taste and abdominal upset, but no fever, rash or itching. Physical examination showed jaundice, but no evidence of chronic liver disease. Laboratory testing showed a total serum bilirubin of 9.5 mg/dL (direct 6.0 mg/dL) and marked elevations in serum aminotransferase levels (ALT 640 U/L, AST 1000 U/L), with minimal increase in alkaline phosphatase (5.4 Bodansky Units) and gamma glutamyl transpeptidase (60 U/L). The total white count was normal without eosinophilia. The prothrombin time and serum albumin values were normal. Tests for hepatitis B were negative as were autoantibodies. Hydrochlorothiazide was stopped and laboratory tests fell to normal within a month. Because of continuing hypertension, hydrochlorothiazide was restarted. Seventeen days later, he presented again with jaundice and serum aminotransferase levels were again elevated. A liver biopsy showed acute hepatocellular necrosis and inflammation compatible with an acute hepatitis due to a medication. Tests for hepatitis A and B and autoantibodies were negative. Hydrochlorothiazide was stopped again and laboratory values fell rapidly into the normal range. Several years later, he was seen at another medical center in another country and hydrochlorothiazide was restarted. Eighteen days later, he presented for the third time with jaundice. Stopping the medication led to improvements in laboratory tests that were normal two months later.

Key Points

Medication:	Hydrochlorothiazide (50 mg daily)
Pattern:	Hepatocellular (R=13)
Severity:	3+ (jaundice, hospitalization)
Latency:	17-20 days to onset of jaundice on three occasions
Recovery:	4-8 weeks
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0		Hydrochlorothiazide (50 mg daily) given for 20 days			
3 weeks	0	640	5.4	9.5	Admission
7 weeks	4 weeks	Normal	Normal	Normal	
0		Hydrochlorothiazide (50 mg daily) given for 17 days			
2.5 weeks	0	900		5.8	
9 weeks	7 weeks	Normal	Normal	Normal	
		Hydrochlorothiazide (50 mg daily) given for 18 days			
2.5 weeks	0	1450		8.2	
10 weeks	8 weeks	Normal	Normal	Normal	
Normal Values		**<35**	**<4.5**	**<1.2**	

Comment

A remarkably convincing case history of recurrent acute hepatitis arising 2 to 3 weeks after starting hydrochlorothiazide for hypertension. With each exposure the pattern of injury was hepatocellular, and the clinical phenotype was a mild acute hepatitis with rapid recovery upon stopping the medication. With each reexposure, the liver injury appeared again, each time without signs of hypersensitivity (no rash, fever or eosinophilia) and without shortening of the latency or worsening of the clinical syndrome. These features suggest that metabolic idiosyncrasy rather than hypersensitivity was the cause of the hepatic injury. Despite their use in millions of patients worldwide over the previous 50 years, this is one of the only convincing published cases of hepatotoxicity from thiazide diuretics.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bendroflumethiazide – Generic, Naturetin®

Chlorothiazide – Generic, Diuril®

Chlorthalidone – Generic, Hygroton®

Hydrochlorothiazide – Generic, Esidrix®

Indapamide – Generic, Lozol®

Methyclothiazide – Generic

Metolazone – Generic, Zaroxolyn®

Polythiazide – Generic, Renese®

DRUG CLASS

Diuretics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

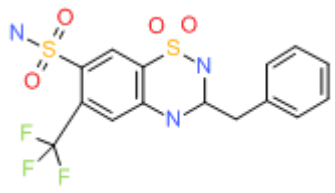
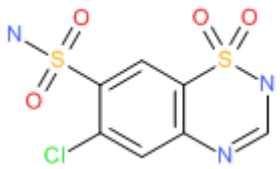
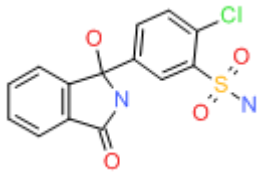
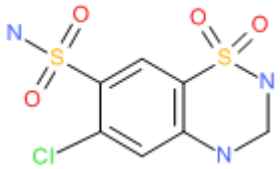
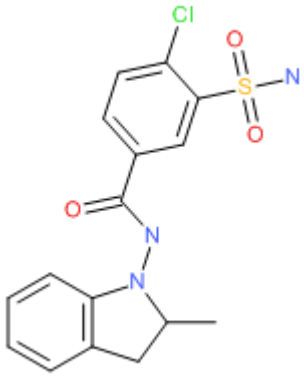
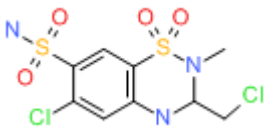
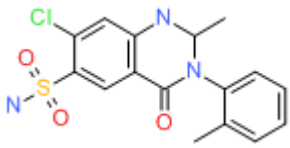
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Bendroflumethiazide	73-48-3	C15-H14-F3-N3-O4-S2	

Table continued from previous page.

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Chlorothiazide	58-94-6	C7-H6-Cl-N3-O4-S2	
Chlorthalidone	77-36-1	C14-H11-Cl-N2-O4-S	
Hydrochlorothiazide	58-93-5	C7-H8-Cl-N3-O4-S2	
Indapamide	26807-65-8	C16-H16-Cl-N3-O3-S	
Methyclothiazide	135-07-9	C9-H11-Cl2-N3-O4-S2	
Metolazone	17560-51-9	C16-H16-Cl-N3-O3-S	
Polythiazide	346-18-9	C11-H13-Cl-F3-N3-O4-S3