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Triamterene

Updated: October 13, 2021.

OVERVIEW

Introduction

Triamterene is a potassium-sparing diuretic widely used in the therapy of edema. Triamterene has been linked to rare cases of clinically apparent drug induced liver disease.

Background

Triamterene (trye am' ter een) is an inhibitor of renal epithelial sodium channels in the late distal tubule and collecting ducts of the kidney. As a result, triamterene promotes a mild sodium diuresis, but maintains body potassium levels. Triamterene is used largely in therapy of edema and can be safely used in patients with cirrhosis. Because of its potassium-sparing actions, triamterene is also used in combination with thiazide or loop diuretics in an attempt to prevent hypokalemia. Triamterene was approved for use in the United States in 1964 and continues to be widely used with more than 20 million prescriptions filled yearly. Triamterene is available in tablets and capsules of 50 and 100 mg in generic forms and under the brand name of Dyrenium. The typical dose of triamterene is 50 to 200 mg daily in one or two divided doses. Triamterene is also available in fixed dose combinations with hydrochlorothiazide (Maxide, Dyazide and generically). Triamterene is usually well tolerated but side effects can include dizziness, fatigue, headache, dry mouth, hyperkalemia and dehydration. Rare but potentially severe adverse events include rash, photosensitivity, and anaphylaxis.

Hepatotoxicity

Triamterene therapy has been associated with rare instances of idiosyncratic, clinically apparent liver injury which have invariably been mild and anicteric. The liver injury typically arises after 4 to 12 weeks of therapy and the pattern of serum enzyme elevations is usually hepatocellular or mixed. Fever is a prominent symptom and the reaction is often more typical of drug-fever than hepatotoxicity (Case 1). Rash and eosinophilia can occur, but are usually not prominent. Autoantibodies are rare. All published cases of triamterene associated liver injury have been self-limited in course and resolved rapidly upon withdrawal.

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

Mechanism of Injury

The mechanism of triamterene hepatic injury is unknown, but it likely to be due to hypersensitivity.

Outcome and Management

Most instances of triamterene associated liver injury have been mild and rapidly reversible upon drug withdrawal. Rapid recurrence upon rechallenge has been reported. There is no evidence of cross reactivity to the hepatic injury with other diuretics.

Drug Class: Diuretics, Potassium-Sparing Diuretics

Other Drugs in the Subclass: Amiloride, Eplerenone, Spironolactone

CASE REPORT

Case 1. Triamterene induced fever and liver injury.(1)

A 44 year old woman developed fever, malaise and right upper quadrant pain one month after starting triamterene (100 mg daily) for peripheral edema. On examination, she was febrile (39^{o} C) and had hepatic tenderness, but no rash or lymphadenopathy. Laboratory tests showed elevations in serum enzymes with AST 428 U/L and Alk P 170 U/L and slightly elevated total white blood cell count (12,000/μL). Abdominal ultrasound showed fatty liver, but no evidence of biliary obstruction. Serum bilirubin levels, prothrombin time, hepatitis A or B markers and autoantibodies were not mentioned. Triamterene was stopped and her fever abated. She was discharged but presented 1 day later with recurrence of symptoms and fever. The white blood cell count was again raised and was accompanied by eosinophilia (2,520/μL). Serum enzymes were more elevated than before. Careful history revealed that she had restarted triamterene six hours before the reappearance of fever. Withholding further triamterene therapy was followed by resolution of fever and fall of white count and liver test abnormalities to normal levels within 6 days.

Key Points

Medication:	Triamterene (100 mg daily)
Pattern:	Hepatocellular (R=6.8)
Severity:	Mild (enzyme elevations without jaundice)
Latency:	1 month initially, 1 day on rechallenge
Recovery:	1-2 weeks
Other medications:	None

Comment

This patient developed drug fever one month after starting triamterene and had an accompanying increase in liver enzyme values. Rechallenge let to a prompt recurrence. These features were compatible with a hypersensitivity reaction with minor hepatic involvement. While rash and drug fever have been described with triamterene therapy, acute liver injury with jaundice has not.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Triamterene – Generic, Dyrenium®

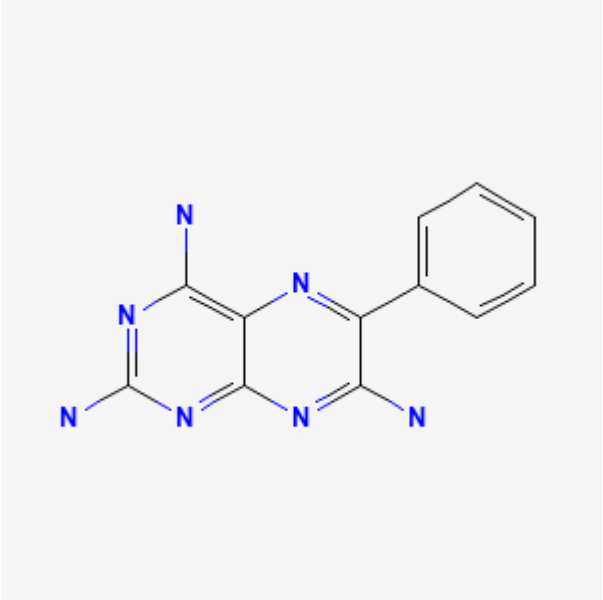
DRUG CLASS

Diuretics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Triamterene	396-01-0	C12-H11-N7	

CITED REFERENCES

1. Nolan PJ, D'Arcy G. Triamterene drug fever and hepatitis. Med J Aust. 1987;147:262. PubMed PMID: 3670184.

ANNOTATED BIBLIOGRAPHY

References updated: 13 October 2021

Zimmerman HJ. Diuretic drugs. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 662-4.

(Expert review of hepatotoxicity of diuretics published in 1999 mentions that clinically apparent liver injury due to diuretics is rare; hepatocellular jaundice has been reported with triamterene).

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 519-40.

(Review of hepatotoxicity of cardiovascular agents, mentions that thiazide diuretics can rarely cause cholestatic hepatitis; no mention of potassium sparing diuretics).

Jackson EK. Drugs affecting renal excretory function. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 445-70.

(Textbook of pharmacology and therapeutics).

Safdi MA. Fever secondary to triamterene therapy. N Engl J Med. 1980;303:701. PubMed PMID: 7402257.

(53 year old woman with alcoholic liver disease developed fever 10 days after starting triamterene and hydrochlorothiazide, resolving within 3 days of stopping and recurring twice with rechallenge using triamterene alone; no evidence of worsening of liver test abnormalities).

Nolan PJ, D'Arcy G. Triamterene drug fever and hepatitis. Med J Aust. 1987;147:262. PubMed PMID: 3670184.

(44 year old woman developed fever, abdominal pain and anorexia ~3 weeks after starting triamterene [AST 428 U/L, Alk P 170 U/L, bilirubin not mentioned], resolving within days upon withdrawal with abrupt recurrence with eosinophilia upon restarting: Case 1, triamterene).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl. 2004;10:1018–23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 137 [0.5%] were done for idiosyncratic drug induced acute liver failure, none were attributed to a diuretic).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology. 2005;129:512–21. PubMed PMID: 16083708.

(Reports of drug induced liver injury to a Spanish network found 570 cases; diuretics not mentioned as cause).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis. 2006;38:33–8. PubMed PMID: 16054882.

(Survey of drug induced liver fatalities reported to WHO database between 1968-2003 revealed 4690 reports [89% from the US]; no diuretic found in the 20 most commonly implicated agents).

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther. 2007;25:1401–9. PubMed PMID: 17539979.

(Population based survey of 126 cases of acute liver injury [24 with acute liver failure] due to drugs between 1993-1999 in Spain calculated relative risk of injury compared to the general population: hydrochlorothiazide was being taken by 7 and furosemide by 8 patients, but relative risk was not increased in comparison to a control group).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, no case was attributed to a diuretic).

Drugs for hypertension. Treat Guidel Med Lett. 2009;7:1–10. PubMed PMID: 19107095.

(Brief overview of currently available drugs for hypertension with guidelines on their use and information on prices and toxicities: "thiazide diuretics are the first-line therapy for many patients with hypertension").

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol. 2010;105:2396–404. PubMed PMID: 20648003.

(Among 313 cases of drug induced liver injury seen over a 12 year period at a large hospital in Bangalore, India, none were attributed to a diuretic).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70:721–8. PubMed PMID: 21039766.

(Among 624,673 adverse event reports in children between 2000 and 2006 in the WHO VigiBase, no diuretic was mentioned among the 30 most common causes of liver injury).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, of which none were attributed to a diuretic).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, none of which were attributed to a diuretic).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to a diuretic).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to a diuretic).

Drugs for hypertension. Med Lett Drugs Ther. 2020;62(1598):73–80. PubMed PMID: 32555118.

(Concise summary of efficacy, safety and costs of drug therapy of hypertension including the diuretics, focusing upon relative usefulness; no mention of hepatic adverse events).