



Triazolam

Updated: January 24, 2017.

OVERVIEW

Introduction

Triazolam is an orally available benzodiazepine used predominantly for therapy of insomnia. As with most benzodiazepines, triazolam therapy has not been associated with serum aminotransferase or alkaline phosphatase elevations, and clinically apparent liver injury from triazolam has been reported but is very rare.

Background

Triazolam (trye az" oh lam) is a benzodiazepine that is widely used as a sleeping aid in the therapy of insomnia. The soporific activity of the benzodiazepines is mediated by their ability to enhance gamma-aminobutyric acid (GABA) mediated inhibition of synaptic transmission through binding to the GABA A receptor. Triazolam was approved in the United States in 1982 and was formerly the most common prescription sleeping pill used in the United States. Concerns over its safety led to its withdrawal from use in the UK, and the availability of other potent, shorter acting sleeping pills has caused its decrease in general use in the United States. Current indications are for the short term management of insomnia. Triazolam is available in multiple generic forms and under the brand name Halcion in tablets of 0.125 and 0.25 mg. The recommended initial dose for adults is 0.125 mg immediately before bedtime, increasing to 0.25 as needed; rarely, higher doses are used. The most common side effects of triazolam are dose related and include daytime drowsiness, lethargy, ataxia, dysarthria and dizziness. Tolerance develops to these side effects, but tolerance may also develop to the soporific effects. Triazolam is classified as a schedule IV controlled substance, indicating that it has a potential for physical and psychological dependence and abuse.

Hepatotoxicity

Triazolam, like other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from triazolam is rare. There have been no well described case reports of acute liver injury from triazolam, except for a single report of a fatality after a severe and prolonged cholestatic liver injury. Cases of clinically apparent hepatitis have been reported with other benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, diazepam, and flurazepam. The clinical pattern of acute liver injury from benzodiazepines is typically cholestatic and mild-to-moderate in severity with a latency of 1 to 6 months. Fever and rash are uncommon as is autoantibody formation.

Likelihood score: E* (Unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

Triazolam is metabolized by the liver to inactive metabolites that are excreted in the urine. Liver injury from benzodiazepines is probably due to a rarely produced intermediate metabolite. The relative safety of triazolam is probably related to its low daily dose (<1 mg).

Outcome and Management

The case reports of hepatic injury due to benzodiazepines were followed by prompt and complete recovery upon stopping the medication, without evidence of residual or chronic injury. A single case of liver failure due to prolonged cholestatic hepatitis after triazolam therapy has been described in the literature. There is no information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity should be assumed.

Drug Class: [Sedatives and Hypnotics](#), [Benzodiazepines](#)

CASE REPORT

Case 1. Severe cholestatic liver injury attributed to triazolam.

[Modified from: Cobden I, Record CO, White RWB. Fatal intrahepatic cholestasis associated with triazolam. *Postgrad Med J* 1981; 57: 730-1. [PubMed Citation](#)]

A 44 year old man developed jaundice approximately 4 months after starting triazolam (0.25 mg nightly) for insomnia which he took 2 to 3 times per week. He had a history of ampullary carcinoma of the pancreas that had been successfully resected 6 years before. A month before the onset of jaundice, he developed atrial fibrillation and was treated with digoxin, hydrochlorothiazide and amiloride. He had no history of liver disease. On presentation, one month after onset of jaundice, he was found to have bilirubin of 10.6 mg/dL, AST 97 U/L and Alk P 104 U/L. A percutaneous cholangiogram showed no evidence of biliary obstruction and subsequent laparotomy revealed no cause for the jaundice. A liver biopsy showed intrahepatic cholestasis. He was discharged, but continued to worsen and was readmitted several weeks later with progressive hepatic failure. Autopsy showed no biliary obstruction and liver histology again revealed severe intrahepatic cholestasis without cirrhosis.

Comment

Cholestatic hepatitis is typical of the few cases of clinically apparent liver injury that have been linked to benzodiazepine use. The current case, however, is distinctive for the severe and relentless degree of cholestasis. There was no mention of bile duct damage, but the course is not incompatible with rapidly evolving vanishing bile duct syndrome. As stated by the authors, the attribution of the liver injury to triazolam is conjectural. The intermittent use and low doses (less than 1 mg per week) make it an unlikely or only possible cause.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Triazolam – Generic, Halcion®

DRUG CLASS

Sedatives and Hypnotics

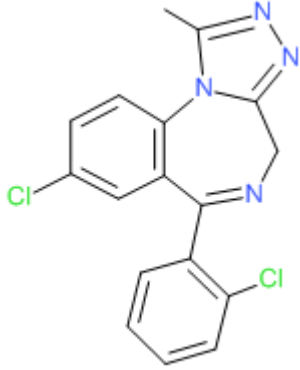
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COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Triazolam	28911-01-5	C ₁₇ H ₁₂ Cl ₂ N ₄	

ANNOTATED BIBLIOGRAPHY

References updated: 24 January 2017

Zimmerman HJ. Benzodiazepines. Psychotropic and anticonvulsant agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 491-3.

(Expert review of benzodiazepines and liver injury published in 1999; mentions rare instances of cholestatic hepatitis have been reported due to alprazolam, chlordiazepoxide, diazepam, flurazepam, and triazolam, and hepatocellular injury with clorazepate and clonazepam, but no reports of hepatic injury with lorazepam, oxazepam or temazepam).

Larrey D, Ripault MP. Anxiolytic agents. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 455.

(Review of drug induced liver injury mentions that rare instances of acute liver injury [usually cholestatic] have been reported with alprazolam, clonazepam, chlordiazepoxide, diazepam, flurazepam and triazolam).

Mihic SJ, Harris RA. Hypnotics and sedatives. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 457-80.

(Textbook of pharmacology and therapeutics).

Cobden I, Record CO, White RWB. Fatal intrahepatic cholestasis associated with triazolam. Postgrad Med J 1981; 57: 730-1. PubMed PMID: 6122205.

(44 year old man developed jaundice after 5 months of intermittent triazolam therapy for insomnia [bilirubin 10.6 mg/dL, AST 97 U/L and Alk P 104 U/L]; jaundice deepened and patient died, autopsy showed intrahepatic cholestasis without obstruction or cirrhosis: Case 1).

Davion T, Capron-Chivrac D, Andrejak M, Capron JP. [Hepatitis due to antiepileptic agents] *Gastroenterol Clin Biol* 1985; 9: 117-26. PubMed PMID: 3920108.

(Review of hepatotoxicity of anticonvulsants; among benzodiazepines, cases of cholestatic hepatitis have been linked to chlordiazepoxide and diazepam, but liver injury from this class of drugs is exceptionally rare).

Hindmarch I, Fairweather DB, Rombaut N. Adverse events after triazolam substitution. *Lancet* 1993; 341: 55: 8093301 PubMed PMID: 8093301.

(Survey of UK physicians, one year after withdrawal of triazolam in the UK, found higher rate of adverse reactions [largely CNS] with replacements such as temazepam, loprazolam, nitrazepam and lormetazepam, but no mention of hepatotoxicity).

Lewis JH, Zimmerman HJ. Drug- and chemical-induced cholestasis. *Clin Liver Dis* 1999; 3: 433-64, vii. Erratum in: *Clin Liver Dis* 1999; 3: 917. PubMed PMID: 11291233.

(Review of drug induced cholestatic syndromes, listing many causes including chlordiazepoxide and flurazepam; "Benzodiazepines may cause cholestatic injury, although this is rare").

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.

(Among 126 cases of drug induced liver injury seen in Spain between 1993-2000, 20 were attributed to benzodiazepines including 5 for clorazepate, 5 alprazolam, 6 lorazepam and 4 diazepam, but compared to controls, relative risk of injury was increased only for clorazepate [8.3: estimated frequency 3.4 per 100,000 person-year exposures]).

Chalasanani 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 from 2004 to 2008, none attributed to a benzodiazepine).

Björnsson E. Hepatotoxicity associated with antiepileptic drugs. *Acta Neurol Scand* 2008; 118: 281-90. PubMed PMID: 18341684.

(Review of hepatotoxicity of all anticonvulsants focusing upon phenytoin, valproate, carbamazepine; "furthermore, hepatotoxicity has not been convincingly shown to be associated with the use of benzodiazepines").

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, but none were linked to a benzodiazepine).

Drugs for insomnia. *Treat Guidel Med Lett* 2012; 10 (119): 57-60. PubMed PMID: 22777275.

(Guidelines for therapy of insomnia mentions that benzodiazepines are controlled substances and when used for sleep may impair next day performance).

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, but none were attributed to triazolam or any other benzodiazepine, despite the fact that millions of prescriptions for them are filled yearly).

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.

(Systematic review of literature on drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to a benzodiazepine).

Chalasanani 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: 1340-1352.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to triazolam or any other benzodiazepine).