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Estazolam

Updated: June 22, 2023.

OVERVIEW

Introduction

Estazolam is an orally available benzodiazepine used to treat insomnia. As with most benzodiazepines, estazolam has not been associated with serum aminotransferase or alkaline phosphatase elevations during therapy, and clinically apparent liver injury from estazolam has not been reported and must be very rare, if it occurs at all.

Background

Estazolam (es taz' oh lam) is a benzodiazepine used as a sleeping aid in the therapy of insomnia. The antianxiety (anxiolytic) and 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. Estazolam was approved in the United States in 1990 for the short term management of insomnia and is now rarely used, having been replaced by more effective and better tolerated agents. Estazolam is available in tablets of 1 and 2 mg in several generic forms and formerly under the brand name ProSom. The recommended initial oral dose for adults is 1 mg at bedtime, which can be increased to 2 mg nightly, but is not recommended as chronic therapy. The most common side effects of estazolam 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 effects on insomnia. Estazolam like all oral benzodiazepines has a boxed warning in its product label stressing (1) the risks of severe sedation and potentially fatal respiratory depression when combined with opiates, (2) with prolonged use, the risks of abuse, misuse, and addiction which can lead to overdose and death, and (3) with continued use, the risks of physical and psychological dependence and severe potentially life-threatening withdrawal symptoms if discontinued suddenly. Benzodiazepines are all categorized as Schedule IV controlled substances, having potential for dependence, tolerance, and abuse.

Hepatotoxicity

Estazolam, as with other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from estazolam is extremely rare, if it occurs at all. There have been no published case reports of symptomatic, acute liver injury from estazolam. Isolated cases of clinically apparent hepatitis have been reported with other benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, and triazolam. 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 and full recovery within 1 to 2 months. Fever and rash have not been described nor has autoantibody formation.

Likelihood score: E (Unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Estazolam is metabolized by the liver to inactive metabolites and excreted in the urine. Liver injury from benzodiazepines is probably due to the toxic effects of a rarely produced intermediate metabolite.

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. No cases of acute liver failure or chronic liver injury due to estazolam have been described. There is no information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity may occur.

Drug Class: Sedatives and Hypnotics, Benzodiazepines

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Estazolam – Generic, ProSom® *(Trade name discontinued)*

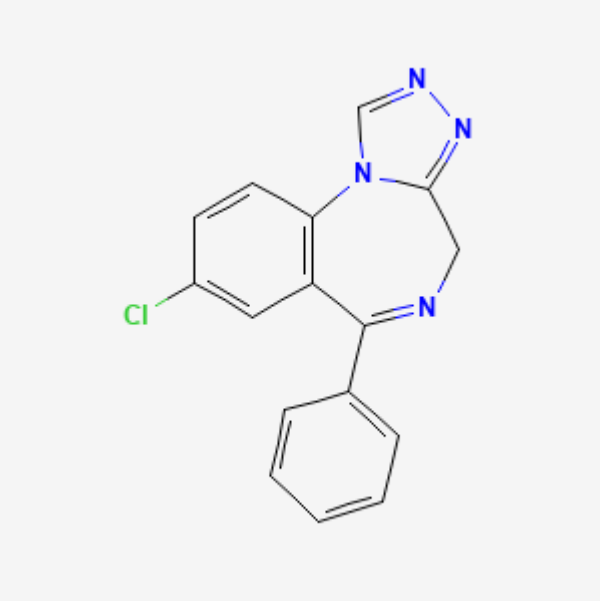
DRUG CLASS

Sedatives and Hypnotics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Estazolam	29975-16-4	C16-H11-Cl-N4	

ANNOTATED BIBLIOGRAPHY

References updated: 22 June 2023

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 clotiazepam, but no reports of hepatic injury with lorazepam, oxazepam, or temazepam).

Larrey D, Ripault MP. Benzodiazepines. 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 due to psychotropic drugs; rare instances of acute liver injury [usually cholestatic] have been reported with alprazolam, chlordiazepoxide, diazepam, flurazepam, and triazolam; a hepatitis-like pattern has been reported with clonazepam and clorazepate; no mention of estazolam).

Mihic SJ, Mayfield J, Harris RA. Hypnotics and sedatives. 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. 339-53.

(Textbook of pharmacology and therapeutics).

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

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]).

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 from 2004 to 2008, none were 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, hepatoxicity has not been convincingly shown to be associated with the use of benzodiazepines").

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 estazolam or any other benzodiazepine, despite millions of prescriptions 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).

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;148:1340–1352.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 estazolam or any other benzodiazepine).

Drugs for chronic insomnia. Med Lett Drugs Ther. 2023;65:1–6. PubMed PMID: 36630579.

(Concise review of drugs for chronic insomnia mentions that tolerance and dependence can occur with use of benzodiazepines and their use should be discouraged, and that benzodiazepines are CNS suppressants and can impair next day performance including driving and can cause complex behavior disorders, anterograde amnesia, dependence, tolerance, abuse and rebound insomnia; no mention of ALT elevations or hepatotoxicity).