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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-. Lorazepam. [Updated 2017 Jan 24].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Lorazepam

Updated: January 24, 2017.

OVERVIEW

Introduction

Lorazepam is an orally available benzodiazepine used widely in the therapy of anxiety and insomnia. As with most benzodiazepines, lorazepam therapy has not been associated with serum aminotransferase or alkaline phosphatase elevations, and clinically apparent liver injury from lorazepam has not been reported and must be very rare, if it occurs at all.

Background

Lorazepam (lor az' e pam) is a benzodiazepine that is widely used in the therapy of anxiety. Lorazepam is also used in parenteral form for therapy of status epilepticus and in preoperative sedation and management of nausea and vomiting. 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. Lorazepam was approved in the United States in 1977, and currently more than 20 million prescriptions are filled yearly. Indications include management of anxiety disorders and short term relief of symptoms of anxiety. Lorazepam is available in tablets of 0.5, 1 and 2 mg in several generic forms and under the brand name Ativan. Parenteral formulations of lorazepam (2 and 4 mg per mL) are available for use in status epilepticus and for preoperative sedation and control of nausea and vomiting after cancer chemotherapy. The recommended oral dose for adults is 0.5 to 1 mg two to three times daily, increasing as needed to a maximum dose of 10 mg daily in divided doses. The most common side effects of lorazepam are dose related and include drowsiness, lethargy, ataxia, dysarthria and dizziness. Tolerance develops to these side effects, but tolerance may also develop to the effects on anxiety and insomnia.

Hepatotoxicity

Lorazepam, as with other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from lorazepam is extremely rare, if it occurs at all. There have been no case reports of symptomatic, acute liver injury from lorazepam. Cases of clinically apparent hepatitis have been reported with other benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, diazepam, flurazepam 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. Fever and rash are not common nor is autoantibody formation.

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

Mechanism of Injury

Lorazepam is metabolized by the liver to inactive metabolites and is considered the benzodiazepine best tolerated by patients with advanced liver disease. 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 lorazepam 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

Lorazepam – Generic, Ativan®

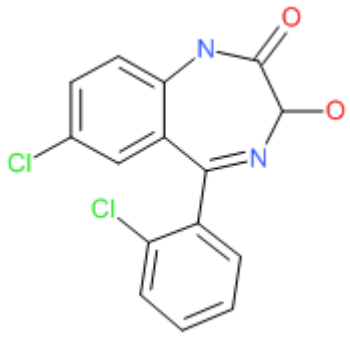
DRUG CLASS

Benzodiazepines, Antianxiety Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Lorazepam	846-49-1	C15-H10-Cl2-N2-O2	

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 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: Elsever, 2013, pp. 455.

(Review of liver injury due to psychotropic drugs; rare instances of acute liver injury [usually cholestatic] have been reported with alprazolam, clonazepam, chlordiazepoxide, diazepam, flurazepam, triazolam and bentaepam).

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. 339-354.

(Textbook of pharmacology and therapeutics).

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).

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, the relative risk of injury was increased only for clorazepate [8.3 and 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").

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 attributed to a benzodiazepine).

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 a benzodiazepine, despite the fact that millions of prescriptions 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).

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 lorazepam or any other benzodiazepine).