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Oxazepam

Updated: June 22, 2023.

OVERVIEW

Introduction

Oxazepam is an orally available benzodiazepine used in the therapy of anxiety and acute alcohol withdrawal syndromes. As with most benzodiazepines, oxazepam has not been associated with serum aminotransferase or alkaline phosphatase elevations during therapy, and clinically apparent liver injury from oxazepam has not been reported and must be very rare, if it occurs at all.

Background

Oxazepam (ox az' e pam) is a benzodiazepine that is used largely in the therapy of anxiety and alcohol withdrawal states. The antianxiety (anxiolytic) 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. Oxazepam was approved in the United States in 1965 and currently is still in use but has been replaced in large part by other benzodiazepines with better pharmacokinetics and tolerance. Current indications are for management of anxiety disorders and acute alcohol withdrawal and it is considered particularly useful in older patients. Oxazepam is available in capsules or tablets of 10, 15 and 30 mg in several generic forms and formerly under the brand name Serax. The recommended oral dose for adults is 10 to 15 mg three to four times daily. Somewhat higher doses are used for the severe anxiety of alcohol withdrawal states. The most common side effects of oxazepam 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. Oxazepam 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 dependence and severe, potentially life-threatening withdrawal symptoms if discontinued suddenly. Benzodiazepines are all categorized as Schedule IV controlled substances, having potential for abuse, addiction, and dependence.

Hepatotoxicity

Oxazepam, like other benzodiazepines, is rarely associated with serum ALT or alkaline phosphatase elevations, and clinically apparent liver injury from oxazepam is extremely rare, if it occurs at all. Despite its availability for more than 50 years, there have been no case reports of symptomatic, acute liver injury from oxazepam. Nevertheless, the possibility of liver dysfunction and jaundice are mentioned in the product label for oxazepam. Isolated single cases of clinically apparent liver injury 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. Fever and rash are uncommon as is autoantibody formation.

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

Mechanism of Injury

Oxazepam is metabolized by the liver to inactive metabolites which are 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 oxazepam have been described. There is no information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity may occur.

Drug Class: Benzodiazepines, Antianxiety Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Oxazepam – Generic, Serax® *(Trade name discontinued)*

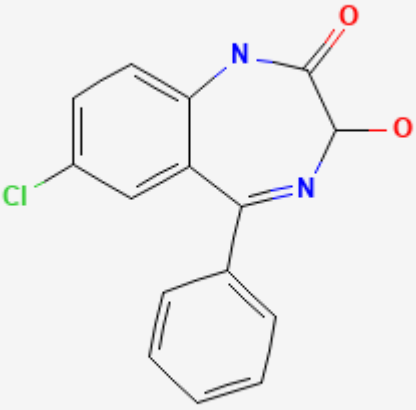
DRUG CLASS

Benzodiazepines

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Oxazepam	604-75-1	C15-H11-Cl-N2-O2	

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. 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 sedative induced liver injury mentions that rare instances of acute liver injury [usually cholestatic] have been reported with alprazolam, bentazepam, clotiazepam, chlordiazepoxide, diazepam, flurazepam and triazolam, and a hepatitis-like pattern has been reported with clonazepam and clorazepate, but no mention is made for oxazepam).

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").

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 linked to oxazepam or other benzodiazepines).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N. Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. J Pediatr Gastroenterol Nutr. 2011;53:182–9. PubMed PMID: 21788760.

(Among 30 children with suspected drug induced liver injury, half [n=15] were due to antimicrobials [minocycline 4, INH 3, azithromycin 3] and the rest largely due to CNS agents and anticonvulsants; none were due to oxazepam or other benzodiazepines).

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 oxazepam 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).

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 oxazepam or any other benzodiazepine).

Drugs for anxiety disorders. Med Lett Drugs Ther. 2019;61(1578):121–6. PubMed PMID: 31386647.

(Concise review of drugs for anxiety including benzodiazepines summaries mechanism of action, clinical efficacy, safety, and costs; comments that benzodiazepines can provide immediate relief of anxiety symptoms, but long term therapy can cause tolerance and dependence, and sudden withdrawal can cause severe and even life-threatening symptoms; no mention of ALT elevations or hepatotoxicity).