



Chlordiazepoxide

Updated: January 24, 2017.

OVERVIEW

Introduction

Chlordiazepoxide is an orally available benzodiazepine used for therapy of anxiety and alcohol withdrawal syndromes. As with other benzodiazepines, chlordiazepoxide therapy is not associated with serum aminotransferase or alkaline phosphatase elevations, and clinically apparent liver injury from chlordiazepoxide has been reported, but is very rare.

Background

Chlordiazepoxide (klor" dye az" e pox' ide) is the prototype of benzodiazepines used in the therapy of anxiety and acute alcohol withdrawal. 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. Chlordiazepoxide was approved in the United States in 1960 and for many years was one of the most prescribed medications. Currently, it is not commonly used, having been replaced by benzodiazepines with more favorable pharmacokinetics, half-life and tolerance. Indications include anxiety disorders and alcohol withdrawal syndrome. Chlordiazepoxide is available in multiple generic forms and under the brand name of Librium in capsules of 5, 10 and 25 mg. The recommended initial dose for adults is 5 to 10 mg three to four times per day, but higher doses are used for severe anxiety disorders. Chlordiazepoxide is also available for parenteral administration (100 mg/ampule) for use in acute anxiety, preoperative sedation and acute alcohol withdrawal syndromes. In addition, combinations of chlordiazepoxide with clidinium bromide or amitriptyline have been marketed under generic as well as brand names (Librax and Limbitrol). The most common side effects of chlordiazepoxide are dose related and include drowsiness, lethargy, ataxia, dysarthria and dizziness. Tolerance develops to these side effects, but tolerance may also develop to the anxiolytic effects.

Hepatotoxicity

Chlordiazepoxide, as with other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from its use is rare. There have been several case reports of acute liver injury from chlordiazepoxide, published largely before 1980. The latency to onset of acute liver injury was 1 to 4 months, and the pattern of liver enzyme elevations varied from hepatocellular to cholestatic and mixed. The injury was usually mild-to-moderate in severity and self-limited. Fever and rash were uncommon, as was autoantibody formation.

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

Mechanism of Injury

Chlordiazepoxide is metabolized extensively in the liver and has a prolonged half-life. The liver injury from benzodiazepines is probably due to a rarely produced metabolic intermediate metabolite.

Outcome and Management

The case reports of hepatic injury due to benzodiazepines were marked 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 chlordiazepoxide have been described. There is little information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity should be assumed.

Drug Class: [Benzodiazepines](#)

CASE REPORT

Case 1. Mild acute liver injury due to chlordiazepoxide.

[Modified from: Lo KJ, Eastwood IR, Eidelman S. Cholestatic jaundice associated with chlordiazepoxide hydrochloride (Librium) therapy. Report of a case and review of the literature. *Am J Dig Dis* 1967; 12: 845-9. [PubMed Citation](#)]

A 26 year old woman developed nausea, anorexia and fatigue 2 days after starting chlordiazepoxide (30 mg per day). She was given an injection of penicillin followed by several days of oral penicillin. Ten days later she developed jaundice and pruritus and chlordiazepoxide was stopped. She had no previous history of liver disease or known exposures to viral hepatitis. She had delivered a healthy, full-term baby shortly before starting the chlordiazepoxide. She had no known drug allergies. Physical examination showed jaundice and a tender liver, without fever or skin rash. Laboratory tests showed elevated serum bilirubin (5.0 mg/dL) and elevations in both serum alkaline phosphatase and aminotransferase levels (Table). She had severe pruritus that persisted for several weeks, even while her laboratory test results improved. A liver biopsy showed intra-hepatic cholestasis. Two months later her symptoms had resolved and all blood tests had returned to normal.

Key Points

Medication:	Chlordiazepoxide
Pattern:	Cholestatic (R=0.3)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 days to symptoms, 11 days to jaundice
Recovery:	2 months
Other medications:	Penicillin G

Laboratory Values

Time After Starting	Time After* Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
2 weeks	0	51	69	5.0	Admission
3 weeks	7 days	45	50	4.4	Liver biopsy
4 weeks	14 days	55	47	4.3	
4.5 weeks	18 days	52	39	3.4	
5 weeks	3 weeks	54	35	2.8	

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Time After Starting	Time After* Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
6 weeks	4 weeks	35	20	1.6	
7 weeks	5 weeks		21	1.2	
8 weeks	6 weeks		15	1.1	
Normal Values		<35	<13	<1.2	

* Some dates and values estimated from Figure 1

Comment

An acute cholestatic hepatitis arose within two weeks of starting chlordiazepoxide in a patient whose only other medical exposure was to a few days of penicillin. While both benzodiazepines and the penicillins can cause cholestatic hepatitis, penicillin induced liver injury is usually accompanied by other signs of hypersensitivity such as fever and rash. Cholestatic drug induced liver injury tends to be slower to resolve than hepatocellular injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Chlordiazepoxide – Generic, Librium®

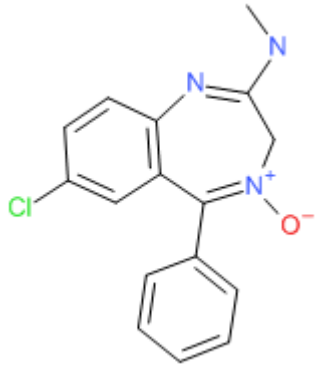
DRUG CLASS

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
Chlordiazepoxide	58-25-3	C ₁₆ H ₁₄ ClN ₃ O	 <p>The chemical structure of Chlordiazepoxide is a 7-chloro-1-methyl-5-phenyl-1,5-dihydro-2H-1,4-benzodiazepin-2-ylidene-1-oxide. It features a benzodiazepine ring system with a chlorine atom at the 7-position, a methyl group on the nitrogen at the 1-position, and a phenyl ring at the 5-position. The nitrogen at the 2-position is double-bonded to the ring and carries a positive charge, with an oxygen atom carrying a negative charge (oxide).</p>

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).

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, pp. 455.

(Review of drug induced liver injury mentions that isolated 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).

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).

Cacioppo J, Merlis S. Chlordiazepoxide hydrochloride (Librium) and jaundice: report of a case. *Am J Psychiatry* 1961; 117: 1040-1. PubMed PMID: 13689710.

(39 year old man with schizophrenia and seizures on phenytoin developed jaundice 5 days after starting chlordiazepoxide [50 mg/day] [icterus index 49.6, Alk P 3 times ULN], resolving within 3 months of stopping).

Abbruzzese A, Swanson J. Jaundice after therapy with chlordiazepoxide hydrochloride. *N Engl J Med* 1965; 273: 321-2. PubMed PMID: 21417069.

(51 year old man developed jaundice and pruritus 4-5 weeks after starting chlordiazepoxide [bilirubin ~4.0 mg/dL, AST 300 U/L, Alk P 2.5 times ULN], biopsy showed inflammation and cholestasis, recovery not mentioned).

Pickering D. Hepatic necrosis after chlordiazepoxide therapy. *N Engl J Med* 1966; 274: 1449. Not in PubMed

(64 year old woman developed jaundice 3 weeks after 12 day course of chlordiazepoxide [bilirubin ~32 mg/dL, ALT 225 U/L, Alk P 38 U/L], prolonged course, transient ascites, prednisone therapy).

Lo KJ, Eastwood IR, Eidelman S. Cholestatic jaundice associated with chlordiazepoxide hydrochloride (Librium) therapy. Report of a case and review of the literature. *Am J Dig Dis* 1967; 12: 845-9. PubMed PMID: 4952749.

(26 year old woman developed nausea after 2 and jaundice after 11 days of chlordiazepoxide therapy [bilirubin 5.0 mg/dL, AST 51 U/L, Alk K 69 KA ~5 times ULN], recovery over 8 weeks, marked pruritis: Case 1).

Kratzsch KH, Buttner W, Reinhardt G. [Intrahepatic cholestasis following chlordiazepoxide-contribution to the differential diagnosis of drug jaundice]. *Z Gesamte Inn Med* 1972; 27: 408-11. German. PubMed PMID: 5055057.

(3 cases of cholestatic hepatitis during chlordiazepoxide use, after 4 weeks, 6 years and 2 days [bilirubin 6.0, 1.0 and 6.4 mg/dL, ALT 245, 18 and 25 U/L, Alk P 1.6 1.0 and 20 times ULN], with rapid recovery in 1-2 months, all 3 had biopsies showing intrahepatic cholestasis).

Franks E, Jacobs WH. Cholestatic jaundice possibly due to benzodiazepine-type drugs. *Mo Med* 1975; 72:605-6. PubMed PMID: 1181510.

(40 year old woman on multiple drugs including chlorpromazine developed jaundice [bilirubin 2.0 rising to 9.7 mg/dL, ALT 280 U/L, Alk P 546 U/L, 16% eosinophils], seemed to worsen on benzodiazepines including chlordiazepoxide, diazepam and flurazepam, resolving rapidly when they were stopped, but attribution to benzodiazepines difficult).

Døssing M, Andreassen PB. Drug-induced liver disease in Denmark. An analysis of 572 cases of hepatotoxicity reported to the Danish Board of Adverse Reactions to Drugs. *Scand J Gastroenterol* 1982; 17: 205-11. PubMed PMID: 6982502.

(Among 572 cases of hepatotoxicity reported to a Danish registry between 1968 and 1978, 97 were due to psychotropic agents, but only two attributed to benzodiazepines).

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).

Wallace SJ. A comparative review of the adverse effects of anticonvulsants in children with epilepsy. *Drug Saf* 1996; 15: 378-93. PubMed PMID: 8968693.

(Systematic review; ALT elevations occur in 4% of children on phenytoin, 6% on valproate, 1% on carbamazepine; "No child taking... benzodiazepines had raised liver enzyme levels.")

Lewis JH, Zimmerman HJ. Drug- and chemical-induced cholestasis. *Clin Liver Dis* 1999; 3: 433-64, vii. 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 none attributed to chlordiazepoxide).

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, 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 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 chlordiazepoxide or other benzodiazepines).

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 chlordiazepoxide or other 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 chlordiazepoxide or any other benzodiazepine).