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Clonazepam

Updated: January 25, 2017.

OVERVIEW

Introduction

Clonazepam is a benzodiazepine used predominantly as an anticonvulsant as adjunctive therapy in management of epilepsy. Therapy with clonazepam is not associated with serum aminotransferase elevations, and clinically apparent liver injury from clonazepam, if it occurs at all, must be exceedingly rare.

Background

Clonazepam (kloe naz' e pam) is a benzodiazepine with particularly potent activity against spread of seizure activity in several animal models. The antiseizure 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. Clonazepam was approved in the United States for treatment of epilepsy in 1997 and currently more than 20 million prescriptions are filled yearly. Clonazepam is currently indicated for management of absence seizures and myoclonic seizures in children as well as generalized seizure disorders in both adults and children. Clonazepam is effective in status epilepticus, but diazepam and lorazepam are preferable because of their longer half lives. Clonazepam is also used for restless leg syndrome, dysarthria, tic disorders, panic disorder and acute mania. Clonazepam is available in generic forms and under the brand name Klonopin in tablets of 0.5, 1.0 and 2 mg as well as in orally disintegrating tablets for pediatric use. The recommended initial dose for adults is 1.5 mg daily in three divided doses, increasing as needed to a maximum dose of 20 mg daily. The most common side effects of clonazepam are dose related and include drowsiness, lethargy, ataxia, dysarthria and dizziness. Tolerance develops to these side effects, but tolerance may also develop to the antiseizure effects.

Hepatotoxicity

Clonazepam, as with other benzodiazepines, is rarely associated with serum ALT elevations, and clinically apparent liver injury from clonazepam is extremely rare. However, at least one convincing case report of acute liver injury from clonazepam with recurrence on reexposure has been reported. Rare instances of drug induced liver injury has been reported with other benzodiazepines, such as chlordiazepoxide, diazepam, flurazepam, triazolam, clorazepate and alprazolam. In benzodiazepine related cases of acute liver injury, the latency has ranged from a few weeks to 6 months; the typical pattern of liver enzyme elevations has been cholestatic or mixed, but hepatocellular patterns have also been reported. The injury is usually mild to moderate in severity and self-limited. Fever and rash have not been described nor has autoantibody formation.

Likelihood score: D (possible but rare cause of clinically apparent liver injury).

Mechanism of Injury

The liver injury from benzodiazepines is probably due to a rarely produced intermediate metabolite. Their relative safety may relate to the low daily doses used (typically 5 to 10 mg).

Outcome and Management

The case reports of hepatic injury due to clonazepam were followed by complete recovery, without evidence of residual or chronic injury. No cases of acute liver failure or chronic liver injury due to clonazepam have been described. There is no information about cross reactivity with other benzodiazepines (clobazam, clorazepate, lorazepam or diazepam), but some degree of cross sensitivity should be assumed.

Drug Class: Anticonvulsants, Benzodiazepines

CASE REPORTS

Case 1. Cholestatic hepatitis due to flurazepam.

[Modified from: Fang MH, Ginsberg AL, Dobbins WO 3rd. Cholestatic jaundice associated with flurazepam hydrochloride. Ann Intern Med 1978; 89: 363-4. PubMed Citation]

A 70 year old man developed anorexia, weakness and fatigue 2 months after starting flurazepam for insomnia. Two and a half months later he developed dark urine and jaundice. He had no previous history of liver disease, risk factors for acquiring hepatitis and drank no alcohol. He had coronary artery disease, angina pectoris and type 2 diabetes for which he took chlorthalidone, isosorbide dintitrate, digoxin and tolbutamide chronically. On admission he was jaundiced, but had no fever or rash. Liver tests, which had been normal before starting flurazepam, were elevated (Table). Ultrasound of the abdomen was unremarkable, HBsAg was negative, and a percutaneous cholangiogram was normal. A liver biopsy showed intrahepatic cholestasis. Flurazepam was stopped and liver tests improved, although pruritus did not resolve for four months. The other medications were apparently continued.

Key Points

Medication:	Flurazepam (30 mg orally as needed)
Pattern:	Mixed→Cholestatic (R=2.4→1.8)
Severity:	3+ (jaundice and hospitalization)
Latency:	2 months until nausea, 4.5 months to jaundice
Recovery:	Complete recovery 2 months after stopping
Other medications:	Isosorbide dinitrate, chlorthalidone, digoxin, tolbutamide

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		40	90	0.5	
0	Flurazepam started				
4.5 months		225	207	7.0	
5 months	0	159	232	6.6	
	Flurazepam stopped				

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Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
	4 days	174	230	5.0	
	7 days	181	225	4.5	Liver biopsy
	24 days	79	183	1.7	
6 months	4 weeks	59	142	1.0	
6.5 months	7 weeks	47	104	0.6	
Normal Values		**<49**	**<90**	**<1.2**	

Comment

Cholestatic hepatitis arising after 4 months of intermittent use of flurazepam. Other possible causes were tolbutamide, but the liver injury resolved despite it being continued. Mild self-limited cholestatic hepatitis is the typical pattern of benzodiazepam induced acute liver injury, but it is very rare and has not been associated with acute liver failure or chronic liver injury.

Case 2. Cholestatic hepatitis due to flurazepam.

[Modified from: Reynolds R, Lloyd DA, Slinger RP. Cholestatic jaundice induced by flurazepam hydrochloride. Can Med Assoc J 1981; 124: 893-4. PubMed Citation]

A 44 year old Dutch woman visiting relatives in Canada developed anorexia, nausea and abdominal discomfort. She had been taking flurazepam for insomnia intermittently for 6 months, but more frequently while visiting. After developing jaundice and pruritis, she was admitted for evaluation. She had no previous history of liver disease, risk factors for acquiring hepatitis and drank little alcohol. She took no other medications. She was jaundiced but had no fever, rash or signs of chronic liver disease. Liver tests were elevated (Table). Ultrasound of the abdomen was unremarkable and HBsAg was negative. A liver biopsy showed intrahepatic cholestasis. Flurazepam was stopped and liver tests improved rapidly.

Key Points

Medication:	Flurazepam (30 mg orally as needed)
Pattern:	Mixed (R=2.5)
Severity:	3+ (jaundice and hospitalization)
Latency:	6 months to onset of symptoms
Recovery:	Complete recovery one month after stopping
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
6 months	0	106	209	8.2	8% eosinophils
	1 day	122	203	8.3	
	3 days	134	201	7.2	Liver biopsy
	6 days	185	195	6.6	
	17 days	108	121	2.0	

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Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
	4 weeks	60	111	1.8	
7 months	7 weeks	16	96	1.0	
Normal Values		**<24**	**<120**	**<1.2**	

Comment

The benzodiazepines are widely used agents for therapy of anxiety, insomnia, tremor and some forms of seizures. They are extremely well tolerated and only rarely associated with significant liver injury. This case is typical of the rare instances of hepatotoxicity reported with benzodiazepines, marked by a self-limited cholestatic hepatitis arising after several months of use. Signs of hypersensitivity or autoimmunity are uncommon, although this patient had mild eosinophilia. Liver enzymes were only modestly elevated and the calculated R value suggested that the pattern of injury was "mixed." However, the prominence of jaundice and pruritis along with the liver biopsy findings indicate that the injury was predominantly cholestatic.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Clonazepam – Klonopin®

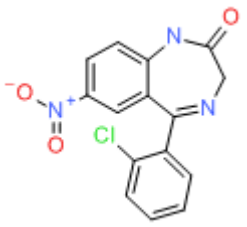
DRUG CLASS

Anticonvulsants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Clonazepam	1622-61-3	C15-H10-Cl-N3-O3	

REFERENCES

References updated: 25 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, clonazepam, diazepam, flurazepam, and triazolam, and hepatocellular injury with clorazepate, but no reports of hepatic injury with lorazepam, oxazepam or temazepam).

Larrey D, Ripault M-P. 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 mentions that there have been rare instances of acute liver injury [usually cholestatic] reported with alprazolam, bentazepam, chlordiazepoxide, clonazepam, clorazepate, clotiazepam, diazepam, flurazepam, and triazolam; a hepatitis-like pattern was reported with alprazolam and diazepam).

Pirmohamed M, Leeder SJ. Anticonvulsant agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp 423-42.

(Review of anticonvulsant induced liver injury; benzodiazepines are not discussed).

McNamara JO. Pharmacology of the epilepsies. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 583-607.

(Textbook of pharmacology and therapeutics).

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).

Parker JLW. Potassium clorazepate (Tranxene)-induced jaundice. Postgrad Med J 1979; 55: 908-10. PubMed PMID: 44913.

(27 year old man developed jaundice, pruritus and fever, 2 months after starting clorazepate [bilirubin 7.6 mg/dL, ALT 880 U/L, Alk P 2.3 times ULN] and had 3 liver biopsies done over 5 months showing intrahepatic cholestasis with thin portal-portal fibrosis septae that persisted as cholestasis and inflammation resolved).

Bonkowsky HL, Sinclair PR, Emery S, Sinclair JF. Seizure management in acute hepatic porphyria: risks of valproate and clonazepam. Neurology 1980; 30: 588-92. PubMed PMID: 6770287.

(38 year old man with acute intermittent porphyria and seizures did not respond to clonazepam, and testing in chicken embryos showed that it increased hepatic prophyrins and ALA synthase activity).

Døssing M, Andreasen 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).

Keränen T, Sivenius J. Side effects of carbamazepine, valproate and clonazepam during long-term treatment of epilepsy. Acta Neurol Scand Suppl 1983; 97: 69-80. PubMed PMID: 6424398.

(Clonazepam has many dose related sedative side effects, but compared to carbamazepine and valproate, few serious or long term side effects; no mention of hepatic side effects of clonazepam).

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 rare).

Olsson R, Zettergren L. Anticonvulsant-induced liver damage. Am J Gastroenterol 1988; 83: 576-7. PubMed PMID: 3364416.

(30 year old man developed fever, rash and jaundice 6 weeks after starting phenytoin; he was switched to carbamazepine and clonazepam, but redeveloped jaundice 3 months later; resolved with stopping, but recurred with restarting clonazepam alone [bilirubin 1.8 mg/dL, ALT 1380 U/L, Alk P 176 U/L] without rash, fever or eosinophilia; resolving in 6 weeks of stopping clonazepam).

Suzuki A, Aso K, Ariyoshi C, Ishimaru M. Acute intermittent porphyria and epilepsy: safety of clonazepam. Epilepsia 1992; 33: 108-11. PubMed PMID: 1733741.

(13 year old girl with acute intermittent porphyria worsened on valproate and on phenytoin therapy, but clonazepam led to control of seizures and no worsening of porphyria).

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").

Selim K, Kaplowitz N. Hepatotoxicity of psychotropic drugs. Hepatology 1999; 29: 1347-51. PubMed PMID: 10216114.

(Review of hepatotoxicity of phenothiazines, butyrophenones, tricyclics, MAO inhibitors, acetylcholesterase inhibitors, and psychotropic drugs of abuse; "benzodiazepines…have a very low hepatotoxic potential, with only case reports in the literature, usually with a cholestatic pattern).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the US between 1990 and 2002, 137 [0.2%] were done for idiosyncratic drug induced acute liver failure, of which 10 were attributed to phenytoin, 10 to valproate and 1 to carbamazepine, but none to benzodiazepines).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(36 years of reporting to Swedish registry identified 103 cases of acute liver failure due to drugs, of which 1 was attributed to phenytoin, 1 to valproate and 1 to carbamazepine, but none to benzodiazepines).

Gil-Martin A, Saez-Royuela F, Arias L, Angulo ML, Nogal B. [Hepatic fibrosis after antidepressant treatment] Rev Esp Enferm Dig 2005; 97: 461-2. Spanish. PubMed PMID: 16048430.

(32 year old woman developed pruritis and jaundice 1-2 months after starting sertraline, aprazolam and clorazepate, resolving with stopping sertraline, but had persistent minor ALT elevations and biopsy showing mild bridging fibrosis 4 months later).

Andrade RJ, Lucena MI, Kaplowitz N, García-Muņoz B, Borraz Y, Pachkoria K, García-Cortés M, et al. Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. Hepatology. 2006; 44: 1581-8. PubMed PMID: 17133470.

(28 of 493 [5.7%] cases of drug induced liver disease had evidence of chronicity, including 3 cases due to bentazepam and one with clorazepate, the latter with recovery at 25 months).

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").

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children; benzodiazepines were not among the top 40 agents implicated).

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 benzodiazepine use).

Wick JY. The history of benzodiazepines. Consult Pharm 2013; 28: 538-48. PubMed PMID: 24007886.

(History of the development, approval, widescale use and eventual restriction and decrease in use of the benzodiazepines).

Drugs for epilepsy. Treat Guidel Med Lett 2013; 11: 9-18. PubMed PMID: 23348233.

(Concise review of indications and side effects of anticonvulsants including clonazepam; no mention of hepatotoxicity).

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 linked to 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 of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, but none 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: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 40 [4.5%] were attributed to anticonvulsants, but none to benzodiazepine anticonvulsants).