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Flurazepam

Updated: June 22, 2023.

OVERVIEW

Introduction

Flurazepam is an orally available benzodiazepine used for therapy of insomnia. As with most benzodiazepines, flurazepam has not been associated with serum aminotransferase or alkaline phosphatase elevations during therapy, and clinically apparent liver injury from flurazepam has been reported, but is rare.

Background

Flurazepam (flur az' e pam) is a benzodiazepine used as a sleeping aid in the therapy of insomnia. The sedating 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. Flurazepam was approved in the United States in 1970 for the short term management of insomnia. For many years flurazepam was one of the most prescribed medications for sleep. Currently, it is less commonly used, having been replaced by benzodiazepines and benzodiazepine analogues with shorter half-life and better tolerance. Flurazepam is available in multiple generic forms and formerly under the brand name of Dalmane in capsules of 15 and 30 mg. The recommended dose for adults is 15 or 30 mg shortly before bedtime. Chronic use is often followed by tolerance and decrease in effectiveness. The most common side effects of flurazepam are dose related and include daytime drowsiness, lethargy, and dizziness. Flurazepam 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 continue 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 dependence, tolerance and abuse.

Hepatotoxicity

Flurazepam, as with other benzodiazepines, is rarely associated with serum ALT or alkaline phosphatase elevations, and clinically apparent liver injury is rare. Only a few case reports of acute liver injury from flurazepam have been published and mostly before 1980. The latency to onset of acute liver injury varied between 2 to 6 months and the pattern of liver enzyme elevations was cholestatic. The injury was usually mild-to-moderate in severity and self-limited in course. Fever and rash were not described nor autoantibody formation. Similar rare cases of self-limited, mild-to-moderate, cholestatic liver injury have been reported with other benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, and triazolam.

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

Mechanism of Injury

Flurazepam is metabolized extensively in the liver to its active metabolite that is then excreted in the urine. The liver injury from benzodiazepines is probably due to a rarely produced intermediate metabolite.

Outcome and Management

The hepatic injury due to benzodiazepines in case reports was followed by prompt and complete recovery upon stopping the medication, without evidence of residual or chronic injury. There have been no case reports of acute liver failure and no instances of chronic liver injury attributed to flurazepam. There is little information about cross reactivity with other benzodiazepines, but some degree of cross sensitivity may occur.

Drug Class: Sedatives and Hypnotics, Benzodiazepines

CASE REPORTS

Case 1. Cholestatic hepatitis due to flurazepam.(1)

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 or 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 took 4 months to resolve. The other medications were apparently continued.

Key Points

Medication:	Flurazepam (30 mg orally nightly as needed)
Pattern:	Mixed→cholestatic (R=2.4→1.8)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 months until nausea, 4.5 months to jaundice
Recovery:	Complete recovery 4 months after stopping
Other medications:	Isosorbide dinitrate, chlorthalidone, digoxin, tolbutamide

Laboratory Values

Time After Starting	Days 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	
5 months	Flurazepam stopped				
	4 days	174	230	5.0	Liver biopsy
	7 days	181	225	4.5	

Table continued from previous page.

Time After Starting	Days After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
	24 days	79	183	1.7	
6 months	1 month	59	142	1.0	
6.5 months	1.5 months	47	104	0.6	
Normal Values		**<49**	**<90**	**<1.2**	

Comment

Cholestatic hepatitis arose 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 benzodiazepine 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.(2)

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 pruritus, she was admitted for evaluation. She had no previous history of liver disease or 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 nightly as needed)
Pattern:	Mixed (R=2.5)
Severity:	3+ (jaundice, hospitalization)
Latency:	6 months to onset of symptoms
Recovery:	Complete recovery within one month after stopping
Other medications:	None

Laboratory Values

Time After Starting	Days After Stopping	AST (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	
	4 weeks	60	111	1.8	
7 months	5 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 pruritus along with the liver biopsy findings indicate that the injury was predominantly cholestatic.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Flurazepam – Generic, Dalmane® *(Trade name discontinued)*

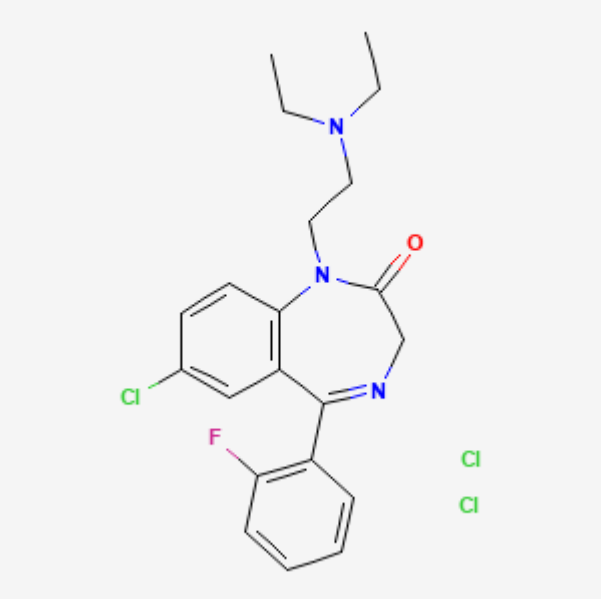
DRUG CLASS

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
Flurazepam	1172-18-5	C21-H23-Cl-F-N3-O.2Cl-H	

CITED REFERENCES

1. Fang MH, Ginsberg AL, Dobbins WO 3rd. Cholestatic jaundice associated with flurazepam hydrochloride. Ann Intern Med. 1978;89:363–4. PubMed PMID: 28685.
2. Reynolds R, Lloyd DA, Slinger RP. Cholestatic jaundice induced by flurazepam hydrochloride. Can Med Assoc J. 1981;124:893–4. PubMed PMID: 7214289.

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, pp. 517.

(Review of benzodiazepine associated liver injury mentions that flurazepam is a rare cause of acute liver injury, most reported cases being cholestatic).

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).

Fang MH, Ginsberg AL, Dobbins WO 3rd. Cholestatic jaundice associated with flurazepam hydrochloride. Ann Intern Med. 1978;89:363–4. PubMed PMID: 28685.

(70 year old man developed fatigue and pruritis 2 months and jaundice 4 months after starting flurazepam [bilirubin 6.6 mg/dL, ALT 179 U/L, Alk P 232 U/L, no eosinophilia], improving only when drug withdrawn: Case 1).

Reynolds R, Lloyd DA, Slinger RP. Cholestatic jaundice induced by flurazepam hydrochloride. Can Med Assoc J. 1981;124:893–4. PubMed PMID: 7214289.

(44 year old woman taking flurazepam intermittently for 6 months developed abdominal pain [bilirubin 8.2 mg/dL, AST 106 U/L, Alk P 209 U/L], resolving rapidly upon stopping, biopsy showed intrahepatic cholestasis. Case 2).

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 from Denmark, 97 were due to psychotropic agents, but only two attributed to benzodiazepines).

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).

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. 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").

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 between 2004 and 2008, none were attributed to a benzodiazepine or sleeping pill).

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 a benzodiazepine or sleeping pill).

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 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 flurazepam or any 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 flurazepam 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 cause complex behavior disorders, retrograde amnesia, dependence, tolerance, abuse and rebound insomnia; no mention of ALT elevations or hepatotoxicity).