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Midazolam

Updated: January 24, 2017.

OVERVIEW

Introduction

Midazolam is a benzodiazepine used intravenously as an anesthetic for conscious sedation or as an adjunct for general anesthesia. Midazolam therapy has not been associated with serum aminotransferase elevations and has not been linked to cases of clinically apparent liver injury.

Background

Midazolam (mi daz' oh lam) is a benzodiazepine with particularly potent sedative activity. The sedative 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. The use of midazolam has been largely as an intravenous anesthetic agent. Midazolam is used for conscious sedation for outpatient procedures such as upper and lower endoscopy, liver biopsy and cardiac catheterization. It is also used for induction of general anesthesia and for preoperative sedation. Midazolam is associated with anterograde amnesia which is often convenient for uncomfortable, minimally invasive procedures. Midazolam is available generically (and formerly under the brand name Versed) in parenteral forms for injection [1 mg/dL in 1, 2, 5 and 10 mL vials], in disposal syringes and as an oral solution for pediatric use perioperatively. The typical dose for conscious sedation is 1 to 2.5 mg intravenously over 2 to 5 minutes. Common side effects of the use of intravenous midazolam include nausea, confusion, acute agitation and respiratory depression. Acute overdose of midazolam can cause respiratory arrest and death.

Hepatotoxicity

Midazolam, like other benzodiazepines, is rarely associated with serum ALT elevations. Clinically apparent liver injury from midazolam has not been reported and must be extremely rare, if it occurs at all. Cases of clinically apparent liver injury 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, but hepatocellular patterns of injury have been reported with chlorazepate and clotiazepam. The injury is usually mild to moderate in severity with a time to onset 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

Midazolam is extensively metabolized by the liver to inactive metabolites which are excreted in the urine. The liver injury from benzodiazepines is probably due to a rarely produced intermediate metabolite. The absence of liver injury is perhaps due to the short duration of therapy and low doses used.

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 midazolam 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

Midazolam – Generic, Versed®

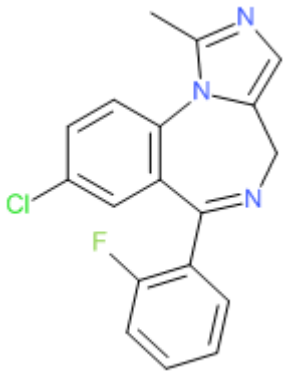
DRUG CLASS

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
Midazolam	59467-70-8	C18-H13-Cl-F-N3	

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: Elsevier, 2013, pp. 455.

(Review of benzodiazepine induced liver injury mentions that increases in liver enzymes during therapy are rare and significant hepatotoxicity uncommon; only a few cases [usually cholestatic] have been reported with alprazolam, chlordiazepoxide, diazepam, flurazepam and triazolam).

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).

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").

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 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").

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 midazolam or any other benzodiazepine, despite the fact 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 midazolam 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 midazolam or any other benzodiazepine).