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Remimazolam

Updated: June 22, 2023.

OVERVIEW

Introduction

Remimazolam is an ultra-short acting benzodiazepine used intravenously for induction and maintenance of sedation for adults undergoing short term procedures not requiring general anesthesia. Remimazolam sedation has not been associated with serum aminotransferase elevations and has not been linked to cases of clinically apparent liver injury.

Background

Remimazolam (rem" a maz' oh lam) is a unique benzodiazepine with a rapid onset and ultra-short duration of action that is used for sedation for short term procedures that do not require general anesthesia. 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. Remimazolam is a unique benzodiazepine in having a carboxylic ester in its chemical structure that is rapidly cleaved by tissue esterases accounting for its short half-life (0.6 to 0.9 hours compared to 1.8 to 6.4 hours for midazolam). Remimazolam was approved for induction and maintenance of sedation in adults for short term procedures not requiring general anesthesia. Remimazolam is available under the brand name Byfavo in lyophilized powder for reconstitution. The typical dose is 5 mg given over 1 minute which can be supplemented with doses of 2.5 mg in intervals of 2 minutes as needed. Common side effects of the use of intravenous remimazolam include hypotension, hypertension, bradycardia, and tachycardia. Less common adverse events include nausea, confusion, and acute agitation. Rare but potentially severe adverse events include severe respiratory depression and hypersensitivity reactions in patients with allergy to dextran. Acute overdose of remimazolam can cause respiratory arrest and death.

Hepatotoxicity

Remimazolam, like other intravenously administered benzodiazepines, has not been associated with serum ALT elevations and no instances of clinically apparent liver injury from remimazolam have been reported. Rare cases of clinically apparent liver injury have been reported with oral benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, diazepam, flurazepam and triazolam. The clinical pattern of acute liver injury from benzodiazepines usually arises only after 1 to 6 months of continuous or intermittent therapy and the pattern of injury is typically cholestatic. The injury from benzodiazepine is usually mild-to-moderate in severity. Fever and rash are uncommon as is autoantibody formation.

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

Mechanism of Injury

Remimazolam has a carboxylic ester in its chemical structure that is rapidly cleaved by tissue esterases resulting in a short half-life. As a consequence it has minimal hepatic metabolism and no effect on CYP enzymes. Remimazolam does not appear to have clinically significant drug-drug interactions. The absence of liver injury is perhaps due to its rapid, non-hepatic metabolism and 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 injury, cholestatic hepatitis, acute liver failure or chronic liver injury due to remimazolam have been described in the literature. There is no information about cross sensitivity to hepatic injury with other benzodiazepines, but such cross sensitivity is unlikely.

Drug Class: Sedatives and Hypnotics, Benzodiazepines

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Remimazolam – Byfavo®

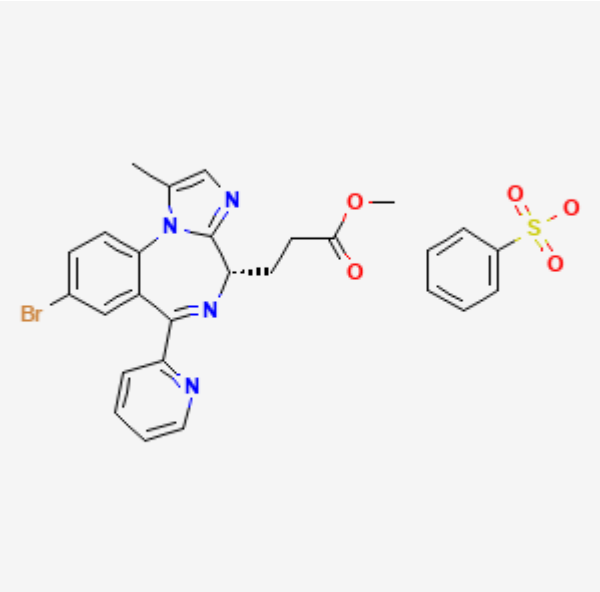
DRUG CLASS

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
Remimazolam	1001415-66-2	C21-H19-Br-N4-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; does not mention remimazolam).

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, 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).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212295Orig1s000MedR.pdf

(FDA website with product labels and the integrated review of the efficacy and safety of remimazolam that supported its approval for use as procedural sedation mentions that serum levels of ALT, AST, alkaline phosphatase and bilirubin actually decreased through day 4 after remimazolam therapy; no mention of hepatotoxicity).

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, 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).

Rex DK, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etzkorn K, Barish CF, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. Gastrointest Endosc. 2018;88:427-437.e6. PubMed PMID: 29723512.

(Among 461 adults undergoing colonoscopy who received remimazolam, midazolam or placebo as a procedural sedative after a single dose of fentanyl, adequate sedation was achieved more frequently with remimazolam and onset after starting and recovery of full alertness after stopping was more rapid with remimazolam, with similar rates of adverse events and no serious adverse event).

Pastis NJ, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, Wahidi M, et al.; PAION Investigators. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest. 2019;155:137-146. PubMed PMID: 30292760.

(Among 446 patients undergoing bronchoscopy who received procedural sedation with remimazolam, midazolam or placebo, the onset of adequate sedation was faster with remimazolam than midazolam and time to being fully alert was more rapid after stopping, while total and severe adverse event rates were similar in the three groups and success rates in completing the procedure were similar; no mention of ALT elevations or hepatotoxicity).

Stöhr T, Colin PJ, Ossig J, Pesic M, Borkett K, Winkle P, Struys MMRF, et al. Pharmacokinetic properties of remimazolam in subjects with hepatic or renal impairment. Br J Anaesth. 2021;127:415-423. PubMed PMID: 34246461.

(Pharmacokinetic studies in patients with liver dysfunction found a 38% decrease in rate of clearance of remimazolam resulting in prolonged sedative effect, averaging 8 minutes in healthy, 12 minutes for moderate and 16.7 minutes for severe hepatic impairment).

Rex DK, Bhandari R, Lorch DG, Meyers M, Schippers F, Bernstein D. Safety and efficacy of remimazolam in high risk colonoscopy: A randomized trial. Dig Liver Dis. 2021;53:94-101. PubMed PMID: 33243567.

(Among 77 patients at high risk for anesthesia who underwent colonoscopy who received remimazolam, midazolam or placebo sedation, remimazolam led to a more rapid onset of adequate sedation and a more rapid return to being fully alert, while adverse event rates were similar in the 3 groups and there was no mention of ALT elevations or hepatotoxicity).

Remimazolam (Byfavo) for short-term procedural sedation. Med Lett Drugs Ther. 2022;64(1644):26-28. PubMed PMID: 35171895.

(Concise review of the mechanism of action, clinical efficacy, safety, and cost of remimazolam, an ultrashort acting intravenous benzodiazepine, mentions adverse events of hypotension, hypertension, bradycardia, tachycardia, and dextran hypersensitivity reaction).