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Nizatidine

Updated: January 25, 2018.

OVERVIEW

Introduction

Nizatidine is a histamine type 2 receptor antagonist (H2 blocker) which is widely used for treatment of acid-peptic disease and heartburn. Nizatidine has been linked to rare instances of clinically apparent acute liver injury.

Background

Nizatidine (nye za' ti deen) was the fourth histamine type 2 receptor blocker (H2 blocker) introduced into clinical practice in the United States and is a commonly used agent for treatment of duodenal and gastric ulcer and gastroesophageal reflux disease. Other H2 blockers in clinical use include cimetidine, ranitidine and famotidine. The H2 blockers are specific antagonists of the histamine type 2 receptor, which is found on the basolateral (antiluminal) membrane of gastric parietal cells. The binding of the agent to the H2 receptor results in inhibition of acid production and secretion, and improvement in symptoms and signs of acid-peptic disease. The H2 blockers inhibit an early, "upstream" step in gastric acid production and are less potent that the proton pump inhibitors, which inhibit the final common step in acid secretion. Nevertheless, the H2 blockers inhibit 24 hour gastric acid production by about 70% and are most effective in blocking basal and nocturnal acid production. Nizatidine was first approved for use in the United States in 1988 and is now available both by prescription and over-the-counter. The listed indications for nizatidine are duodenal and gastric ulcer disease, gastroesophageal reflux and prevention of stress ulcers. Nizatidine is available by prescription in capsules of 150 and 300 mg in several generic forms and in both oral and parenteral forms under the brand name Axid. Over-the-counter preparations of nizatidine are usually tablets of 75 mg (Axid-AR). Side effects are uncommon, usually minor, and include diarrhea, constipation, fatigue, drowsiness, headache and muscle aches.

Hepatotoxicity

Chronic therapy with nizatidine and other H2 blockers is associated with minor elevations in serum aminotransferase levels in 1% to 4% of patients, but similar rates have been reported in placebo recipients. The ALT elevations are usually asymptomatic and transient and may resolve without dose modification. Rare instances of clinically apparent liver injury have been reported in patients receiving nizatidine, but too few cases have been reported to characterize a typical time to onset or pattern of injury. More information is available on the hepatotoxicity of other H2 blockers such as ranitidine and cimetidine which have been implicated in causing clinically apparent liver injury in 1:20,000 to 1:100,000 users. The time to onset of H2 blocker induced liver injury tends to be short, between 1 and 6 weeks of starting. The typical pattern of serum enzyme elevations varies from hepatocellular to cholestatic, most cases being "mixed". The injury can be severe, but is typically

mild-to- moderate in severity and self-limited in course, resolving within 4 to 12 weeks of stopping. Immunoallergic features (rash, fever, eosinophilia) are uncommon, as is autoantibody formation. Liver biopsy histology often shows centrolobular (zone 3) necrosis with mixed cellular infiltrates and mild cholestasis.

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

Mechanism of Injury

Nizatidine is metabolized by the microsomal P450 drug metabolizing enzymes and injury may be the result of its activation to a toxic intermediate. Despite its metabolism by the P450 system, nizatidine does not result in significant inhibitor or induction of the enzymes and thus is less likely to cause drug-drug interactions than cimetidine.

Outcome and Management

The hepatic injury caused by nizatidine is usually rapidly reversible with stopping the medication, but an instance of severe hepatitis with incomplete recovery and cirrhosis has been reported (Case 1). Nizatidine has been in use for a shorter time than cimetidine or ranitidine and remains unknown whether there is cross reactivity in hepatic injury between nizatidine and other H2 blockers. If acid suppression is required, use of an unrelated proton pump inhibitor is probably prudent for patients with clinically apparent nizatidine induced liver injury.

The H2 receptor blockers include cimetidine, famotidine, nizatidine, and ranitidine. General references on all four agents are given together after the overview section on H2 Blockers, while specific references are given for each drug. See also the Proton Pump Inhibitors.

Drug Class: Antiulcer Agents

Other Drugs in the Subclass, Histamine Type 2 Receptor Antagonists: Cimetidine, Famotidine, Ranitidine

CASE REPORT

Case 1. Severe acute liver injury leading to cirrhosis caused by nizatidine.

[Modified from: Chey WD, Kochman ML, Traber PG, Appelman HD, Gumucio JJ. Possible nizatidine-induced subfulminant hepatic failure. J Clin Gastroenterol 1995; 20: 164-7. PubMed Citation]

A 39 year old man developed rash after 7 days and jaundice after 14 days of nizatidine therapy for dyspepsia. Despite the symptoms and jaundice, he continued nizatidine for a total of 28 days. One month after stopping he was still jaundiced and sought medical care. He denied a history of liver disease, exposure to viral hepatitis or recent excessive alcohol intake. He was taking no other medications and had no history of drug allergies. Laboratory testing revealed marked elevations in serum bilirubin, AST and alkaline phosphatase (Table). The prothrombin time was prolonged at 18.7 seconds. Abdominal ultrasound and computerized tomography showed no evidence of gallstones or biliary obstruction, and endoscopic retrograde pancreatocholangiography showed no abnormality of the extra- or intra-hepatic biliary system. Ten weeks after starting and 6 weeks after stopping nizatidine, he was hospitalized because of increasing fatigue, jaundice and abdominal swelling. On physical examination, he was deeply jaundiced and had mild asterixis and ascites. Tests for hepatitis A, B and C were negative and autoantibodies were not present. A liver biopsy showed massive multi-lobular necrosis without significant fibrosis. He was referred for liver transplantation, but was managed conservatively and slowly improved, allowing for discharge from the hospital after 19 days. While liver tests improved, they did not become completely normal, and one year later serum bilirubin, aminotransferases and alkaline phosphatase

levels were still abnormal. Upper endoscopy revealed esophageal varices. A liver biopsy several months later revealed irregular, but relatively inactive cirrhosis.

Key Points

Medication:	Nizatidine (dose not provided)
Pattern:	Hepatocellular (R=8.8)
Severity:	4+ (jaundice and signs of hepatic failure)
Latency:	2 weeks to onset of jaundice, 8 weeks to laboratory confirmation
Recovery:	Incomplete
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
		Nizatidine given for 4 weeks			
2 months	1 month	461	152	21.7	Protime 18.7 sec
3.5 months	2.5 months	255	188	16.8	Protime 20.0 sec
4 months	3 months	270	202	16.6	Biopsy: massive necrosis
5 months	4 months	258	256	26.2	Discharge
12 months	11 months	74	252	1.8	Protime 13.4 sec
16 months	15 months				Biopsy: cirrhosis
Normal Values		**<40**	**<115**	**<1.2**	

Comment

This patient developed a severe hepatitis within a few weeks of starting nizatidine but continued taking the medication for two weeks after jaundice was noticed by his wife. He still delayed getting medical advice for another month after stopping nizatidine at which time he was deeply jaundiced and had signs of hepatic failure. When he developed ascites and hepatic encephalopathy, he was referred for liver transplant evaluation, but then began to improve spontaneously. He had a slow an incomplete recovery and was found to have cirrhosis on a liver biopsy done over a year later. Follow up is available from the authors. This patient has been followed at the transplant center from which this publication came for more than 15 years after this event and still has borderline hepatic decompensation, but has yet to require liver transplantation. No other source for the liver disease has been identified. Thus, cirrhosis induced by medications may not be completely reversible, but tends to be stable and nonprogressive as long as the medication is not restarted and other forms of hepatic injury (alcohol, hepatitis) are avoided.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nizatidine – Generic, Axid®

DRUG CLASS

Antiulcer Agents

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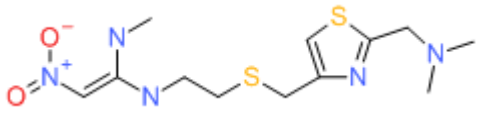
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Nizatidine	76963-41-2	C12-H21-N5-O2-S2	

ANNOTATED BIBLIOGRAPHY

References updated: 25 January 2018

Zimmerman HJ. H2 Receptors antagonists. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 719-20.

(Expert review of hepatotoxicity published in 1999 states that cimetidine and ranitidine, despite enormous use, have been implicated in a small number of cases of hepatic injury, 39 for cimetidine, 35 for ranitidine and only 1 for famotidine, all cases recovering and signs of hypersensitivity being rare).

Wallace JL, Sharkey KA. Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1309-22.

(Textbook of pharmacology and therapeutics).

Black M. Hepatotoxic and hepatoprotective potential of histamine(H2)-receptor antagonists. Am J Med 1987; 83: 68-75. PubMed PMID: 2892410.

(Review of hepatotoxicity of cimetidine and ranitidine and their potential role in ameliorating acetaminophen hepatotoxicity, perhaps via their inhibition of P450 activity).

Cloud ML. Safety of nizatidine in clinical trials conducted in the USA and Europe. Scand J Gastroenterol Suppl 1987; 136: 29-36. PubMed PMID: 2892253.

(Analysis of clinical trials of nizatidine in 3800 patients; there were no drug related deaths and the most common side effects were headache, rhinitis, abdominal discomfort, diarrhea, and nausea, but none were more frequent than with placebo; ALT elevations >3 times ULN occurred in 1% of nizatidine- and 0.9% of placebo recipients; among 7 patients with marked liver test abnormalities, none were symptomatic and none were clearly related to nizatidine therapy).

Lewis JH. Hepatic effects of drugs used in the treatment of peptic ulcer disease. Am J Gastroenterol 1987; 82: 987-1003. PubMed PMID: 2889354.

(Thorough review of hepatotoxicity of antiulcer medications; 10 published cases of hepatotoxicity due to cimetidine and 12 for ranitidine, none fatal and not all convincingly due to the medication; little information available on famotidine or nizatidine).

Price AH, Brogden RN. Nizatidine. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in peptic ulcer disease. Drugs 1988; 36: 521-39. PubMed PMID: 2905640.

(Review of pharmacology, clinical efficacy and side effects of nizatidine based upon 3800 patients in therapeutic trials; discontinuation for side effects was more common with placebo [6.5%] than nizatidine [2.5%], and common events occurred equally with placebo except for urticaria [0.5%], somnolence [2.4%] and sweating [1%]; low rates of ALT elevations, similar in placebo and ranitidine treated patients; no mention of hepatitis).

Chey WD, Kochman ML, Traber PG, Appelman HD, Gumucio JJ. Possible nizatidine-induced subfulminant hepatic failure. J Clin Gastroenterol 1995; 20: 164-7. PubMed PMID: 7769203.

(39 year old developed dyspepsia after 1 and jaundice after 2 weeks of nizatidine, not stopping until 4 weeks; 1 month later he was deeply jaundiced [bilirubin 21.7 mg/dL, AST 461 U/L, Alk P 152 U/L, prothrombin time 18.7 sec] and went on to have hepatic failure with ascites and encephalopathy, beginning to improve after referral for liver transplant; one year later he had varices and liver test abnormalities [bilirubin 1.8 mg/dL, ALT 98 U/L, Alk P 252 U/L], liver biopsies showing multilobular collapse acutely and inactive cirrhosis 16 months later: Case 1).

García Rodríguez LA, Ruigómez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. Pharmacotherapy 1997; 17: 721-8. PubMed PMID: 9250549.

(Combined analysis of 8 epidemiologic studies using the UK General Practice Research Database estimated incidence rates of acute liver injury to be highest for isoniazid and chlorpromazine [4 and 1.3 per 1000 users], intermediate for amoxicillin-clavulanate, cimetidine and ranitidine [2.3, 2.3 and 0.9 per 10,000] and lowest for trimethoprim/sulfamethoxazole, omeprazole, amoxicillin and nonsteroidals [5.2, 4.3, 3.9 and 3.7 per 100,000]).

García Rodríguez LA, Wallander MA, Stricker BH. The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. Br J Clin Pharmacol 1997; 43: 183-8. PubMed PMID: 9131951.

(Case control study in cohort of 100,000 users of antiulcer drugs in a UK general practice database; 33 cases of acute liver injury found, 12 on cimetidine for a relative risk [RR] of 5.5, 1 on omeprazole and 5 on ranitidine did not raise RR above baseline. Latency was <2 months in 80% of cases; most antiulcer drug cases had hepatocellular or mixed enzyme patterns [15 of 18]).

Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H2 receptor antagonists. Drug Saf 2001; 24: 39-57. PubMed PMID: 11219486.

(Review of renal and hepatic complications of H2 blocker therapy).

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 reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, but none were attributed to an H2 blocker or proton pump inhibitor).

de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58: 71-80. PubMed PMID: 15206996.

(Analysis of General Practice Research Database from UK on 1.6 million persons from 1994-2000 found 128 cases of drug induced liver injury [2.4/100,000 person years]; 3 cases were attributed to cimetidine for an odds ratio of 2.0 compared to controls [n=5000], which was not statistically significant; no mention of nitazidine).

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.

(Survey of all cases of DILI with fatal outcome from Swedish Adverse Drug Reporting system from 1966-2002; 103 cases identified as highly probable, probable or possible, one case was attributed to ranitidine and one to omeprazole; none to nitazidine).

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.

(Population based survey of 126 cases of acute liver injury due to drugs between 1993-1999 in Spain; 8 were attributed to ranitidine alone [incidence 5.1/100,000 person-years] and 5 to omeprazole alone [2.1/100,000]; nitazidine not mentioned).

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, 2 were attributed to ranitidine, none to cimetidine, nitazidine or omeprazole).

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, there were no antiulcer agents in the top 40 causes).

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 due to H2 blockers or other antiulcer medications).

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 cimetidine or other antiulcer medications).

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, the most commonly implicated agents being nimesulide [n=53], cyproterone [n=18], nitrofurantoin [n=17] and antituberculosis drugs [n=13]; no case was linked to nizatidine or other antiulcer agent or H2 blocker).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 6 cases were attributed to antiulcer medications, 3 to ranitidine and 3 to proton pump inhibitors, but none to nizatidine).