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Nisoldipine

Updated: January 11, 2017.

OVERVIEW

Introduction

Nisoldipine is a second generation calcium channel blocker and commonly used antihypertensive agent. Nisoldipine therapy is associated with a low rate of serum enzyme elevations, but has not been specifically linked to instances of clinical apparent acute liver injury.

Background

Nisoldipine (nye sol' di peen) belongs to the dihydropyridine class of calcium channel blockers (similar to amlopdine, felodipine and nifedipine) and is used predominantly for hypertension. Like other calcium channel blockers, nisoldipine acts by blocking the influx of calcium ions into cardiac and vascular smooth muscle cells during membrane depolarization. This action causes relaxation of arterial smooth muscle cells, resulting in arterial vasodilation and a decrease in cardiac work and oxygen consumption. Nisoldipine was approved in the United States in 1995 and current indications are for treatment of hypertension. It is available as extended release tablets of 8.5, 17, 25.5 and 34 mg generically and under the commerical name Sular. The recommended dose in adults is 17 mg once daily, adjusting to 17 to 34 mg per day based upon clinical effects and tolerance. Like other calcium channel blockers, nisoldipine is generally well tolerated, but side effects can include headache, flushing, dizziness, fatigue, nausea, diarrhea, palpitations, peripheral edema and skin rash.

Hepatotoxicity and Outcome and Management

Nisoldipine has been associated with a low rate of serum aminotransferase or alkaline phosphatase elevations during long term therapy, but the elevations are usually asymptomatic, mild, transient and resolve even with continuation of treatment. Cases of idiosyncratic liver injury due to nisoldipine have not been published. Large trials of nisoldipine have not mentioned liver injury, serum aminotransferase elevations or discontinuation of drug because of hepatic adverse events. Thus, liver injury from nisoldipine must be rare, if it occurs at all.

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

The reason why some calcium channel blockers (such as amlodipine, diltiazem and nifedipine) cause idiosyncratic liver injury while others (such as nisoldipine) do not, is not known. Because liver injury from calcium channel blockers is rare, there may have been inadequate exposures to the uncommonly used agents to lead to clinically manifest cases. Nisoldipine like many calcium channel blockers is metabolized in the liver by CYP 3A4 and is susceptible to drug-drug interactions with substrates, inhibitors and induces of CYP 3A4.

Drug Class: Cardiovascular Agents, Calcium Channel Blockers

Other Drugs in the Subclass, Calcium Channel Blockers: Amlodipine, Diltiazem, Felodipine, Isradipine, Nicardipine, Nifedipine, Nimodipine, Verapamil

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nisoldipine – Generic, Sular®

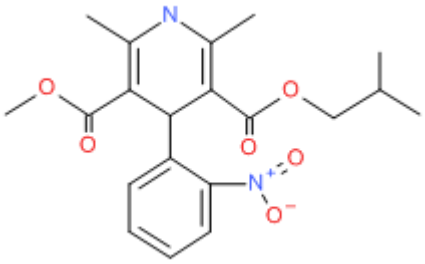
DRUG CLASS

Cardiovascular Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Nisoldipine	63675-72-9	C20-H24-N2-O6	

ANNOTATED BIBLIOGRAPHY

References updated: 11 January 2017

Zimmerman HJ. Calcium channel blockers. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 646-7.

(Expert review of hepatotoxicity published in 1999; among calcium channel blockers, diltiazem, nifedipine, bepridil and verapamil have been incriminated in instances of hepatic injury; nisoldipine is not mentioned).

De Marzio DH, Navarro VJ. Calcium channel blockers. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 524.

(Review of hepatotoxicity of calcium channel blockers mentions that diliazem, nifedipine and verapamil have been implicated in causing cholestatic liver injury; nisoldipine is not mentioned).

Michel T, Hoffman BB. Calcium channel antagonists. Treatment of myocardial ischemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 755-60.

(Textbook of pharmacology and therapeutics).

Knorr A. The pharmacology of nisoldipine. Cardiovasc Drugs Ther 1987; 1: 393-402. (Review of pharmacology of nisoldipine). PubMed PMID: 3154674.

Friedel HA, Sorkin EM. Nisoldipine. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of angina pectoris, hypertension and related cardiovascular disorders. Drugs 1988; 36: 682-731. *(Review of pharmacology, efficacy and safety of nisoldipine;* PubMed PMID: 3065058.

side effects are largely due to the vasodilating activty of nisoldipine, and in clinical trials no "clinically important" biochemical laboratory changes occurred).

Frishman WH, Heiman M. Usefulness of oral nisoldipine for stable angina pectoris. The Nisoldipine Multicenter Angina Study Group. Am J Cardiol 1991; 68: 1004-9. PubMed PMID: 1927911.

(Controlled trial of 5 week course of one of 3 doses of nisoldipine vs placebo in 178 patients with angina pectoris, only minor side effects occurred and no mention is made of liver injury or ALT elevations).

Mitchell J, Frishman W, Heiman M. Nisoldipine: a new dihydropyridine calcium-channel blocker. J Clin Pharmacol 1993; 33: 46-52. PubMed PMID: 8429113.

(Review of structure, pharmacodynamics, clinical efficacy and safety of nisoldipine, "Side effects... appear to be dose-related, mild in severity and transient"; no mention is made of ALT elevations or liver injury).

DEFIANT-II Research Group. Doppler flow and echocardiography in functional cardiac insufficiency: assessment of nisoldipine therapy. Results of the DEFIANT-II Study. Eur Heart J 1997; 18: 31-40. PubMed PMID: 9049513.

(Trial of 6 month course of nisoldipine in 542 patients reported no hepatic adverse events or withdrawals due to liver complications).

Fodor JG. Nisoldipine CC: efficacy and tolerability in hypertension and ischemic heart disease. Cardiovasc Drugs Ther 1997; 10: (Suppl 3): 873-9. PubMed PMID: 9126676.

(Nisoldipine is available in an extended release formulation that has favorable pharmokinetics allowing once daily administration, with tolerability that is similar to other calcium channel blockers and "no significant changes in laboratory parameters").

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 a calcium channel blocker).

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.

(Summary of 25 years of adverse drug reaction reporting in Sweden identified 103 cases of drug induced acute liver failure; only one case was possibly linked to a calcium channel blocker: felodipine).

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, calcium channel blockers were implicated as a sole agent in 2 cases [1 amlodipine, 1 verapamil] and as one of several agents in 2 cases [both amlodipine]).

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 no case was attributed to nisoldipine or other calcium channel blockers).

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, none of which were attributed to a calcium channel blocker or other antihypertensive medication).

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; one case was attributed to verapamil, but none were linked to nisoldipine or other calcium channel blockers).

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, 39 [4%] were due to antihypertensive agents including 4 due to calcium channel blockers [amlodipine in 1 and verapamil in 3 instances], but none to nisoldipine).