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Ranolazine

Updated: May 20, 2018.

OVERVIEW

Introduction

Ranolazine is a unique, orally available antiangina agent. Chronic ranolazine therapy has not been associated with serum enzyme elevations, but has been linked to rare cases of mild, clinically apparent liver injury.

Background

Ranolazine (ra nol' a zeen) is a piperazine derivative which has unique activity against symptoms of angina pectoris. Its mechanism of action is unclear, but is believed to involve inhibition of fatty acid oxidation and blockage of the inward sodium currents in cardiomyocytes which reduces intracellular calcium accumulation and improves left ventricular function. Unlike other antiangina agents, ranolazine does not decrease heart rate, blood pressure or vascular resistance. In multiple clinical trials, extended release formulations of ranolazine were shown to reduce angina attacks and prolong exercise tolerance in patients with coronary artery disease. It also appears to have some degree of antiarrhythmia activity. Ranolazine was approved for use in the United States in 2006 and current indications are for chronic angina, either alone or in combination with other angina medications (such as beta blockers or calcium channel blockers). Ranolazine is available in extended release tablets of 500 and 1000 mg generically and under the trade name Ranexa. The typical dose is 500 to 1000 mg twice daily. Ranolazine is generally well tolerated, but side effects can include fatigue, weakness, dizziness, headache, nausea and constipation. Higher doses may be associated with syncope, prolongation of the QTc interval and renal dysfunction.

Hepatotoxicity

In large preregistration clinical trials, ranolazine was not associated with serum aminotransferase and alkaline phosphatase elevations during treatment and no instances of symptomatic acute liver injury were reported. Since its approval and more wide spread use, ranolazine has been linked to a single instance of mildly symptomatic, rapidly reversible, anicteric liver injury (Case 1). Immunoallergic and autoimmune features were not present. Recovery was rapid once ranolazine was discontinued.

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

Mechanism of Liver Injury

The mechanism by which ranolazine might cause liver injury is not clear. It is extensively metabolized in the liver largely via CYP 3A4 and is susceptible to drug-drug interactions. Inhibitors of CYP 3A4 cause increase the ranolazine levels while inducers (such as rifampin) cause reduced serum levels of ranolazine.

Outcome and Management

The hepatic injury reported to be caused by ranolazine has been mild and rapidly reversible upon withdrawal of the agent. Ranolazine has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no evidence that there is cross sensitivity to hepatic injury between ranolazine and other oral antiangina or antiarrhythmic agents.

Drug Class: Antiangina Agents

CASE REPORT

Case 1. Mild anicteric hepatitis attributed to ranolazine.

[Modified from: Sancho-del-Val L, Barrio-Andrés J, Herranz-Bachiller MT, Alcaide-Suárez N. Hepatotoxicity and insomnia secondary to ranolazine. Rev Esp Enferm Dig 2013; 105: 304-5. PubMed Citation]

A 63 year old woman with hypertension and angina pectoris developed fatigue and insomnia 3 months after starting ranolazine (375 mg every 8 hours). She had no history of liver disease, risk factors for viral hepatitis or history of alcohol abuse. Her other medications included bisoprolol, amlodipine and atorvastatin. Initially, her serum bilirubin was 0.6 mg/dL, ALT 201 U/L, AST 97 U/L, GGT 213 U/L and alkaline phosphatase 150 U/L. Tests for hepatitis B and C were negative as were routine autoantibodies. An abdominal ultrasound was normal. Ranolazine was stopped and liver tests were normal when tested two months later.

Key Points

Medication:	Ranolazine (375 mg every 12 hours)
Pattern:	Mixed (R=4.5)
Severity:	1+ (no jaundice, mild symptoms)
Latency:	3 months
Recovery:	Within 2 months
Other medications:	Bisoprolol, amlodipine, atorvastatin

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
3 months	0	201	150	0.6	Fatigue, insomnia
5 months	2 months	46	75		
Normal Values		**<35**	**<120**	**<1.2**	

Comment

A woman with unstable angina developed fatigue 3 months after starting ranolazine and was found to have mild elevations in serum aminotransferase and alkaline phosphatase levels. These were normal or near normal two months after stopping the ranolazine. She has also taking other antiangina and cholesterol lowering agents, but these were evidently continued. Fatigue is a not uncommon side effect of ranolazine and attribution of fatigue to the liver enzyme elevations cannot be made with complete assurance. The case report was somewhat sparsely documented, but suggests that ranolazine can cause mild liver enzyme elevations that may be accompanied by constitutional symptoms. The injury was, however, quite mild and resolved rapidly upon stopping ranolazine.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ranolazine – Ranexa®

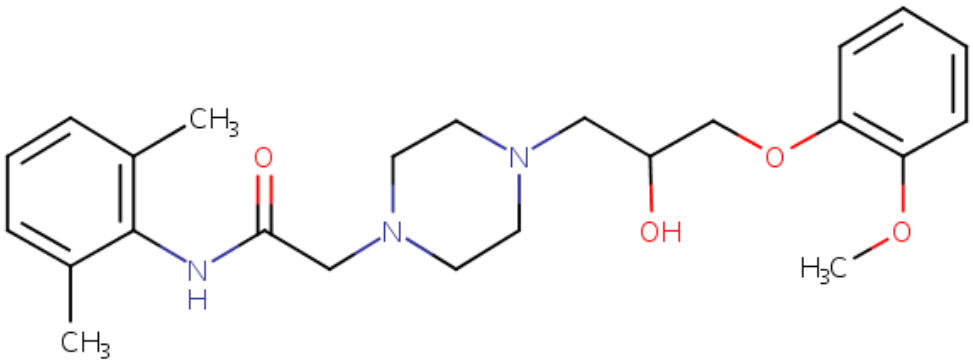
DRUG CLASS

Antiangina Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ranolazine	95635-55-5	C24-H33-N3-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 20 May 2018

Zimmerman HJ. 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. 639-71.

(Expert review of hepatotoxicity published in 1999 before the availability of ranolazine).

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 519-40.

(Review of hepatotoxicity of cardiovascular drugs; ranolazine is not discussed).

Michel T, Hoffman BB. Treatment of myocardial ischemia and hypertension. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 745-88.

(Textbook of pharmacology and therapeutics).

Thadani U, Ezekowitz M, Fenney L, Chiang YK. Double-blind efficacy and safety study of a novel anti-ischemic agent, ranolazine, versus placebo in patients with chronic stable angina pectoris. Ranolazine Study Group. Circulation 1994; 90: 726-34. PubMed PMID: 8044941.

(Among 318 patients with angina pectoris treated with intermediate release ranolazine [30, 60 or 120 mg] or placebo 3 times daily for 4 weeks, exercise tolerance was not different in the 4 groups and side effects included headaches, dizziness and fatigue while differences in laboratory tests were not "clinically significant").

Pepine CJ, Wolff AA. A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is responsive to conventional antianginal agents. Ranolazine Study Group. Am J Cardiol. 1999; 84: 46-50. PubMed PMID: 10404850.

(Among 312 patients with angina pectoris treated with intermediate release ranolazine [600, 800 or 1200 mg daily] or placebo, exercise tolerance improved compared to placebo at peak plasma levels and the only side effects were mild gastrointestinal upset; there were "no significant changes in…clinical laboratory blood tests").

Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, et al.; Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004; 291: 309-16. PubMed PMID: 14734593.

(Among 823 patients with symptomatic angina despite antianginal medications who were treated with ranolazine [750 or 100 mg] or placebo twice daily for 12 weeks, exercise tolerance was increased with ranolazine; the most common side effects were constipation, dizziness, nausea and fatigue; no mention of ALT changes or hepatotoxicity).

Chaitman BR. Efficacy and safety of a metabolic modulator drug in chronic stable angina: review of evidence from clinical trials. J Cardiovasc Pharmacol Ther 2004; 9 Suppl 1: S47-64. PubMed PMID: 15378131.

(Review of the efficacy and safety of sustained release ranolazine which results in significant improvement in angina and has modest side effects such as fatigue, dizziness, nausea and constipation and rarely syncope; "ranolazine does not cause deleterious changes in laboratory parameters").

Ranolazine (ranexa) for chronic angina. Med Lett Drugs Ther 2006; 48 (1236): 46-7. PubMed PMID: 16770296.

(Concise review of pharmacology, clinical efficacy, safety and costs of ranolazine shortly after its approval in the US; mentions side effects of constipation, nausea, dizziness and headache, but does not mention ALT elevations or hepatotoxicity).

Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the Ranolazine Open Label Experience (ROLE). J Am Coll Cardiol 2007; 49: 1027-34. PubMed PMID: 17349881.

(Among 746 patients with chronic angina treated with ranolazine [500 to 1000 mg twice daily] in an open label extension study for an average of 2.8 years, the drug was well tolerated and there was no mention of ALT elevations or clinically apparent liver injury).

Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, Wolff AA, et al.; MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007; 297: 1775-83. PubMed PMID: 17456819.

(Among 6580 patients with acute coronary syndrome treated with ranolazine [1000 mg twice daily] or placebo, there were no differences in acute or one year mortality and adverse events included dizziness [13% vs 7%], nausea [9% vs 6%], constipation [9% vs 3%] and syncope [3.3% vs 2.3%]; no mention of ALT elevations or hepatotoxicity).

Miles RH, Passman R, Murdock DK. Comparison of effectiveness and safety of ranolazine versus amiodarone for preventing atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2011; 108: 673-6. PubMed PMID: 21726841.

(Among 393 patients undergoing bypass grafting who were treated with either amiodarone or ranolazine for 14 days, there was a higher rate of atrial fibrillation with ranolazine [26.5% vs 17.5%]; no mention of changes in ALT levels during therapy).

Sendón JL, Lee S, Cheng ML, Ben-Yehuda O; CARISA study investigators. Effects of ranolazine on exercise tolerance and angina frequency in patients with severe chronic angina receiving maximally-tolerated background therapy: analysis from the Combination Assessment of Ranolazine In Stable Angina (CARISA) randomized trial. Eur J Prev Cardiol 2012; 19: 952-9. PubMed PMID: 22689417.

(In a post hoc analysis of a trial of 2 doses of ranolazine vs placebo in patients with chronic angina [Chaitman 2004] focusing upon patients receiving the maximally tolerated dose, ranolazine decreased angina symptoms and adverse events were similar to what has been previously published).

Sancho-del-Val L, Barrio-Andrés J, Herranz-Bachiller MT, Alcaide-Suárez N. Hepatotoxicity and insomnia secondary to ranolazine. Rev Esp Enferm Dig 2013; 105: 304-5. PubMed PMID: 23971665.

(63 year old woman with angina developed fatigue and serum enzyme elevations without jaundice 3 months after starting ranolazine, symptoms and liver tests improving once the drug was stopped: Case 1).

Aldakkak M, Stowe DF, Camara AK. Safety and efficacy of ranolazine for the treatment of chronic angina pectoris. Clin Med Insights Ther 2013; 2013: 1-14. PubMed PMID: 24574825.

(Review of safety and efficacy of ranolazine as therapy of angina discusses common side effects of dizziness, nausea, constipation, headache and fatigue and minor laboratory changes such as increases in creatinine and eosinophils and decreases in hematocrit and HbA1c levels; no mention of changes in ALT or hepatotoxicity).

De Ferrari GM, Maier LS, Mont L, Schwartz PJ, Simonis G, Leschke M, Gronda E, et al.; RAFFAELLO Investigators. Ranolazine in the treatment of atrial fibrillation: Results of the dose-ranging RAFFAELLO study. Heart Rhythm 2015; 12: 872-8. PubMed PMID: 25602175.

(Among 238 patients undergoing cardioversion for atrial fibrillation treated with ranolazine [375, 500 or 750 mg twice daily] or placebo, the 2 higher doses reduced recurrence of fibrillation; side effects included fatigue [16-17% vs 9% with placebo] and there were no liver related serious adverse events and "no significant changes in safety laboratory tests").

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury from the US enrolled in a prospective database between 2004 and 2012, none were attributed to ranolazine).

Alexopoulos D, Kochiadakis G, Afthonidis D, Barbetseas J, Kelembekoglou P, Limberi S, Spanos A, et al. Ranolazine reduces angina frequency and severity and improves quality of life: Observational study in patients with chronic angina under ranolazine treatment in Greece (OSCAR-GR). Int J Cardiol 2016; 205: 111-6. PubMed PMID: 26730841.

(Among 189 patients with chronic angina treated with ranolazine for 6 months, angina symptoms decreased and quality of life indices improved, while side effects were usually mild and "no adverse events involving routine laboratory values were reported").

Olivotto I, Camici PG, Merlini PA, Rapezzi C, Patten M, Climent V, Sinagra G, et al. Efficacy of ranolazine in patients with symptomatic hypertrophic cardiomyopathy: the RESTYLE-HCM randomized, double-blind, placebo-controlled study. Circ Heart Fail 2018; 11: e004124. PubMed PMID: 29321131.

(Among 80 adults with hypertrophic cardiomyopathy treated with ranolazine or placebo for 5 months, ranolazine had no overall effect on exerice performance or quality of life, but was well tolerated with similar rates of adverse events as with placebo and ALT elevations in only one treated subject).