U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Bile Acid Resins or Sequestrants. [Updated 2017 Sep 28].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Bile Acid Resins or Sequestrants

Updated: September 28, 2017.

OVERVIEW

The bile acid resins or sequestrants are the oldest and safest lipid lowering agents, but are less potent than other classes now available and are not always well tolerated. The bile acid sequestrants are highly positively charged molecules that bind to the negatively charged bile acids in the intestine, inhibiting their lipid solubilizing activity and thus blocking cholesterol absorption. They also inhibit the reabsorption of bile acids (which is typically 95%) and thus cause a contraction of the bile acid pool which leads to increased bile acid synthesis that competes with cholesterol synthesis in the liver, which also contributes to the lowering of serum cholesterol levels. Three bile acid sequestrants are available in the United States (common brand name and year of approval): cholestyramine (Questran, 1973), colesevelam (Welchol, 2000) and colestipol (Colestid, 1977). These agents are also used for therapy of pruritus for their activity in lowering the "pruritogens" that accumulate in cholestatic forms of liver disease. The bile acid resins are not absorbed and thus have not been linked to clinically apparent drug induced liver injury. They have the potential to bind to vitamins, hormones or medications in the intestine and result in subtherapeutic serum levels.

The bile acid resins have not been associated with clinically apparent acute liver injury, which is probably because of their lack of absorption. For unexplained reasons, however, therapy with these agents is associated with a low rate of mild (1 to 3 fold) serum aminotransferase and alkaline phosphatase elevations which are self-limited and not associated with symptoms or jaundice and resolve rapidly with stopping therapy.

Drug Class: Antilipemic Agents

Drugs in the Subclass, Bile Acid Resins/Sequestrants: Cholestyramine, Colesevelam, Colestipol

ANNOTATED BIBLIOGRAPHY

References updated: 28 September 2017

Zimmerman HJ. Drugs used in the treatment of hypercholesterolemia and hyperlipidemia. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 660-2.

(Expert review of hepatotoxicity published in 1999; cholestyramine has been mentioned as a cause of serum aminotransferase elevations, but "This is a curious phenomenon for a nonabsorbed drug").

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs. Lipid regulating agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 526-7.

(Review of hepatotoxicity of lipid lowering agents; the bile acid resins are not discussed).

Bersot TP. Drug therapy for hypercholesterolemia and dyslipidemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 877-908.

(Textbook of pharmacology and therapeutics).

The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251: 351-64. PubMed PMID: 6361299.

(Landmark trial of cholesterol lowering using cholestyramine for primary prevention of symptomatic coronary artery disease; patients on cholestyramine had higher serum AST levels that those on placebo during the first year of therapy; no hepatic serious adverse events or episodes of acute liver injury).

Di Padova C, Tritapepe R, Rovagnati P, Rossetti S. Double-blind placebo-controlled clinical trial of microporous cholestyramine in the treatment of intra- and extra-hepatic cholestasis: relationship between itching and serum bile acids. Methods Find Exp Clin Pharmacol 1984; 6: 773-6. PubMed PMID: 6397677.

(Placebo controlled trial of cholestyramine [3 g three times daily] in 10 patients with cholestasis; itching and bile acids were reduced, but no mention of serum enzymes or bilirubin levels).

The Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. JAMA 1988; 260: 359-66. PubMed PMID: 2898027.

(Controlled trial of lovastatin [20 or 40 mg/day] vs cholestyramine [16 g/day] for 12 weeks in 264 patients with hypercholesterolemia; mean ALT levels increased in cholestyramine treated patients and ALT levels >2 times normal occurred in 9% of cholestyramine vs 1% of lovastatin treated patients).

LaRosa J. Review of clinical studies of bile acid sequestrants for lowering plasma lipid levels. Cardiology 1989; 76 Suppl 1: 55-61. PubMed PMID: 2653624.

(Review of efficacy and safety of bile acid sequestrants; no mention of hepatotoxicity or serum enzyme elevations).

Stein E, Kreisberg R, Miller V, Mantell G, Washington L, Shapiro DR. Effects of simvastatin and cholestyramine in familial and nonfamilial hypercholesterolemia. Multicenter Group I. Arch Intern Med 1990; 150: 341-5. PubMed PMID: 2405804.

(Controlled trial of simvastatin [20 or 40 mg] vs cholestyramine [4-12 g/day] in 251 patients with hypercholesterolemia; "simvastatin was better tolerated", week 12 ALT levels were >1.5 times ULN in 7.1% of cholestyramine treated vs 2.4% and 8.6% of simvastatin treated; Alk P elevated in 13% vs none on simvastatin).

Pravastatin Multicenter Study Group II. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. Arch Intern Med 1993; 153: 1321-9. PubMed PMID: 8507122.

(Controlled trial of pravastatin vs cholestyramine vs both in 311 patients with hyperlipidemia treated for 8 weeks found that ALT elevations occurred in 21% of patients receiving cholestyramine alone and average ALT levels rose by 25%).

Ito MK, Shabetai R. Pravastatin alone and in combination with low-dose cholestyramine in patients with primary hypercholesterolemia and coronary artery disease. Am J Cardiol 1997; 80: 799-802. PubMed PMID: 9315597.

(Controlled trial of pravastatin alone vs combination with cholestyramine [10 g/day] for 18 weeks in 59 patients with hypercholesterolemia; there was a 44% increase in mean ALT levels in the combination group vs 8% increase in the pravastatin only group).

Davidson MH, Dillon MA, Gordon B, Jones P, Samuels J, Weiss S, Isaacsohn J, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. Arch Intern Med 1999; 159: 1893-900. PubMed PMID: 10493319.

(Controlled trial of colesevelam [4 dosages] vs placebo for 6 weeks in 149 patients with hypercholesterolemia; fatigue, flatulence, constipation and dyspepsia were most common adverse events; mean ALT and Alk P increased in some dosage groups, but there were no clinically significant changes, jaundice or symptoms).

Sirmans SM, Beck JK, Banh HL, Freeman DA. Colestipol-induced hepatotoxicity. Pharmacotherapy 2001; 21: 513-6. PubMed PMID: 11310528.

(65 year old man developed marked serum aminotransferase elevations [ALT 593 U/L] without symptoms or increases in Alk P [105 U/L] or bilirubin [0.6 mg/dL] 27 weeks after starting colestipol [10 g/day], resolving within a week of stopping; also on acetaminophen).

Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis 2001; 158: 407-16. PubMed PMID: 11583720.

(Controlled trial of atorvastatin vs colesevelam vs the combination in 94 patients with hypercholesterolemia; mild increases in ALT and Alk P occurred in all three groups).

Aldridge MA, Ito MK. Colesevelam hydrochloride: a novel bile acid-binding resin. Ann Pharmacother 2001; 35: 898-907. PubMed PMID: 11485143.

(Review of pharmacology, efficacy and side effects of colesevelam; no serious adverse events have been reported; minor increases occur in ALT and Alk P, but average values remain in the normal range).

Knapp HH, Schrott H, Ma P, Knopp R, Chin B, Gaziano JM, Donovan JM, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med 2001; 110: 352-60. PubMed PMID: 11286949.

(Controlled trial of simvastatin vs colesevelam vs the combination vs placebo in 241 patients with hypercholesterolemia; "no clinically notable changes in chemistry or hematology values").

Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology 2005; 129: 894-901. PubMed PMID: 16143129.

(Controlled trial of ursodiol vs cholestyramine [8 mg/day] for 2 weeks in 84 women with intrahepatic cholestasis of pregnancy; serum ALT levels fell in ursodiol, but increased slightly in cholestyramine treated patients as did Alk P to a lesser extent).

Kawashiri MA, Higashikata T, Nohara A, Kobayashi J, Inazu A, Koizumi J, Mabuchi H. Efficacy of colestimide coadministered with atorvastatin in Japanese patients with heterozygous familial hypercholesterolemia (FH). Circ J 2005; 69: 515-20. PubMed PMID: 15849435.

(Open label study of atorvastatin followed by addition of colestimide in 15 patients with severe hypercholesterolemia; no changes in ALT or Alk P during therapy and no serious adverse events).

Bhardwah SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. Clin Liver Dis 2007; 11: 597-613. PubMed PMID: 17723922.

(Review of hepatotoxicity of lipid lowering agents: bile acid resins are mostly safe for the liver; mentions the case report of anicteric hepatitis due to colestipol [Sirmans 2000]).

Davidson MH. The use of colesevelam hydrochloride in the treatment 0f dyslipidemia: a review. Expert Opin Pharmacother 2007; 8: 2569-78. PubMed PMID: 17931091.

(Review of structure, pharmacology, mechanism of action, efficacy and safety of colesevelam; colesevelam has less side effects and fewer drug interactions than cholestyramine, no mention of changes in serum enzymes or hepatotoxicity).

Stein EA, Marais AD, Szamosi T, Raal FJ, Schurr D, Urbina EM, Hopkins PN, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. J Pediatr 2010; 156: 231-6. PubMed PMID: 19879596.

(Controlled trial of colesevelam vs placebo in 194 children with hypercholesterolemia; side effects were mild and largely gastrointestinal; "there were no clinically meaningful changes in safety laboratory measurements").

Kuiper EM, van Erpecum KJ, Beuers U, Hansen BE, Thio HB, de Man RA, Janssen HL, et al. The potent bile acid sequestrant colesevelam is not effective in cholestatic pruritus: results of a double-blind, randomized, placebo-controlled trial. Hepatology 2010; 52: 1334-40. PubMed PMID: 20683930.

(Controlled trial of colesevelam vs placebo for 3 weeks in 35 patients with pruritus due to chronic liver disease found a reduction in bile acid levels, but no change in pruritus; no mention of changes in serum enzymes).

Goldfine AB, Fonseca VA, Jones MR, Wang AC, Ford DM, Truitt KE. Long-term Safety and Tolerability of Colesevelam HCl in Subjects with Type 2 Diabetes. Horm Metab Res 2010; 42: 23-30. PubMed PMID: 19862667.

(A 52 week open label extension of trial of colesevelam in 509 patients with type 2 diabetes; 1 patient [0.2%] had ALT and 2 [0.4%] had AST elevations >3 times ULN, but these resolved without complications, with or without stopping colesevelam).

Le TA, Chen J, Changchien C, Peterson MR, Kono Y, Patton H, Cohen BL, et al.; San Diego Integrated NAFLD Research Consortium (SINC). Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology 2012; 56: 922-32. PubMed PMID: 22431131.

(Controlled trial of 24 weeks of colesevelam vs placebo in 50 patients with nonalcoholic steatohepatitis found that colesevelam therapy was associated with a small increase in ALT [22.5 U/L], Alk P [8 U/L] and hepatic fat [14.2-17%], but decrease in serum cholesterol and no change in weight).

Singhal R, Harrill AH, Menguy-Vacheron F, Jayyosi Z, Benzerdjeb H, Watkins PB. Benign elevations in serum aminotransferases and biomarkers of hepatotoxicity in healthy volunteers treated with cholestyramine. BMC Pharmacol Toxicol 2014;15:42. PubMed PMID: 25086653.

(Among 67 healthy adult volunteers given placebo followed by cholestyramine [8 g daily] for 11 days, serum ALT levels rose above 3 times ULN in 11 subjects, starting 3 days into treatment, peaking at 119-967 U/L [3.5 to 28 times ULN], occurring without symptoms, jaundice or bilirubin elevations, and resolving within 2 weeks of stopping).

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, none were attributed to a bile acid resin).