

Chapter 26

OTHER LIPID LOWERING AGENTS

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Bile Acid Sequestrants

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- Indications
- Contraindications
- Side Effects
- Dosage

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- Rosuvastatin
- Ezetimibe
- Torcetrapib
- Cannabinoid receptor antagonist (Rimonabant)

NICOTINIC ACID (NIACIN)

- Niacin (nicotinic acid) improves all lipoprotein abnormalities.
- It significantly reduces LDL-cholesterol, triglyceride levels, while increasing HDL-C levels.
- Niacin-induced changes in serum lipid levels produce significant improvements in both CAD and clinical outcomes.
- Niacin is the most effective pharmacologic agent currently on the market for raising HDL-C levels.
- Most of the rise in HDL-C with niacin occurs at daily doses of 1 to 1.5 gram. There is a relatively flat dose-response curve.
- Niacin effects on lipid levels have been shown to be additive when combined with other lipid-altering therapies.

PREPARATIONS

- Immediate-release: crystalline nicotinic acid.
- Slower-release (extended release)- absorption over 8-12 hr: Niaspan.

MECHANISM OF ACTION

Not clear

- Inhibits lipolysis in adipose tissue, leading to a decreased formation and transport of FFAs to the liver and reduced VLDL production.
- Inhibits hepatic synthesis or secretion of apo B-containing lipoproteins.

THERAPEUTIC EFFICACY

Lipid profile

- Most effective available drug for raising HDL-C.
- Increases HDL-C by 15-35%.
- Reduces LDL-C by 5-25%.
- Reduces triglycerides by 20-25%.

Cardiovascular events

- Reduction of total mortality by 11%.
- In combination with statins: reduces coronary stenosis progression.

INDICATIONS

- Metabolic syndrome dyslipidemia (low HDL-C, elevated TG, small dense LDL-C). When there is an elevated LDL-C, nicotinic acid should be combined with statins or other lipid lowering agent.
- Low HDL-C.
- Mixed hyperlipidemia: niacin should be combined with other lipid lowering agents.
- Familial and non familial hypercholesterolemia – should be combined with statin.

CONTRAINDICATIONS

1. Hypersensitivity.
2. Liver disease – jaundice.
3. Severe gout.
4. Peptic ulcer.

Relative Contraindications

1. Diabetes mellitus – significant glucose intolerance.
2. Gall bladder disease.
3. Hyperuricemia.
4. Inflammatory bowel disease.

LIMITATIONS AND SIDE EFFECTS

- Flushing.
- Skin itching.
- Gastrointestinal irritation.
- Hyperuricemia.
- Hepatotoxicity: more common with sustained-release preparations and with higher doses. Liver damage presents as markedly increased transaminases and jaundice.

- All the above side effects are less common with slow release preparation (niaspan).

DOSAGES

Crystalline nicotinic acid:

- 1.5 to 3.0 gm/day – maximum 4.5 gm/day in divided doses 3 times/day.

Extended release nicotinic acid (Niaspan):

- 1-2 gm/day – maximum 2 gm/day. Given once before bed time.

INITIATION AND MONITORING

- Initiate therapy at low doses.
- Premedicate with aspirin (325 mg enteric coated) or ibuprofen (200 mg) 30 min before nicotinic acid is taken.
- Nicotinic acid should be taken with meals.
- Baseline determinations and follow-up of plasma glucose, serum uric acid and serum transaminase and alkaline phosphatase.
- Testing should be done at:
 - 6-8 weeks interval after a change in dose.
 - Every 3-6 months when the dosage is stable.
- With the exception of Niaspan, nicotinic acid is usually administered in two or three doses a day.
 - Niaspan is taken once at bed time after a low-fat snack. Daily dosage should not be increased by more than 500 mg in any 4-week period.

FIBRIC ACID DERIVATIVES

PREPARATIONS

- Gemfibrozil.
- Fenofibrate.
- Bezafibrate.

MECHANISM OF ACTION

Complex and not clear.

- Down-regulate the apo C-III gene.
- Up-regulate genes for apo A-I, fatty acid transport protein, fatty acid oxidation and LPL.
- These actions enhance the catabolism of TGRL and decrease the formation of TGRL TG.
- Reduction in plasma TG and increased synthesis of apo A-I and apo A-II tend to raise HDL-C.

Molecular basis of mechanism of action

Fibrates are agonists for peroxisome proliferator-activated receptor α (PPAR- α), a member of the nuclear hormone receptor family. PPAR- α regulates gene transcription of a number of apolipoproteins.

Non-lipid Actions

- Inhibition of coagulation.
- Enhancement of fibrinolysis.
- Reduction in plasma fibrinogen.
- Decrease platelet activity.
- Decrease insulin resistance.
- Increase in plasma homocysteine.

THERAPEUTIC EFFICACY

- Lipid profile
 - Reduction in plasma TG by 20-50%.
 - Increase in HDL-C by 10-20%.
 - Effect on LDL-C is variable from marked decrease to a marked increase (particularly when TG is significantly lowered).
- Cardiovascular events
 - Reduction in coronary events and a stroke in men with low HDL-C (gemfibrozil).
 - No evidence for improvement in overall survival.

INDICATIONS

- Combined hyperlipidemia, fibrates should be combined with statins.
- Hypertriglyceridemia.
- Type IIb hyperlipidemia: elevated LDL-C and TG and reduced HDL-C.
- Dysbetalipoproteinemia.
- Metabolic syndrome dyslipidemia.

CONTRAINDICATION

- Hepatic dysfunction.
- Severe renal impairment and diabetic nephropathy.
- Gall-bladder disease.

SIDE EFFECTS

Side effects are uncommon and include:

- Upper gastrointestinal disturbances.
- Headache, anxiety, fatigue, sleep disorders.
- Myalgia.
- Reversible myopathy with elevation of CK is rare, but is more likely when there is impairment of renal function.

DRUG INTERACTION

- Potentiation of the effects of warfarin-type oral anticoagulant and of oral hypoglycemic agents.
- Combinations with statins increase the risk of myopathic complications.

Patients receiving this combination (fibrates+ statins) should:

- Have normal renal function.
- Educated about symptoms of myopathy.
- CK measured before therapy or if there are symptoms of myopathy. If CK exceeds 10 times the upper limit of normal with muscle symptoms, drug therapy should be stopped.
- Liver enzymes should be monitored:
 - After the initiation of fibrate therapy.
 - At 4 to 6 months intervals.

DOSAGE

- Gemfibrozil: 600 mg bid 30 min before meals.
- Fenofibrate: 150 mg bid.

- Bezafibrate: - sustained release tablet - 400 mg once daily.
 - Standard tablet - 200 mg bid or tid.

BILE ACID SEQUESTRANTS

(Anion Exchange Resins)

PREPARATIONS

- Cholestyramine.
- Colestipol.
- Colesevelam.

MECHANISM OF ACTION

- Bind bile acids in the gut, increasing the bile salts fecal excretion.
- Decreased bile acid reabsorption leads to an increased flux of intrahepatic cholesterol into the production of bile acids.
- Decreased intrahepatic cholesterol results in increased expression of high-affinity LDL receptors on liver cell membranes. This effect leads to increased removal of LDL particles from plasma.

THERAPEUTIC EFFICACY

- Lipid profile
 - LDL-C reduction by 15-30%.
 - HDL-C increase by 3-5%.
 - TG no change or increase (particularly in hypertriglyceridemic patients).
- Cardiovascular events
 - Primary prevention:
 - Reduction in incidence of MI or CAD death by 19%.
 - Reduction of new onset angina by 20%.
 - Reduction in need of CABG by 21%
 - Secondary prevention: colestipol combined with either lovastatin or nicotinic acid- reduction in incidence of cardiovascular events by 25%.

INDICATIONS

Used as adjuncts to other lipid-lowering drugs. Combined with statins in refractory hypercholesterolemia in order to achieve LDL-C therapeutic goal.

Whereas doubling the dose of statin may produce only a 6% additional reduction in LDL-C, adding a sequestrant may reduce LDL-C by an additional 12-16%.

CONTRAINDICATIONS

1. Biliary obstruction.
2. Type III hyperlipidemia.
3. Fasting TG greater than 400 mg/dl.

SIDE EFFECTS

- Sequestrants are very safe drugs. They are not absorbed from gastrointestinal tract. They have little or no systemic toxicity.
- Chief side effects are gastrointestinal including:
Constipation, bloating, epigastric fullness, indigestion, nausea and flatulence.
- Colesevelam is better tolerated than other sequestrants
- They decrease absorption of fat soluble vitamins increasing bleeding tendency.
- They reduce or delay absorption of warfarin, thiazide diuretics, tetracyclines, propranolol, digitalis, NSAIDs, and statins.

DOSAGE

- Cholestyramine: 4-16 gm/day (maximum 24 gm).
- Colestipol (packets): 5-20 gm/day (maximum 30 gm).
- Colesevelam (tablets): 2.6-3.8 gm/day (maximum 4.4 gm).

Drugs are effective at lower dosages. Increasing the dose may have little effect on LDL-C reduction.

NEW AGENTS

Rosuvastatin

- A very effective new statin that enables more patients to achieve their LDL-cholesterol targets than commonly used doses of other statins.
- When compared with other statins (atorvastatin, simvastatin and pravastatin) rosuvastatin achieved a superior LDL cholesterol reduction at both 8 and 16 weeks across the dose range. It causes 40 to 65% reduction in LDL-C.
- Increases in HDL-C and decreases in triglycerides levels were greater with rosuvastatin than with other statins.
- Starting dose is 5-10 mg/day which achieve LDL-C reduction similar to 40-80 mg atorvastatin and 80 mg simvastatin.
- Fewer dose titrations are needed. Dose can be increased to 40 mg/day.
- It is hydrophilic, avoids cytochrome P450 pathway metabolism with limited drug interactions.
- Switching to a more effective statin is a successful strategy in improving lipid goal achievement in high-risk patients.

Ezetimibe

- A potent and selective inhibitor of cholesterol absorption in the small intestine. Both dietary cholesterol as well as that entering the intestine from the liver through the bile excretion are not absorbed.
- Reduction in cholesterol delivery to the liver induces the synthesis of LDL-C receptors resulting in increased removal of LDL-C from plasma.
- Optimal dose is 10 mg which is associated with 16-20% reduction in LDL-C.
- It undergoes glucuronidation and is returned through the bile into the intestine where it is avidly reabsorbed.
- It is used in combination with statins in refractory hypercholesterolemia, and to reach target LDL-C.
- Ezetimibe has an anti-inflammatory action, it reduces CRP levels.

Torcetrapib

- Cholesterol ester protein (CETP) inhibitor.
- It markedly increases high-density lipoprotein cholesterol (HDL-C) levels.
- CETP is a plasma glycoprotein that facilitates the transfer of cholesterol esters from HDL-C and LDL-C to TG rich lipoprotein. Triglycerides are transferred simultaneously in the reverse direction to HDL and LDL.

- Torcetrapid when given as monotherapy to patients with low HDL-C (< 40 mg/dl) for 4 weeks it increased HDL-C by 46% when compared with placebo and by 106% after 8 weeks. It decreased LDL-C by 17 %.
- Dose: 120 mg/day.
- CETP inhibitors hold great promise as a new class of drugs, when combined with statins they have the potential of reducing the risks of cardiovascular events.

Experimental Therapies to Increase HDL-C.

- *Therapies that increase HDL-C through infusion of apolipoprotein A-1 phospholipid complexes induced regression of coronary atherosclerosis.*

Cannabinoid Receptor Antagonist

Rimonabant

- Rimonabant is the first selective cannabinoid type 1 (CB₁) receptor antagonist.
- It proved effective in reduction of body weight and waist circumference as well as a substantial increase in HDL-cholesterol and significant reduction in triglyceride levels.
- The endocannabinoid system is present in the brain (mainly hypothalamus and mesolimbic system) and peripheral tissues (adipocytes) and is involved in the control of energy balance and body weight.
- Patients treated with rimonabant 20 mg/day for 1 year showed a significant increase in HDL-cholesterol and reduction in triglycerides levels compared with placebo.
- This improvement in both HDL-C and triglycerides was independent from the loss of body weight. An improved insulin response was also observed.
- Side-effects were mainly mild and transient and included nausea, diarrhea and dizziness.
- Rimonabant seems to be particularly indicated in patients with the metabolic syndrome.
- Rimonabant proved effective in helping patients quitting smoking and markedly reduced post-cessation weight gain.

REFERENCES AND SUGGESTED READINGS

1. Ahsan CH, Shah A, Ezekowitz M. Acute statin treatment in reducing risk after acute coronary syndrome: the MIRACL (myocardial ischemia reduction with aggressive cholesterol lowering) trial. *Current Opinion in Cardiology* 2001; 16:390-393
2. Aronow HD, Topol EJ, Roe MT, et al. Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet* 2001;357:1063-68
3. Ballantyne CM. Achieving greater reductions in cardiovascular risk: lessons from statin therapy on risk measures and risk reduction. *Am Heart J* 2004;148:S3-8
4. Brewer HB, Bethesda. Focus on high-density lipoproteins in reducing cardiovascular risk. *Am Heart J* 2004; 148:SI 4-8
5. Brown WV. Novel approaches to lipid-lowering: what is on the horizon? *Am J Cardiol* 2001; 87[*suppl*]:23B-27B
6. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes. *JAMA* 2004;292:1307-1316
7. Ferdinand KC. Coronary heart disease and lipid-modifying treatment in African American patients. *Am Heart J* 2004; 147:774-82
8. Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent trials for the national cholesterol education program adult treatment Panel III guidelines. *Circulation* 2004;110:227-239
9. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein and apolipoprotein B as targets of lipid-lowering therapy. *Circulation* 2002;106:2526-2529
10. Huse DM, Russell MW, Miller JD, et al. Cost-effectiveness of statins. *Am J Cardiol* 1998;82: 1357-1363
11. Jones PH. Statins as the cornerstone of drug therapy for dyslipidemia: monotherapy and combination therapy options. *Am Heart J* 2004;148:S9-13
12. Kastelein JJ.P., Stroes ESG., de Groot E. Subclinical atherosclerosis as a target of therapy: potential role of statins. *Am J Cardiol* 2004;93:737-740
13. Kayikcioglu M, Payzin S, Yavuzgil O, et al. Benefits of statin treatment in cardiac syndrome-X. *Euro Heart J* 2003; 24:1999-2005
14. Kearney D, Fitzgerald D. The anti-thrombotic effects of statins. *JACC*. 1999;33:1305-7
15. Kinlay S, Selwyn AP. Effects of Statins on inflammation in patients with acute and chronic coronary syndromes. *Am J Cardiol* 2003; 91(*suppl*): 9B-13B
16. Knatterud GL, Rosenberg Y, Campeau L, et al. Long -term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass Graft trial. *Circulation*.2000;102:157-165
17. Kon Koh KW, Won Son J, Yeul Ahn J, et al. Non-lipid effects of statin on hypercholesterolemic patients established to have coronary artery disease who remained hypercholesterolemic while eating a stepp-II diet. *Coronary Artery Disease* 2001;12:305-311
18. McKenney J. New perspectives on the use of Niacin in the treatment of lipid disorders. *Arch Intern Med*.2004;164:697-705
19. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*.2004;291:1071-1080
20. O'Keefe JH, Cordain L, Harris WH, et al. Optimal low-density lipoprotein is 50 to 70 mg/dl. *JACC*.2004;43(11):2142-6
21. Riesen WF, Darioli R, Noll G. Lipid-lowering therapy: strategies for improving compliance. *Curr Med Res Opin* 2004; 20(2):165-173
22. Schaefer EJ, McNamara JR, Tayler T, et al. Comparisons of effects of statins (atovastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects. *Am J Cardiol* 2004; 93:31-39
23. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711-1718

24. Shah PK. Low-density lipoprotein lowering and atherosclerosis progression. *Circulation* 2002;106:2039
25. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001;285:430-436
26. Tiefenbacher CP, Friedrich S, Bleeke T, et al. ACE inhibitors and statins acutely improve endothelial dysfunction of human coronary arterioles. *Am J Physiol Circ Physiol* 2004; 286: H1425-H1432