Hypolipidemic Drugs

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Introduction

- Cardiovascular & cerebrovascular ischemic diseases are leading cause of morbidity & mortality.
- Dyslipidaemia is the major cause of ischemia.
- Hypolipidaemic drugs lower the levels of lipids & lipoproteins in blood.
- Lipids are transported in plasma in lipoproteins, which are associated with several proteins called as apoproteins.

Lipoproteins are divided based on their particle size & density .

Table 45.1: Characteristics and function of plasma lipoproteins

	Lipoprotein class	*Diameter (nm)*	*Lipid contained*	*Source of lipid*	*Function*
1.	Chy.	100–500	TG >> CHE	Diet	Dietary TG transport
2.	Chy. rem.	30–50	CHE>> TG	Diet, Chy.	Dietary CH transport
3.	VLDL	40–80	TG >> CHE	Liver	Endogenous TG transport
4.	IDL	30–35	CHE ≥ TG	VLDL	Transport CHE & TG to liver, source of LDL
5.	LDL	20–25	CHE	IDL	Transport CH to tissues and liver
6.	HDL	5–10	Phospholipid, CHE	Tissues, cell memb.	Removal of CH from tissues

Lipoprotein disorders

- LDL transport CH for peripheral utilization .
- Excess CH gets deposited in arterial wall as atheroma & in skin as xanthoma.

- Hyperlipoproteinaemias can be classified as

1. **Primary:**
   - Familial/genetic due to single gene defect
   - Multifactorial/polygenic

2. **Secondary:** associated with diseases & drugs.

Pharmacotherapy

Classification:

1. HMG-CoA Reductase inhibitors: (Statins)
   - Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Pitavastatin
2. Bile acid binding resins:
   - Cholestyramine, Colestipol, colesevelam.
3. Sterol absorption inhibitor: Ezetimibe, Gugulipid
4. Newer drugs (CEPT inhibitors):
   - Torcetrapib, Anacetrapib.

5. Activators of LPL: (PPAR activators Fibrates)
   - Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate
6. Inhibitors of lipolysis & TG synthesis
   - Nicotinic acid (Niacin)
7. Miscellaneous agents
   - Gugulipid & fish oil derivatives.

- These are 2nd line lipid lowering agents.
- More effective in lowering TGL & VLDL.

HMG-CoA Reductase inhibitors: (Statins)

MOA:

- ↓[se] cholesterol synthesis by competitively inhibiting rate limiting HMG CoA reductase.

HMG CoA

↓ statins - HMG CoA reductase

Mevalonic acid

↓

↓[se] cholesterol synthesis Compensatory ↑[se] in

↓

LDL receptor expression in liver

- Statins differ in their potency & max efficacy in reducing LDL cholesterol.
- Statins shows the ceiling effect due to compensatory induction of HMG CoA reductase.
- Dose - dependent lowering of LDL – CH is seen.
- TG $\downarrow^{se}$ by 10-30 % due to fall in VLDL.
- Statins use also causes rise in HDL (5-15%).
- HMG – CoA reductase activity is maximum at midnight, all statins are administered at Bed time.
- Except rosuvastatin all are metabolized by CYP3A4.

Lovastatin:

- It is lipophilic & given in precursor form (lactone) absorption is incomplete & 1st pass metabolism is extensive.
- Dose: 10-40 mg/day (max 80 mg).

Simvastatin:

- More efficacious & twice potent than lovastatin. It is also lipophilic & given in lactone precursor form.
- Dose: 5-20 mg/day (max 80 mg).

Pravastatin:

- It is hydrophilic & given in active form. It also causes decrease in plasma fibrinogen level.
- Dose: 10-20 mg.

Atorvastatin:

- Newer statin, good LDL – CH lower effect. It has much longer t ½ (18-24hrs). It has additional anti-oxidant property.
- Dose: 10-40 mg/day (max 80 mg)

Rosuvastatin:

- Latest & most potent statin. t ½ - 18 – 24 hrs. It raises maximum HDL level compare to other statin.
- Dose: 5-20 mg/day max 40 mg/day.

Pitavastatin:

- Latest & most potent statin.
- Combination with gemfibrozil is avoided , $\downarrow^{se}$ clearance.
- Dose: 1-4 mg/day.

Adverse effects:

- Headache,
- Sleep disturbance,
- Raise serum transaminase,
- Muscle tenderness & rise in CPK levels.
- Myopathy (<1/1000) is the only serious A/E, it is more when given along with nicotinic acid / gemfibrozil/ CYP3A4 inhibitors e.g ketoconazole.
- Fenofibrate is safe for combining with statins.
- Statins should be avoided in pregnant women.

Uses:

- ✓ 1st choice in primary (↑LDL, TCH-IIa, IIb, V) & secondary hyper lipidaemias.
- ✓ It decreases CVS mortality by decreasing raised LDL level.
- ✓ Improved coronary compliance and atheromatous plague stabilization.
- ✓ Improvement in endothelial function & increased NO production.
- ✓ They are the 1st choice drugs for dyslipidaemia in diabetics.

Bile acid binding resins

- Bile acids (BA) are synthesized in the liver from CH.
- Secreted in the duodenum aids dietary fat absorption. Undergoes EHC.

MOA:

- Non-absorbable anion exchange resins that complex with negatively charged bile acids in SI.
- Resin+ BA complex gets excreted through feces.
- Biosynthesis of BA from CH increases, leads to partial depletion of hepatic CH pool.
- Unsutable as monotherapy for long term use.

- Cholestyramine, colestipol & colesevelam
- Drugs of choice for- type IIa, type IIb- with niacin.
- Pruritis in pt with cholestasis,
- Digitalis toxicity

Dose:

- Cholestyramine, colestipol (16g daily)- granules.
- Mixed with water or juice taken with meals.
- Colesevelam- 625mg tablet, 6 tablets/day

AE

- Constipation , exc of hemorrhoids, GIT distress.
- Absorption of fat sol vit & folic acid impaired.

Lipoprotein lipase activators (Fibrates)

- **Activate lipoprotein lipase (which degrades VLDL) thus lowering circulating TGs level.**
- **Effect is exerted through *peroxisome proliferator activated receptor α (PPAR- α).***

  enhances lipoprotein lipase activity & synthesis.
- **PPAR □ also enhances LDL receptor expression.**
- **This class primarily lower TGs (20 – 50%).**
- **10 –15% decrease in LDL & 10 –15 % increase in HDL is also seen.**

Gemfibrozil:

- Apart from main action it causes suppression of hepatic synthesis of TGs. Additional actions include decreasing level of clotting factor ***VII phospholipid complex*** and ***promotion of fibrinolysis*** (antiatherosclerotic effect)

A/E : GI distress, eosinophilia, impotence and blurred vision. Myopathy is uncommon. C/I in pregnancy.

Uses: 600mg BD before meals is used to treat increased TGs & acute prancreatitis in hypertriglyceridaemia (III, IV & V).

Bezafibrate :

$_2^{nd}$ generation fibric acid derivative & alterative to gemfibrozil in (type III, IV & V).

- Has greater LDL lowering action than gemfibrozil.
- Combination with statin not found to increase risk of rhabdomyolysis.
- A/E are less (G.I. upset, rashes etc). Action of anticoagulant is increased.

Fenofibrate:

2nd generation prodrug of fibric acid derivative.

- Apart from decreasing TGs. It also cause moderate decrease in LDL & increase in HDL levels.

- Longer t ½ (20hrs) hence given OD. Cholelithiasis & rhabdomyolysis is rare (won't potentiate statin induced myopathy).

Lipolysis & TG synthesis inhibitors

Nicotinic acid (Niacin-vit B3)

- ↓[se] VLDL, LDL & LP(a), ↑[se] HDL-CH & inexpensive.

MOA:

Strongly inhibits lipolysis in adipose tissue

↓

Reduced levels of circulating FFAs

↓

↓[se] TG synthesis

↓

↓[se] VLDL & LDL

- ↓[se] catabolism of Apo-I, hence ↑[se] HDL levels.
- Boosts secretion of tissue plasminogen activator & lowers plasma fibrinogen

Uses

- Type IIb & IV.
- Pts with ↑[se] risk of CHD.

AE

- Cutaneous flush & pruritis. In first 14 days. Reduced by premedication with low dose aspirin.
- Cholestasis, hyperuricaemia & hepatic dysfunction.

Sterol absorption inhibitor (Ezetimibe)

1. Inhibit cholesterol absorption by interfering with specific CH transport protein (***NPC1L1***) in intestinal mucosa.
2. Both dietary & biliary CH level decreases.
3. Compensatory increased in CH synthesis take place (blocked by statin & hence good combination).
4. Weak hypolipidaemic drug (LDL ↓by 15 -20 %) when given alone.
5. Hepatic dysfunction & myositis are rare S/Es.

CEPT Inhibitors

- Cholesteryl ester transfer protein (CEPT) facilitates transfer of CE from HDL TO LDL & VLDL.
- In 2004 two CEPT inhibitors are developed.
- Torcetrapib & anacetrapib.
- Anacetrapib ↑ HDLby 129%with statin like ↓ in LDL
- CEPTinhibition potential target for ↑ HDL.

Gugulipid

- Developed at Central Drug Research Institute, Lucknow.
- Contains Z & E gugulsterones isolated from guggul gum.
- Inhibits CH biosynthesis & enhances its excretion.
- Dose: 25mg tablet TDS
- ↓ TCH, LDL, ↑HDL & modest lowering of TG.
- Well tolerated, loose stools are only side effect.

Fish oil derivatives (Omega-3 fatty acids)

- Contains poly unsaturated fatty acids (PUFA).
- Eicosa-pentanoic & docosa-hexanoic acids.
- Used for prophylaxis in high risk pt of CAD with hyperlipidaemia.
- Membrane stabilizing & antioxidant action.
- Usually formulated with Vit-E.

Guidelines on the use of hypolipidemic drugs

Table 241–1. Major Risk Factors (Exclusive of LDL Cholesterol) that Modify LDL Goals	
Cigarette smoking	
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)	Physical inactivity
Low HDL cholesterol* [<1.0 mmol/L (<40 mg/dL)]	Atherogenic diet
	Emerging risk factors
Diabetes mellitus	Lipoprotein(a)
Family history of premature CHD	Homocysteine
CHD in male first-degree relative <55 years	Prothrombotic factors
CHD in female first-degree relative <65 years	Proinflammatory factors
Age (men ≥45 years; women ≥55 years)	Impaired fasting glucose
Lifestyle risk factors	Subclinical atherosclerosis
Obesity (BMI ≥30 kg/m^2)	

Plasma lipid levels (mg/dl)				
	Total CH	**LDL CH**	**HDL CH**	**TGs**
Optimal	<200	<100 <70 CAD	>40(M) >50 (W)	<150
Borderline high	200-239	130-159	-	150-199
High	≥240	160-189	>60	200-499
V.high	-	≥190	-	≥500

Thank you