Pharmacology team

Anti hyperlipidemic agents

Contents:

*Explanation

*Questions

دعوة بظهر الغيب تكفي عن جزيل كلمات الشكر

ANTIHYPERLIPIDEMIC AGENTS

1. **Inhibits cholesterol absorption in the intestine** Ezetimibe
2. **Sequester bile acids in the intestine** Exchange resins
1. **Inhibits synthesis of cholesterol** Inhibitors of hydroxymethylglutaryl coenzyme A reductase (HMG-COA Reductase)
2. **Alter relative levels & patterns of different plasma LPs** Fibrates, Nicotinic acids

ADJUVANT AGENTS
Omega-3-Fatty Acids, Stanols

Targeting Exogenous Pathways:

1. Inhibition of Cholesterol Absorption in Intestine
   - *Selective C Transporter Inhibitors;* ***Ezetimibe***
2. Sequester Bile Acids in Intestine
   - *Sequestrants;* ***Colestipol****, &* ***Cholestyramine****,* ~~*Colesevelam*~~

The doctor said only memorize the first two

Ezetimibe **Is a selective C absorption inhibitor**		
Mechanism	Blocks sterol transporter (NPC1L1) → ↓ pool of cholesterol available to the liver → upregulate LDL receptor (which collect cholesterol from the circulation)	
Pharmacological action *(don't memorize the numbers just know what which drug work best on what)*	**↓LDL 20%** (54% of intestinal cholesterol + phytosterol absorption are blocked) **↓ TG 8%** **↑ HDL 1-4%** To sum up it works more on cholesterol and LDL (no effect on steroids, lipid-soluble vitamins, bile a)	
Pharmacokinetics	• **Absorbed & conjugated in intestine to active glucuronide (> potent)** • Reaches peak blood level in 12–14 hours • Its half-life is 22 hours • **Undergoes enterohepatic circulation (prolong action of drug)** • 80% of the drug is excreted in feces **N.B.** ***Drug level ↑ if with statins & ↓ if with cholystyramine*** (Bile Acid Sequestrant)	
Indications	Monotherapy: • **Pry prevention of low risk of CHD[1]** *(need modest ↓LDL)* • Statin-intolerant patients	Combination Therapy: -With statins; synergistic In moderate/severe ↑ LDL. -Or If must ↓ statin dose because of side effects. -Or With other lipid lowering drugs; As fibrates
ADRs & Interactions	Not common. GIT disturbance, headache, fatigue, artheralgia & myalgia. Seldom reversible impairment of hepatic function	

[1] CHD: Coronary Heart Disease

Bile Acid Sequestrants (Cholestyramine, Colestipol)

Are polymeric cation exchange resins

Mechanism	Bind bile acids [BA] → preventing their enterohepatic recycling & ↑ fecal excretion (10 folds). → "so in liver → ↓BA → ↓ C absorption & its ↑ hepatic breakdown" → compensatory ↑LDL Receptors → ↓LDL	
Pharmacological action	↓LDL 15-30% ↑ HDL 3-5% ↑ TG & VLDL (initial & transient) but **show marked ↑ in type IIb Hyperlipoproteinemia "Mixed hyperlipidemia"**	
Indications	**A. In Hyperlipidemia** **1- Monotherapy:** Seldom given Only if **statin is contraindicated** & LDL & TG levels are not too high **2- Combination:** with **statins in type IIa Hyperlipoproteinemia**. Statins acts in synergism to ↑ LDL Receptors + ↓ LDL levels **N.B.** ***Resins must be taken with meals / lack effect if between meals***	**B. Other Indications:** ◆ **Pruritus** due to biliary stasis ◆ **Digitalis poisoning**
ADRs	◆ ↑ GIT bloating, diarrhea, constipation, dyspepsia ◆ ↓ Absorption of **fat soluble vitamins** *(A, K, E, D) 'أكيد' (you have prescribe these vitamins to your patient)* ◆ Dry flaking skin	
dications	◆ **Type IIb Hyperlipoproteinemia WHY? Because of transient increase of TG and VLVL.** ◆ *Biliary obstruction.* ◆ *Diverticulitis* ◆ *Chronic constipation.* ◆ *Severe hypertriglyceridemia (the cause is the same as 1st contradicted)*	
Interactions	⍰ absorption of some drugs;**Digoxin, Thiazides, Frusemide, Propranolol, Warfarin, L-thyroxin**, … **N.B**. So these drugs must be **taken 1 hr before or 4 hrs after** sequestrantes	

The doctor said only know the first contraindication

Targeting Endogenous Pathways:

- **Inhibits synthesis of cholesterol**
  Inhibitors of hydroxymethylglutaryl coenzyme A reductase (HMG-COA Reductase)
- **Alter relative levels & patterns of different plasma LPs**
  Fibrates, Nicotinic acids

NICOTINIC ACID Is known as Vit B_3. Its amide derivative nicotinamide has no lipid lowering effects		
Mechanism	Bind to a specific receptors in **adipose tissue** *(reverse effect of b-AR stimulation)* → ↓ cAMP → ↓ PKA → -ve TGs breakdown → ↓FFA[2] to liver (it decrease the mobilization of free fatty acid to the liver) → ↓TGs hepatic synthesis & VLDL formation This eventually ↓LDL & ↑ HDL In plasma:**↑ LPL[3] activity** →↑ VLDL & CMs **clearance** (in other way ↓VLDL & CMs)	
Pharmacological actions	◆ ↓LDL 5-25% ◆ **↑ HDL 15-30%** ◆ ↓ TG & VLDL 20-50% **Nicotinic acid works o ALL the lipid profile**	↓ LP(a) "Lipoprotein A = atherogenic lipoprotein" ↓ Fibrinogen ↑Tissue plasminogen activator
Indications	• Type IIa hypercholestrolemia • Type IIb hypercholesterolemia & any combined hyperlipidemia • **Patient with hypertriglyceridemia & low HDL-C ?? (If the patient wasn't diabetic)** • Hyperchylomicronemia.	
ADRs	♦ **Sensation of Warmth & Flushing** (**prostaglandin induced / -ve by aspirin ½ h before niacin**). **N.B *Slow release formulations → ↓incidence of flushing !!!***	♦ Pruritus, rash, dry skin ♦ Dyspepsia: nausea, vomiting, reactivation of peptic ulcer *(↓ if taken after meal).* ♦ Reversible ↑ liver enzymes →hepatotoxicity. ♦ Impairment Of Glucose Tolerance → Overt Diabetes ♦ ↑ Uric Acid
Contraindications	• **Gout.** • Peptic ulcer. (Because of the prostaglandin) • Hepatotoxicity. • **Diabetes mellitus WHY? Bcoz it** Impairment Of Glucose Tolerance	

Diabetes mellitus lipid profile :(↑ TG + normal LDL + ↓ HDL)

[2] FFA: Free Fatty Acids
[3] LPL: Lipoprotein lipase

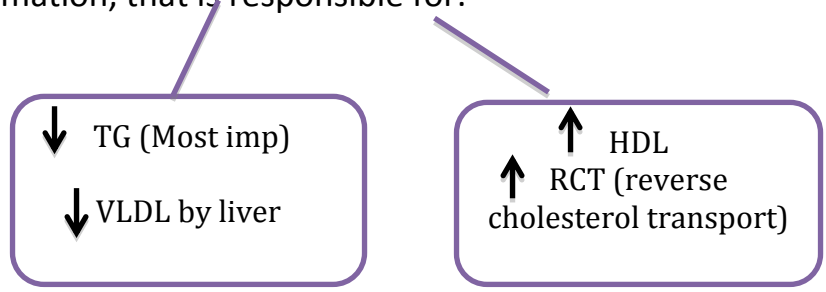
Fibrates: act as Nuclear Transcription Factors

(PPARα Agonist)

- When fibrates bind with Linoleic Acid (α receptor), it's activated and acts on nuclear transcription factors. (They don't reduce Cholesterol very much)

Mechanism:

- Bind and activate PPARα Receptor
- Dimerize with RXR
- Expresses Gene Transcription, and represses other Gene Transcription.
- mRNA Translation.
- Protein formation, that is responsible for:



- It represses other proteins. The most imp. is LDL.

Fibrates:

- Fenofibrate (F) → Used for; 1- Gout + Metabolic Syndromes* -> (because it has uricosuric action"help In excretion of uric acids") 2- Diabetes 3- Hyperuricemia
- Gemfibrozil (G)
- Clofibrate (not used nowadays) it cause: Gall stones/ Cancer

Pharmacological Actions:

- ↓ LDL 5-20%
- ↑ HDL 10-20% > (G)
- ↓ TG & VLDL 20-50%
- ↓ Fibrinogen
- ↓ Vascular inflammation > (G)
- Improve glucose tolerance > (F)

Extra Information:
- (F) & (G): **mostly** used to decrease TG.
- Metabolic Syndromes, such as Insulin Syndrome, are pre-diabetic. This means there is an increase in TG & a decrease in HDL in fatty acid circulation because of obesity which can lead to diabetes. **With or without an increase in cholesterol.**

***metabolic syndrome: metabolic syndrome is pt. has 3 of these:**

1- obesity 2- hyperlipidemia 3- hyperglycemia 4- hyperuricemia 5- hypertension so Fenofibrate is good for n 2, 3 and 4

Indications:

Monotherapy > (G)

Hypertriglcyredemia; Type IV lipoproteinemia

Combined Therapy with Statins:

1. Mixed dyslipidaemia; i.e type IIb
2. . In decrease in HDL and increase in TG + risk of atherothrombosis [type 2 Diabetes].

Very IMPORTANT Note:
In combination of fibrates with lipophilic statins (that interact with cytochrome P450) we best use (F). Because (G) also interacts with CYT P450, so if it's combined with lipophilic statins toxicity will occur which may lead to [myositis & rhabdomyolysis.]

Combined therapy with other lipid lowering drugs:
in severe treatment-resistant dyslipidaemia.

ADRs:

1. G.I.T upset, headache, fatigue, weight gain

2. Rash, urticaria, hair loss

3. Myalagia, Myositis, Rhabdomyolysis, which may cause Acute renal failure, that Occurs in alcoholics. Due to combination with lipophilic statins or impaired Renal function.

Contraindications:

- Renal or hepatic impairment.
- Pregnant or nursing women.
- Gall-bladder disease & morbid obesity
- In hypoalbuminaemia
- In alcoholics
  They ↓ metabolism of lipophylic not hydrophilic statins -> toxicity %myalgia, myositis, ...etc. Give lower doses

Interactions:

- They displace warfarin from their protein binding sites, which increases the tendency for internal bleeding. Therefore, anticoagulant dose must be adjusted. (Warfarin ↓).

- They ↓ metabolism of lipophylic not hydrophilic statins -> toxicity %myalgia, myositis, ...etc. Give lower doses

Statins

(HMG CoA Reductase Inhibitors)
specific, reversible, competitive

- It stops Cholesterol (C) synthesis, so LDL will have to take more (C) which decreases (C) in our circulation.

Mechanism:

HMG CoA Reductase: One of the enzymes in cholesterol synthetic pathways that controls the rate limiting step of conversion to mevalonate.

1. Lipid lowering effect in the Liver:

Decreases hepatic (C) synthesis which decreases hepatic intracellular (C) that results in:

1. ↑ Synthesis of LDL receptors which ↑ clearance of LDL

2. ↓ Secretion of VLDL & ↑ uptake of non-HDL-(C)

2. PLEIOTROPIC ANTIATHEROGENIC effects in Vessels:

Because it blocks cholesterol synthetic pathway, it also blocks signaling molecules responsible for progress of inflammation, vulnerability & athrothrombosis. **This is the 2ndry effect of statins** to excess C accumulation in periphery**.**

This results in:

- Improve endothelial function (NO).
- Decrease vascular inflammation
- Stabilization of atherosclerotic plaque
- decrease platelet aggregability
- Antithrombotic actions
- Enhanced fibrinolysis ...etc

**** So Statins are the drug of choice for Atherogenic Hyper-lipidemia. Because, they decrease (C) Synthesis & Block Signaling Molecules.

Classification of statins:

Simvastatin
Fluvastatin [Weak]
Atorvastatin [Strong]
Lovastatin
} Lipophilic

Pravastatin → Hydrophilic (Not obliged with the rule of (G))

Rosuvastatin [Super/Mega] → Partial (It's the best statin, reduces (C) by 60%).

Pharmacokinetics:

- Absorption varies (40-70%), fluvastatin almost completely
- Absorption enhanced if taken with food, except pravastatin
- All have high first-pass extraction by the liver, except pravastatin
- Simvastatin, Lovastatin, Atorvastatin are the most metabolized
- Metabolized variably
- By CYP3A4 → Simvastatin, Lovastatin, Atorvastatin
- By CYP2C9 → Fluvastatin, Rosuvastatin
- By sulphonation → Pravastatin
- Excreted in bile & 5–20% is excreted in urine, except pravastatin 80-90% urine.
- t½ (V.imp):

  - If short duration (1-3 hrs). Such as, Simvastatin, Lovastatin, Fluvastatin. Then, it's taken only in the evening, because cholesterol synthesis increases at night.
  - If long duration (14 hrs). Such as, Atorvastatin. Or (19 hrs). Such as, Rosuvastatin. Then it is taken any time.

Indications:

As Monotherapy:

- 2ndry prevention: at all times:
  In all ischemic insults [, stroke, ACSs up to AMI, ...etc. So given from1st day of ischemic attack%stabilize plaques + help to limit ischemic zone & to salvage preferential tissues
- Primary prevention:

- 1. Patients with hyperlipidemia and with other risks for ischemic insults.
- 2. Type IIa Hyperlipoprotinemia.

As Combined Therapy:

1. Mixed dyslipidaemias; added to fenofibrates or niacine if necessary.

2. In diabetics and patients with insulin resistance [metabolic syndrome]. Even if there isn't any increase in LDL levels (just low HDL). Because they will already have small dense LDL with endothelial dysfunction and increased thrombotic profile. **So we must take Statins**

Contraindications: In pregnancy and cautiously under age of 18 years

ADRs:

- increase serum transaminase → can progress to evident hepatotoxicity So lab investigations recommended every 6 month → if level increase up to 3 folds at any time, statin must be stopped then dose adjusted.

- Increase CK activity (index of muscle injury): Measured only if there are symptoms such as, myalgia or myositis. If it increases up to 3-5 folds **statins must be decreases/change to hydrophilic statin / omit combination with fibrates.....**
- But, if there was severe elevation with blood in urine, this indicates Rhabdomyolysis → renal failure could be fatal, and dialysis is needed.

Interactions:

- Simvastatin, Atorvastatin. Which are metabolized by CYP3A4 show:
  - Decrease efficacy with INDUCERS (Phenytoin, Rifampin, Barbiturates, TZDs...).
  - Increase toxicity with INHIBITORS (Macrolides, Cyclosporine, Ketoconazole...).
- Fluvastatin & Rosuvastatin. Which are metabolized by CYP2C9 show:
  - Increase toxicity with INHIBITORS (Amiodarone, Cimetidine…)

Adjuvants in hyperlipidemia

Omega-3-FA
found in fish oils containing highly unsaturated fatty acid.
Mechanism & Pharmacological effect:
- Reduces TG synthesis.
- Increases β oxidation of FFA.
- Prolongation of bleeding time.
- Reduction of plasma fibrinogen
- Anti-inflammatory effects

β-Sitosterol
Found in plants with structure similar to (C).
Mechanism & Pharmacological Effects:
Compete with dietary & biliary (C) absorption to decrease LDL levels
+ and – 10%
Indications: Given as food supplement before meal in hypecholestrolemia

*TARGETING DYSLIPIDEMIA & * TARGETING BEYOUND is just for reading if you would like.

MCQ

Choose the ONE best answer.

1. Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure.
B. Gastrointestinal disturbance.
C. Neurologic problems.
D. Heart palpitations.

2. Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I.
B. Type II.
C. Type III.
D. Type IV.

3. Which one of the following drugs decreases de novo cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A. Fenofibrate.
B. Niacin.
C. Cholestyramine.
D. Lovastatin.
.

4. Which one of the following drugs causes a decrease in liver triacylglycerol synthesis by limiting available free fatty acids needed as building blocks for this pathway?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Gemfibrozil.

5. Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Fluvastatin.