PHARMACOLOGY TEAM 432

Hyperlipidemia Lecture

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Learning Objectives:

* Define hyperlipidemia vs normal lipid levels
* Revise the cascade of lipoprotein remodeling, stressing on peripheral TGs utilization and cholesetrol influx & outflux.
* Relate such variables to the development & progression of atherogenesis
* Classify lipid lowering agents targeting exogenous & endogenous pathways
* Expand on the pharmacology of drugs related to each group and relate that to their clinical relevance alone or in combinations
* Hint on adjuvant drugs that can help in lipid lowering

Sum up the therapeutic approach attempting to target hyperlipidemia from quantitative, qualitative and vasculo-protective perspectives

Mind Map:

Note: (Without any medication, if the patients not on emergency situation)

- **TREATMENT OF HYPERLIPIDEMIA**
  - **THERAPEUTIC LIFESTYLE CHANGES**
  - **ANTIHYPERLIPIDEMIC AGENTS**
    - TARGETING **ENDOGENOUS** PATHWAYs (dietery or non diatery sources)
      - Alter relative levels & patterns of different plasma **LPs.** (Fibrates, Nicotinic acids)
      - Inhibits **synthesis** of **cholesterol.**(HMG-COA Reductase)
    - TARGETING **EXOGENOUS** PATHWAYS (dietery sources)
      - **Sequester bile acids** in the intestine. (Exchange resins)
      - Inhibits cholesterol **absorption** in the intestine.(Ezetimibe)

- **Adjuvant Agent**
  - Stanols
  - Omega-3-Fatty Acids

1 Ezetimibe:

Is a selective **cholesterol** (only) absorption inhibitor

		Notes
Mechanism of Action :	**NPC1L1 : it is transporter, it is responsible for absorption of cholesterol and it located in small intestine's wall . Ezetimibe blocks it.** **The result is less pool of cholesterol available to the liver, so more LDL receptor trapping more LDL particles from blood**	**So as a consequence the receptor of LDL with Ezetimibe INCREASED**
Pharmacological Actions:	**Decrease LDL level (So about 50% of intestinal cholesterol and phytosterol absorption are blocked)** **Decrease TG level** **Elevate HDL level** **No effect of steroids , lipid soluble vitamins, bile acid**	
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**	If there combination with other drug 1.With statins, it will increase the concentration of the statins 2.With cholystyramine, it will decrease the concentration of the cholystyramine

Ezetimibe : continue

		Notes
Indication	* As Monotherapy; Pry prevention of low risk of CHD i.e. need modest LDL Statin-intolerant patients As Combination Therapy; safe 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:	Not common. GIT disturbance, headache, fatigue, artheralgia & myalgia. Seldom reversible impairment of hepatic function	**It's the safest drug**

2 Bile Acid Sequestrants..

Ex: cholestyramine, colestipol "most common"

Mechanism	Resins act by binding negatively charged bile acids in the small intestine, forming insoluble complexes that are then excreted in feces. Loss of the bile acid stimulates the liver to increase conversion of stored cholesterol into new bile acids. As more intracellular cholesterol is used to make bile acid, there is a compensatory increase in hepatic LDL receptors. **The net effects is (hepatic Cholesterol uptake). decrease in serum LDL and Cholesterol**
Pharmacological action	↓ LDL (Noticed) ↑ HDL, (unnoticed) ↑ TG & VLDL ! (almost no effect In TG but noticed in type 2b Hyperlipoproteinemia)
Indications	✱Hyperlipidemia → monotherapy: seldom if statin is Contraindicated & levels are Not high! → Combination: with Statin in type 2A Hyperlipoproteinemia. * Statins offsets the compensatory↑ in C synthesis by resins & potentiate↑ LDL→ Synergism.

In type 2B Hyperlipoproteinemia اخاف اعطيهم لانها تزود الـ TG

Resins must be taken in 2-3 doses with meals. Lack effect between meals.

Bile Acid Sequestrants..Count..

Indication	**2) Pruritis: due to biliary stasis or obstruction" احسن دواء يعالج البروراريتس"** **3) Digitalis: poisoning.**
ADR's	• ↑GIT bloating, diarrhea, constipation, dyspepsia. • ↓ Absorption of fat soluble vitamines (A,K,E,D) < اربطوها بكلمة أكيد:p فـ أي احد ياخذ دواء من هالمجموعة لازم ياخذ suplement من الفايتامينز هذي • Dry flaking skin.
Contraindication	• Biliary obstruction. • Diverticulitis. • Chronic constipation. • Severe hypertriglyceridemia • Type 2B Hyperlipoproteinemia. (she said forget all the things above except THIS POINT \^^/)
Interactions	* **Decrease the absorption of some drugs, such as:** Digoxin, Thiazides, Frusemide, Propranolol, L-Thyroxin, Warfarin. (بما انه يتحكم فالامتصاص فـ اقوم ازود الدوز او عشان ابعد عن المخاطر احط كل واحد بوقت مختلف عن الثاني)

3 Nicotinic Acid (Vit. B3)

Targeting endogenous pathway, its drivative Nicotinamide has no lipid lowering effect.

Mechanism	1.it's decrease lipolysis in adipose tissue, which in turn reduces circulating free fatty acids. Without the FFA, hepatic secretion of VLDLs is slowed. 2.It increase the activity of lipoprotein lipase. 3.Stimulants mild-to-moderate increases in HDL. **This an important effect that can be very usefull to patient who have high levels of LDL/VLDL in compination with low levels of HDL.**
Pharmacological action	• ↓: LDL (5-25%) , TG & VLDL (20-50%), LPa, Fibrinogen. } ↓ Risk factor of Thrombosis • ↑: HDL (15-30%) Tissue plasminogen activator.
Indications IMPORTANT	• Mono or combination with fibrate, resin or statin. • Type 2A Hypercholesterolemia. • Type 2B Hypercholesterolemia. • Patients with Hypertriglyceridemia & low HDL-C. • Hyperchylomicronemia.
ADRs "good drug but too much side effects"	• **Sensation of warmth & flushing** (Prostaglandin induced) **–ve by aspirin** 1\2 hr before Niacin. Wich will Slow release formulations →↓ Incidince of flushing (لانها عملت vasodilatation)

Nicotinic Acid (Vit. B3)

ADRs	• **Pruritis , rash, dry skin.** • **Dyspepsia: nausea, vomiting, reactivation of peptic ulcer (if taken after meal)** • **Reversible ↑liver enzymes → hepatotoxicity.** • **Impairment of glucose tolerance → overt diabetes.(نحاول مانعطيهم الناس الي فيهم سكر)** • **↑ Uric acid.**
Contraindications	• Gout. • Peptic ulcer. • Hepatotoxicity. • Diabetes mellitus.

Remember That:
There in Nothing " Impossible"
Because the word its self says:
I'm Possible!
Go & Continue ;p !

3 Fibrate:

It is essentially for hypercholesterolemia and acts as nuclear transcription factors when it is bind with Linoleic Acid (α **receptor)** it's activated.

Mechanism of Action :	* Bind and activate PPARα Receptor. * Dimerize with RXR. (Retinoid X receptor) * Expresses Gene Transcription, and represses other Gene Transcription. * mRNA Translation. • Protein formation, that is responsible for: 1)-↓TG , ↓VLDL by liver. 2)-↑ HDL, ↑RCT (reverse cholesterol transport) * It represses other proteins like ↓LDL.	**Notes** It derivtive of fibric acid that lower TG and increse HDL levels.
Drugs :	**Fenofibrate (F)** **Gemfibrozil (G)** Clofibrate (not used these days) because it cause: Gall Stones and Cancer Bezafibrate (not important)	
Pharmacological Actions:	↓LDL 5-20% ↑ HDL 10-20% > (G) ↓ TG & VLDL 20-50% ↓ Fibrinogen (prevent clotting, thrombus … etc) ↓ Vascular inflammation > (G) best in patient with gout disease Improve glucose tolerance > (F) best in diabetic patient	
Pharmacokinetics	Fenofibrate (F) is long action while Gemfibrozil (G) Is short action, affected by Hepatic (CYP3A4) and pass to placenta.	

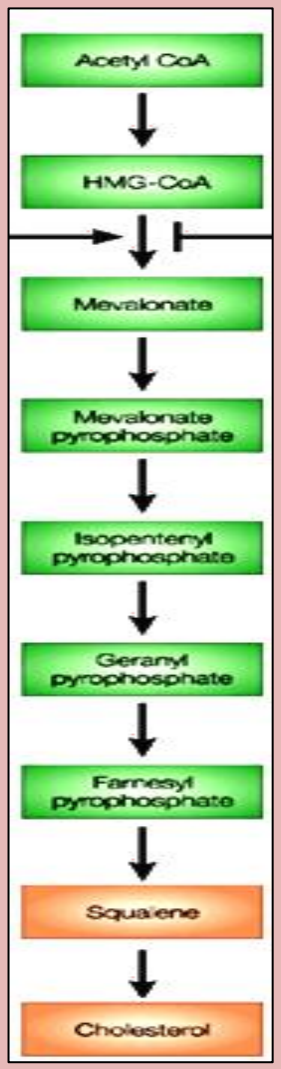
Fibrate: continue

Notes

Indication	* Monotherapy > (G) **Hypertriglcyredemia** • 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]. With other lipid lowering drugs: in severe treatment-resistant dyslipidaemia.	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.]
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.	**Myalagia (pain in muscle)** **Rhabdomyolysis (destruction of striated muscle cells)**
Contraindication:	▪ Renal or hepatic impairment. ▪ **Pregnant** or nursing women. ▪ Gall-bladder disease & morbid obesity ▪ In hypoalbuminaemia ▪ In alcoholics	
Pharmacokinetics	* 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**	

4 Statin :

* ➔**HMGCoA Reductase** INHIBITORS. ***3-hydroxy-3-methyl-glutaryl- (CoA reductase (HMGCR)**⟶ One of the enzymes in cholesterol synthetic pathways that controls the rate limiting step of conversion to mevalonate



You Don't have to memorize the names

Each one of these structures has different function vital to the body
Like: growth , motility and anything in contacts linked with lipid so all markers of endothelium dysfunction and all inflammatory reaction in atherosclerosis will reduce by blocking HMGCO reductase not because it reduced cholesterol only ,but because these precursor molecules response for these problems are stopped. **(pleiotropic effect)**

HMG-CoA reductase inhibitors decrease cholesterol synthesis in the liver, which leads to an increase in LDL receptors on the surface of hepatocyte and a decrease in plasma VLDL/LDL.

They are the most widely used class of antihyperlipidemic drugs because of their effectiveness in lowering LDL and total cholesterol level.

Statin: continue

All of them lipophilic except Pravastatin & Rosuvastatin

Classification of STATINS

Types:	Lipophilic	Simvastatin / Lovastatin / Fluvastatin / Atorvastatin	→ weak → strong
	Hydrophilic Execrated by kidney	Pravastatin	It is very good in combination with any other drug because it is hydrophilic, but it is weak.
	Partial By liver and kidney	Rosuvastatin	Decrease the dose if you give it in combination to prevent toxicity Super / Mega (reduces cholesterol by 60%)
Pharmacokinetics	Metabolism not very imp-to know the name of the enzymes Just know it as group some drug will Interact with the first 3 drugs & some with 2	By CYP3A4	→ Simvastatin, Lovastatin, Atorvastatin
		By CYP2C9	→ Fluvastatin, Rosuvastatin
		sulphonation	→ Pravastatin
	T½ The numbers are not important	Short 1-3 hrs	→ Simvastatin, Lovastatin, Fluvastatin Taken only in evening
		Long 14 hrs 19 hrs	→ Atorvastatin → Rosuvastatin Taken any time

Because the synthesis of (c) at night so if you give it before evening it will degrade before production of C

Statin : continue

Mechanism of Action :

HMG-COA Reductase inhibitor :

1. LIPID LOWERING effects [In Liver] :

↓ hepatic C synthesis → ↓ hepatic intracellular C

↓ secretion of VLDL & ↑ uptake of non-HDL-C

↑. synthesis of LDL receptors → ↑ clearance of LDL

2. PLEIOTROPIC ANTIATHEROGENIC effects[> in Vessels : Because it blocks cholesterol synthetic pathway it is also blocks signalinmolecules responsible for progress of inflammation, vulnerability & athrothrombosis occurring 2ndry to excess C accumulation in periphery →

Improve endothelial function

↓vascular inflammation

Stabilization of atherosclerotic plaque

↓platelet aggregability

Antithrombotic actions

Enhanced fibrinolysis …etc

Notes

Because statins inhibit Cholesterol synthesis and block so many signaling molecules ,so statins are the drug of choice in all in athrogentic dyslipidemia also in diabetic patient ,because it decrease small dense LDL

Indications:

As monotherapy:

Pry (primary) Prevention :

I use it to treat hypercholestremia in same time I prevent consequence of increased cholesterol.

2ndry Prevention In all ischemic insults :

So given from 1st day of ischemic attack → stabilize plaques + help to limit ischemic zone & to salvage preferential tissues

with non hydrophilic like Pravastatin or Rosuvastatin but with low dose

As Combination therapy :

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

2. In diabetics and patients with insulin resistance [metabolic syndrome] even if LDL only hypertriglyceridemia & low HDL without ↑in LDL

Why ???

because these patients will possess small dense LDL (severely atherogenic) + evident endothelial dysfunction + increased thrombotic profile.

in any case except in Familial Hyperlipoproteinemia 11a ,because usually cholesterol is very high it could be 400 or 500 because LDLR not functioning well (use combination). In all acute myocardial infarction (MI) and coronary disease even if the person has no hyperlipidemia use statin as monotherapy.

Statin : continue

Contraindication	**In pregnancy and cautiously under age of 18 years**	**For maturation and formation of sex hormone .**
ADRs: Very Imp>	**1\↑serum transaminase** =liver enzymes can progress to evident hepatotoxicity So lab investigations recommended **every 6 month (routine)** → if levels ↑ **up to 3 folds** at any time, statin must be **stopped** then dose adjusted. **2\↑ creatine kinase activity=muscle enzymes is not routine we do it only if the patient complain of myalgia** (pain in the muscles) **or myositis** (inflammation of the muscles) **or take it in combination like with lipophilic if ↑ 3-5 folds → we ↓ statin doses / change to hydrophilic statin / omit combination with fibrates to prevent developing of Rhabdomyolysis** **#but If severe elevation + blood in urine → this is Rhabdomyolysis →renal failure could be fatal →dialysis is needed**	
interaction:	Those metabolized by CYP3A4 [Simvastatin, Atrovastatin] show ↓ efficacy with INDUCERS (Phenytoin, rifampin….) ↑ toxicity with INHIBITORS (Macrolides, cyclosporine, ketoconazole) Those metabolized by CYP2C9 [Fluvastatin & Rosuvastatin] show ↑ toxicity with INHIBITORS (metronidazole, amiodarone, cimetidine…) antibiotic — Antiarrhythmic	Simvastatin, Atrovastatin Lipophilic Macrolides, cyclosporine antibiotic

Factors Increase HDL :

1- walking
2- estrogen
3- niacin (nicotinic acid)

TARGETING BEYOND :

1-STATINS

- ↓ major coronary events
- ↓ CHD mortality
- ↓ coronary procedures
- ↓ Stroke
- ↓ Total mortality

2- FIBRATE

- ↓ progression of coronary lesions
- ↓ major coronary events

3- NIACIN

- ↓ major coronary events
- Possible ↓ in total mortality

Adjuvants Agent :

Adjuvants Agent :

Omega-3-Fatty Acids:

*found in fishoils containing highly unsaturated fatty acid.

Mechanism of Action :

- ↓ TG synthesis.
- ↑↓ β oxidation of FFA.
- ↓ Platelet function
- 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

Indications:

Given as food supplement before meal in hypecholestrolemia

MCQs ... (from Lippincott) :

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 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.

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.

Answer Key : B, D, C,