Katzung pharmacology
Lec – 3
Summary and Q&A

Summary

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Drug Interactions
Statins				
Atorvastatin, simvastatin, rosuvastatin	Inhibit HMG-CoA reductase	Atherosclerotic vascular disease (primary and secondary prevention) • acute coronary syndromes	Oral administration • P450-dependent metabolism (CYP3A4, CYP2C9) interacts with P450 inhibitors/competitors	Myopathy, hepatic dysfunction, teratogen
Fluvastatin, pravastatin, lovastatin: similar but somewhat less efficacious				
Fibrates				
Gemfibrozil, fenofibrate	PPAR-α agonists[a]	Hypertriglyceridemia, low HDL cholesterol	Oral administration	Myopathy, hepatic dysfunction, cholestasis
Bile acid-binding resins				
Colestipol	Prevents reabsorption of bile acids from the gastrointestinal tract	Elevated LDL cholesterol, pruritus	Oral administration • interferes with absorption of some drugs and vitamins	Constipation, bloating
Cholestyramine, colesevelam: similar to colestipol				

Sterol absorption inhibitor				
Ezetimibe	Reduces intestinal uptake of cholesterol by inhibiting sterol transporter NPC1L1	Elevated LDL cholesterol, phytosterolemia	Oral administration	Rarely, hepatic dysfunction, myositis
Niacin	Decreases VLDL synthesis and LDL cholesterol concentrations • increases HDL cholesterol	Low HDL cholesterol, elevated VLDL and LDL	Oral administration	Gastrointestinal irritation, flushing, hepatic toxicity, hyperuricemia, may reduce glucose tolerance

Q & A

1. PJ is a 4.5-year-old boy. At his checkup, the pediatrician notices cutaneous xanthomas and orders a lipid panel. Repeated measures confirm that the patient's serum cholesterol levels are high (936 mg/dL). Further testing confirms a diagnosis of homozygous familial hypercholesterolemia. Which of the following interventions will be **least** effective in this patient?

(A) Atorvastatin
(B) Ezetimibe
(C) Lomitapide
(D) Mipomersen
(E) Niacin

1. Homozygous familial hypercholesterolemia is caused by mutations leading to dysfunctional LDL receptors incapable of taking up LDL from the bloodstream. Options **B–E** would have a cholesterol-lowering effect. Lomitapide and mipomersen are specifically indicated for patients with familial hypercholesterolemia. Reductase inhibitors such as atorvastatin rely on functional LDL receptors to achieve a LDL-lowering effect and thus will not work in patients with homozygous familial hypercholesterolemia. The answer is **A.**

2. A 46-year-old woman with a history of hyperlipidemia was treated with a drug. The chart below shows the results of the patient's fasting lipid panel before treatment and 6 mo after initiating drug therapy. Normal values are also shown. Which of the following drugs is most likely to be the one that this patient received?

(A) Colestipol
(B) Ezetimibe
(C) Gemfibrozil
(D) Lovastatin
(E) Niacin

Time of Lipid Measurement	Triglyceride	Total Cholesterol	LDL Cholesterol	VLDL Cholesterol	HDL Cholesterol
Before treatment	1000	640	120	500	20
Six months after starting treatment	300	275	90	150	40
Normal values	<150	<200	<130	<30	>35

2. This patient presents with striking hypertriglyceridemia, elevated VLDL cholesterol, and depressed HDL cholesterol. Six months after drug treatment was initiated, her triglyceride and VLDL cholesterol have dropped dramatically and her HDL cholesterol level has doubled. The drug that is most likely to have achieved all of these desirable changes, particularly the large increase in HDL cholesterol, is niacin. Although gemfibrozil lowers triglyceride and VLDL concentrations, it does not cause such large increases in HDL cholesterol and decreases in LDL cholesterol. The answer is E.

Questions 3–6. A 35-year-old woman appears to have familial combined hyperlipidemia. Her serum concentrations of total cholesterol, LDL cholesterol, and triglyceride are elevated. Her serum concentration of HDL cholesterol is somewhat reduced.

3. Which of the following drugs is most likely to increase this patient's triglyceride and VLDL cholesterol concentrations when used as monotherapy?
   (A) Atorvastatin
   (B) Cholestyramine
   (C) Ezetimibe
   (D) Gemfibrozil
   (E) Niacin

4. If this patient is pregnant, which of the following drugs should be avoided because of a risk of harming the fetus?
   (A) Cholestyramine
   (B) Ezetimibe
   (C) Fenofibrate
   (D) Niacin
   (E) Pravastatin

3. In some patients with familial combined hyperlipidemia and elevated VLDL, the resins increase VLDL and triglyceride concentrations even though they also lower LDL cholesterol. The answer is **B**.

4. The HMG-CoA reductase inhibitors are contraindicated in pregnancy because of the risk of teratogenic effects. The answer is **E**.

5. The patient is started on gemfibrozil. Which of the following is a major mechanism of gemfibrozil's action?
   (A) Increased excretion of bile acid salts
   (B) Increased expression of high-affinity LDL receptors
   (C) Increased secretion of VLDL by the liver
   (D) Increased triglyceride hydrolysis by lipoprotein lipase
   (E) Reduced uptake of dietary cholesterol

6. Which of the following is a major toxicity associated with gemfibrozil therapy?
   (A) Bloating and constipation
   (B) Cholelithiasis
   (C) Hyperuricemia
   (D) Liver damage
   (E) Severe cardiac arrhythmia

5. A major mechanism recognized for gemfibrozil is increased activity of the lipoprotein lipase associated with capillary endothelial cells. Gemfibrozil and other fibrates decrease VLDL secretion, presumably by stimulating hepatic fatty acid oxidation. The answer is **D**.

6. A major toxicity of the fibrates is increased risk of gallstone formation, which may be due to enhanced biliary excretion of cholesterol. The answer is **B**.

Questions 7–10. A 43-year-old man has heterozygous familial hypercholesterolemia. His serum concentrations of total cholesterol and LDL are markedly elevated. His serum concentration of HDL cholesterol, VLDL cholesterol, and triglycerides are normal or slightly elevated. The patient's mother and older brother died of myocardial infarctions before the age of 50. This patient recently experienced mild chest pain when walking upstairs and has been diagnosed as having angina of effort. The patient is somewhat overweight. He drinks alcohol most evenings and smokes about 1 pack of cigarettes per week.

7. Consumption of alcohol is associated with which of the following changes in serum lipid concentrations?
   (A) Decreased chylomicrons
   (B) Decreased HDL cholesterol
   (C) Decreased VLDL cholesterol
   (D) Increased LDL cholesterol
   (E) Increased triglyceride

8. If the patient has a history of gout, which of the following drugs is most likely to exacerbate this condition?
   (A) Colestipol
   (B) Ezetimibe
   (C) Gemfibrozil
   (D) Niacin
   (E) Simvastatin

9. After being counseled about lifestyle and dietary changes, the patient was started on atorvastatin. During his treatment with atorvastatin, it is important to routinely monitor serum concentrations of which of the following?
   (A) Blood urea nitrogen
   (B) Alanine and aspartate aminotransferase
   (C) Platelets
   (D) Red blood cells
   (E) Uric acid

10. Six months after beginning atorvastatin, the patient's total and LDL cholesterol concentrations remained above normal, and he continued to have anginal attacks despite good adherence to his antianginal medications. His physician decided to add ezetimibe. Which of the following is the most accurate description of ezetimibe's mechanism of an action?

(A) Decreased lipid synthesis in adipose tissue
(B) Decreased secretion of VLDL by the liver
(C) Decreased gastrointestinal absorption of cholesterol
(D) Increased endocytosis of HDL by the liver
(E) Increased lipid hydrolysis by lipoprotein lipase

7. Chronic ethanol ingestion can increase serum concentrations of VLDL and triglycerides. This is one of the factors that places patients with alcoholism at risk of pancreatitis. Chronic ethanol ingestion also has the possibly beneficial effect of raising, not decreasing, serum HDL concentrations. The answer is **E**.

8. Niacin can exacerbate both hyperuricemia and glucose intolerance. The answer is **D**.

9. The 2 primary adverse effects of the HMG-CoA reductase inhibitors are hepatotoxicity and myopathy. Patients taking these drugs should have liver function tests performed before starting therapy, and at regular intervals as needed during therapy. Serum concentrations of alanine and aspartate aminotransferase are used as markers of hepatocellular toxicity. The answer is **B**.

10. The major recognized effect of ezetimibe is inhibition of absorption of cholesterol in the intestine. The answer is **C**.

END