DRUGS USED IN DYSLIPIDEMIAS

LEARNING OBJECTIVES:

At the end of the lecture, students should be able to:

• Know the drugs used in dyslipidemias.
  – Bile acid sequestrants
  – HMG-CoA reductase inhibitors
  – Fibric acid derivatives
  – Niacin

LIPOPROTEIN PARTICLES

• The major lipid components of a lipoprotein are:
  triglycerides
  phospholipids
  cholesterol
  cholesterol esters

Classification of Lipoproteins:

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Composition</th>
<th>Density</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>TG &gt;&gt; C, CE</td>
<td>Low</td>
<td>Large</td>
</tr>
<tr>
<td>VLDL</td>
<td>TG &gt; CE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDL</td>
<td>CE &gt; TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>CE &gt;&gt; TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>CE &gt; TG</td>
<td>High</td>
<td>Small</td>
</tr>
</tbody>
</table>
Transport of Lipoprotein Particles

LIPOPROTEINS

- Low-density lipoproteins (LDL):
  - Transport cholesterol to the peripheral cells
  - Lipoprotein profile-total cholesterol, LDL, HDL, triglycerides
  - Elevation of LDL:
    - Atherosclerotic plaque formation
    - Increases the risk for heart disease
- High-density lipoproteins (HDL):
  - Take cholesterol from the peripheral cells and transport it to the liver

Drugs used to treat hyperlipidemia:

- Bile acid sequestrants
- HMG-CoA reductase inhibitors
- Fibric acid derivatives
- Niacin

HMG-COA REDUCTASE INHIBITORS: ACTIONS

- Statins**
- HMG-CoA reductase:
– An enzyme that is a catalyst during the manufacture of cholesterol

• Inhibits the manufacture of cholesterol or promotes the breakdown of cholesterol
• Lowers the blood levels of cholesterol and serum triglycerides
• Increases blood levels of HDL’s

**STATINS**

• Statins inhibit the rate-limiting step in the biosynthesis of cholesterol - HMG-CoA reductase.
• Decreased cholesterol biosynthesis steps up the levels of the LDL-receptor resulting in the positive cycle for lowered cholesterol levels in serum.
• For patients who have familial hypercholesterolemia due to defective LDL-receptor genes these drugs are **not** effective.
• Statins are most effective cholesterol lowering drugs.
• statins lower total cholesterol and LDL particles.
• These are competitive inhibitors. The HMG-CoA has a conformation similar to the lactone moiety of statins resulting in binding at the same site without any productive effect.

**BILE ACID SEQUESTRANTS: ACTIONS AND USE**

• Bile: Manufactured, secreted by liver
  – Stored in the gallbladder, emulsifies fat, lipids

• Increased loss of bile acids:
  – Liver uses cholesterol to manufacture more bile
• Used to treat: Hyperlipidemia; Pruritus associated with partial biliary obstruction
• The fall in LDL concentration is apparent in 4 to 7 days. The decline in serum cholesterol is usually evident by 1 month.
• When the resins are discontinued, the serum cholesterol usually returns to baseline within a month.
• When bile acid secretion is partially blocked, serum bile acid concentration rises. For these patients, cholestyramine reduces bile acid deposits in the dermal tissues.
• One of greatest advantage of these polymeric agents is that they can be safely used for pregnant women.
• However, exercise caution for nursing women because presence of these cationic polymeric agents in the GI tract might lower the absorption of vitamin D.
• BAS agents may also lower the amount of anticoagulants (warfarin, coumadin) absorbed due to sequestration.

**FIBRIC ACID DERIVATIVES: ACTIONS**

• Clofibrate:
  – Stimulates liver to increase breakdown of very–low-density lipoproteins (VLDLs) to low-density lipoproteins (LDLs); Decreases liver synthesis of VLDLs and inhibites cholesterol formation

• Fenofibrate:
  – Reduces VLDL; Stimulates catabolism of triglyceride-rich lipoproteins; Decreases plasma triglyceride, cholesterol.

• Gemfibrozil:
  – Increases excretion of cholesterol in the feces
  – Reduces the production of triglycerides by the liver
  – Lowers serum lipid levels

• Gemfibrozil was introduced in 1981 and remains the second most useful antilipidemic agent.
  – It primarily decreases serum triglycerides. Newer drugs including beclofibrates, ciprofibrates, fenofibrates, are more effective in lowering serum LDL cholesterol.
  – However, the fibrates are almost never used alone. They are mostly used in combination with bile acid sequestering agents.

**NICOTINIC ACID (NIACIN)**

• Nicotinic acid is a vitamin and prescription drug classified as a vitamin supplement, antihyperlipidemic, and vasodilator.
  – It is used to reduce cholesterol and triglyceride levels in the blood. Nicotinic acid dilates blood vessels and, with large doses, decreases cholesterol production.
  – This often gives rise to a "flush", which may be considered by some, to be an undesirable side-effect. Related forms include: niacinamide and nicotinamide

-----------------------------------------------------------------------------------------------