ANTI-HYPERLIPIDEMIC AGENTS AND NSAIDS

LECTURE 6
<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Desirable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>&lt;200mg/dL</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;130mg/dL</td>
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<tr>
<td></td>
<td>&lt;100mg/dL – optimal level</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>&gt;40mg/dL</td>
</tr>
<tr>
<td>women</td>
<td>&gt;50mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;120mg/dL</td>
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</tbody>
</table>
GOOD AND BAD CHOLESTEROL

- Bad cholesterol
  - VLDL
  - LDL
  - Triglycerides
- Good cholesterol
  - HDL
MANAGEMENT OF HYPERLIPIDEMIA

- Non-pharmacologic
  - Diet
  - Exercise
- Pharmacologic
MANAGEMENT OF HYPERLIPIDEMIA

• Diet modification
  • Eating this will...
    • Cholesterol and saturated fats = ↑LDL
    • Total fat, alcohol, excess calories = ↑triglycerides
    • Sucrose and fructose = ↑VLDL
    • Alcohol = ↑VLDL
  
• Limit total calories from fat to 20-2%, saturated fats to <8% and cholesterol to <200mg per day
• Use of complex carbohydrates and fiber
• Use of mono-unsaturated fats in diet
• Omega-3 fatty acids in fish oils (not vegetable oils) = ↓triglycerides
BASIC GROUPS

- HMG-CoA Reductase Inhibitors
  - “-statins”
- Niacin
- Fibric acid derivatives
  - “-fibrates”
- Bile acid binding resins
  - “cole-” or “chole-”
HMG-COA REDUCTASE INHIBITORS

• Statins: lovastatin, simvastatin, atorvastatin, rosuvastatin
• MOA:
  • Structural analogues of HMG-CoA
  • Partial inhibition of enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A)
    • Prevents transformation of HMG-CoA to cholesterol
    • Increases LDL receptors in the liver
      • Increases catabolism of LDL and extraction of LDL from the blood

• Extensively metabolized in the liver
• Effects
  • ↓↓LDL
  • Mild ↓triglycerides
  • Mild ↑HDL
HMG-COA REDUCTASE INHIBITORS

• Best given at night
  • Cholesterol synthesis occurs predominantly at night

• Side effects
  • Not for pregnant patients
  • May temporarily elevate liver enzymes (3x the normal)
    • Should be discontinued if there is clinical evidence of liver damage or AST/ALT increases more than 3x the normal
  • Taking in grapefruit juice may increase levels of statins
NIACIN (VITAMIN B3)

- **MOA:**
  - inhibits secretion of VLDL into bloodstream
    - Thus increasing VLDL clearance
  - Inhibits lipase in adipose tissue
    - $\downarrow$ breakdown of fats to free fatty acids $\Rightarrow$ $\downarrow$ production of VLDL by the liver (due to $\downarrow$ building block materials)

- **Effect**
  - $\downarrow$ VLDL and LDL
  - $\uparrow\uparrow$ HDL

- **Side effects**
  - 2x increase in liver enzymes
  - Pruritus, rash, dry skin
  - Hyperuricemia
  - Cutaneous vasodilation
FIBRIC ACID DERIVATIVES

• Gemfibrozil, fenofibrate, clofibrate
• MOA: ligands (agonists) to receptor PPAR-α (peroxisome proliferator-activated receptor-alpha)
  • Upregulate LDL breakdown = ↓LDL
  • ↓VLDL synthesis and secretion from liver
  • Downregulate lipolysis in adipose tissue = ↓FFA
  • Moderate ↑HDL
• Side effects
  • Rash
  • Rhabdomyolysis – renal failure
  • Increase risk for gallstones (due to increase cholesterol content of bile)
Bile Binding Resins

- Colestipol, cholestyramine, colecsevelam
- MOA: binds bile acids in the intestines to prevent reabsorption
- Effect: $\downarrow$ LDL
- Side effects
  - Constipation, bloating
  - Heartburn and diarrhea
  - Steatorrhea
  - Malabsorption of fat soluble vitamins
BREAK
INFLAMMATION

- Inflammation = a response of the immune system
  - Swelling, redness, pain
    - Vasodilation of local blood vessels
    - Increased permeability of capillaries, allowing leakage of large quantities of fluid into interstitial spaces
    - Clotting of fluid in interstitial spaces because of excessive amounts of fibrinogen and protein leakage
      - To “wall off” the inflamed area
  - Migration of large numbers of neutrophils, eosinophils and monocytes
  - Swelling of the tissue cells
INFLAMMATION

- Inflammation = a response of the immune system
  - Swelling, redness, pain
  - Acts on cells to release inflammatory mediators, such as arachidonic acid, prostaglandins, leukotrienes, neutrophils, macrophages, kinins, neuropeptides, histamine, etc.
  - Chronic inflammation results in progressive disability due to pain and destruction of bone and cartilage (ex. rheumatoid arthritis)
- 2 Goals
  - Relief of symptoms and maintenance of function
  - Slowing or arrest of tissue-damaging processes
Arachidonic acid metabolites and inflammation

from Robbins & Cotran's
Pathological Basis of Disease
8th ed
Kumar V et al. (eds).
INFLAMMATION

• COX – clycooxygenase
  • COX1 pathway
    • Constitutive
    • “Housekeeping” prostaglandins = good prostaglandins
      • keeps GI, renal and platelet function normal
  • COX2 pathway
    • Inductive
    • Inflammatory pathway of prostaglandins
Tissue Injury

Release of Phospholipids

Arachidonic Acid

Leukotrienes (bronchoconstriction)

Inhibitors
- Non-selective NSAIDS COX-1 and -2 Inhibitors
- Aspirin

Inflammatory Prostaglandins
- Recruit Inflammatory White cells
- Sensitize Skin Pain Receptors
- Stimulate hypothalamic fever response

Inducers
- Cytokines
- Growth factors
- TNF-α

Inhibitors
- Selective NSAIDS COX-2
- Non-selective NSAIDS COX-1
- and -2 Inhibitors
- Aspirin

COX-1
- Constitutional

Cytoprotective Prostaglandins
- Protective for Gastric Mucosa lining
- Aid Platelet Aggregation

COX-2
- Inducible
NSAID

- Non-steroidal anti-inflammatory drugs
- General properties
  - All are weak acids (except nabumetone)
  - Food does not significantly affect absorption
  - Highly metabolized in the liver and renally excreted
  - May produce gastrointestinal irritation
  - All are effective in joint pains
NSAID

- General MOA: inhibition of prostaglandin biosynthesis
- Other minor MOA:
  - Inhibits chemotaxis,
  - Down-regulation of interleukin-1 production
  - Decreased production of free radicals and superoxide
  - Interference with calcium-mediated intracellular events
  - Decrease sensitivity to bradykinin and histamine
  - Decrease T-lymphocyte function
  - Reverse vasodilation of inflammation
- May be taken orally or topical
NSAID

- General side effects
  - Gastric irritants
  - Nephrotoxicity
  - Hepatotoxicity

- Other possible side effects
  - Headache, dizziness
  - Fluid retention and hypertension
  - Asthma
  - Rashes/allergy
## NSAIDS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Para-aminophenol derivatives</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Indene derivatives</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Fenamates</td>
<td>Mefenamic acid</td>
</tr>
<tr>
<td>Propionic acid derivatives</td>
<td>Ibuprofen, naproxen</td>
</tr>
<tr>
<td>Oxicams</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Arylacetates</td>
<td>Diclofenac, ketorolac</td>
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</table>
ASPIRIN

• ASA or acetylsalicylic acid
• Mainly an anti-platelet drug, but with anti-inflammatory and analgesic activity
• MOA: irreversibly binds platelet COX and CNS COX
  • Anti-platelet aggregation
  • Controls febrile episodes (↓ release of prostaglandin E2 in the hypothalamus)
  • Relief of pain through peripheral and central mechanisms
ASPIRIN

• Not commonly used for its anti-inflammatory effect, except in a few conditions
  • Ex. Kawasaki disease, rheumatic fever and rheumatoid arthritis

• Side effects
  • Reye’s disease – stopped being used in children
    • Encephalopathy and fatty liver
  • Stop aspirin 8-10 days before an operation
NONSELECTIVE COX INHIBITORS

• Acetaminophen or paracetamol
  • Weak COX1 and 2 inhibitor
  • Inhibits prostaglandin in the brain
    • Anti-pyretic activity
  • No anti-inflammatory effect, no anti-platelet effect
  • Peak blood concentrations are reached after 30-60min
  • Minor metabolite (N-acetyl-p-benzoquinone) = hepato-renal toxicity
  • Used for mild to moderate pain
  • Ingestion of 15mg may be fatal due to liver and renal failure
    • Do not exceed 4g/day
  • Do not take with alcohol
NONSELECTIVE COX INHIBITORS

• Ibuprofen
  • MOA: inhibits COX and prostaglandin synthesis
  • 400mg q6h = 4 grams of aspirin in anti-inflammatory effect
  • 200mg q6h = more analgesic effect with minimal anti-inflammatory effect
• Other uses
  • Close PDA
• Side effects
  • Nephrotoxicity and GI upset
NONSELECTIVE COX INHIBITORS

- Naproxen
  - For rheumatologic conditions
  - Side effects
    - Upper GI bleed
    - Allergic pneumonitis
NONSELECTIVE COX INHIBITORS

• Indomethacin
  • COX inhibitor
  • Most potent inhibitor of prostaglandin synthesis
  • Also inhibits phospholipase A and C, reduce neutrophil migration and decrease T and B cell proliferation
• Uses
  • Close PDA
  • JRA (juvenile rheumatoid arthritis)
  • Pleurisy (inflammation of lining of pleural/lung cavity)
• Side effects
  • GI irritation + pancreatitis
  • Headache
  • Psychosis with hallucination
NONSELECTIVE COX INHIBITORS

- **Ketorolac**
  - Used mainly as analgesic for post-surgical pain
  - Side effect
    - More renal toxicity

- **Diclofenac**
  - Side effects
    - Gastrointestinal ulceration
    - Nephrotoxicity
NONSELECTIVE COX INHIBITORS

• Piroxicam
  • COX inhibition
  • Also inhibits polymorphonuclear (PMN) migration, decreases oxygen radical production and inhibits lymphocyte function
  • Used for rheumatologic conditions
  • Side effect
    • High risk for GI bleeding and ulceration
NONSELECTIVE COX INHIBITORS

- Mefenamic acid
  - MOA: inhibits COX and decreases prostaglandin
  - Less anti-inflammatory effect than aspirin, but similar gastric effects
NONSELECTIVE COX INHIBITORS

- Choice of NSAID
  - All NSAIDS are about equally efficacious
  - Choice will depend on basis of toxicity and cost-effectiveness and personal factors
    - Greatest hepato-renal toxicity = indomethacin
    - Least hepato-renal toxicity = aspirin and ibuprofen
    - Hepatotoxicity = diclofenac
    - Safest for GI irritation = coxibs, but expensive with greater risk for cardiovascular toxicity
  - No best NSAID for all persons. But 1 or 2 best NSAID per person.
COX 2 INHIBITORS

- "-Coxibs". Ex. Celecoxib
- No effect on platelet aggregation
- Inhibits COX2 in the vascular endothelium
  - Do not offer the cardioprotective effects of traditional NSAIDS
- Less GI adverse effects
COX 2 INHIBITORS

• Meloxicam
  • Similar to peroxicam
  • Preferentially inhibits COX2 over COX1 (not as selective as coxibs)
  • Less GI irritation
STEROIDS

- Anti-inflammatory agents
  - Non-analgesic
  - Decrease inflammation = decrease pain
- Systemic side effects