Name:____________________________
Class:_____________________________

"Pharmacology"

NSAIDS (2)
Lecture

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Dosage of Aspirin:

- Optimal analgesic dose or antipyretic dose is **less than 0.6 gm orally** (commonly used).
- Large dose will prolong the effect.
- Usual doses can be repeated every 4 hrs and smaller doses (0.3 gm) every 3 hrs.
- Children dose (50-75 mg / kg/day) in divided doses (at least three).
- Anti-inflammatory dose (4 gm/day) is fairly tolerated by adults.
- Blood levels of 15-30 mg/dl are enough for anti-inflammatory effect.

Due to long $t_{1/2}$ (about 12 hrs) of aspirin and its metabolites, frequent dosing is not required.

If daily doses needed are of 4 gm or more, it is better to give the total amount in 3 divided doses and to be taken after meals (meals act as buffer to ↓ adverse effect on GIT).

### Relationship of plasma salicylates level to dynamics and complications:

<table>
<thead>
<tr>
<th>Salicylate level</th>
<th>Effect</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 mg/dl</td>
<td>analgesic, antiplatelet aggregation, antipyretic</td>
<td>gastric intolerance, bleeding, allergy (hypersensitivity reactions) and impaired hemostasis</td>
</tr>
<tr>
<td>10-50 mg/dl</td>
<td>anti-inflammatory, uricosuric, Rheumatoid Arthritis</td>
<td>gastric intolerance, bleeding, allergy (hypersensitivity reactions) and impaired hemostasis</td>
</tr>
<tr>
<td>50-80 mg/dl</td>
<td>mild intoxication</td>
<td>central hyperventilation, tinnitus</td>
</tr>
<tr>
<td>80-110 mg/dl</td>
<td>moderate intoxication</td>
<td>fever, dehydration and metabolic acidosis</td>
</tr>
<tr>
<td>110-160 mg/dl</td>
<td>sever intoxication</td>
<td>vasomotor collapse coma and hypoprothrombinemia</td>
</tr>
<tr>
<td>&gt;160 mg/dl</td>
<td>lethal intoxication</td>
<td>renal and respiratory failure</td>
</tr>
</tbody>
</table>
Adverse Effects of Aspirin:

1. On GIT:
   - At usual doses, Aspirin cause *gastric intolerance* (minimized by suitable buffering food or milk).
   - *Gastritis* associated with Aspirin therapy is due to:
     1. Undissolved tablets.
     2. stomach absorption of non-ionized salicylate.
     3. inhibition of protective PGs (I₂ and E₂).
   - *Vomiting* may occur due to CNS stimulation after absorption of large doses.
   - *Upper GIT bleeding* usually due to large doses leading to erosive gastritis.
   - *Blood loss associated with Aspirin therapy (1 ml daily) increases to (4 ml daily) with usual doses and more for higher doses.*

2. On CNS:
   - Higher doses cause "*salicylism*" → ↓ hearing, vertigo (these are reversible when dosing is reduced or stopped).
   - Large doses cause "*hyperapnea*" by direct effect on medulla.
   - Low toxic doses cause *respiratory alkalosis* which cause increased ventilation, then *acidosis*(metabolic) due to accumulation of salicylic acid derivatives & then *depression of respiratory centre*.

3. Other side effects:
   - Aspirin in doses of 2 mg/day or less *increases* serum level of uric acid(inhibiting its secretion).
     Whereas by the doubling doses exceeding 4 mg/day, it *decreases* urate blood level below 2.5 mg/dl & this is known as *(paradoxic effect of aspirin) inhibiting its reabsorption.*
   - 15% of patients show hypersensitivity, so they are benefited from using other NSAIDs.
Aspirin given during viral infection causes increased incidence of *Reye's syndrome* (fatal hepatitis with cerebral oedema) in children (so they should take *Acetaminophen* instead of Aspirin).

- Toxic doses directly depress cardiac function & dilate peripheral blood vessels.
  - Large doses directly affect smooth m.
  - Hypersensitivity occurs in patients with asthma, nasal polyps (bronchoconstriction & shook) mediated by leukotriens.

*Note:* Since Aspirin inhibit cyclo-oxygenase (COX) so all arachidonic acids possibly metabolized by 5-lipoxygenase leading to excess leukotrien production.

**Contraindications of Aspirin:**

1. In hemophilia patients, since it causes blood loss.
2. Pregnancy, because it may lead to fetal malformation in the first 3 months of pregnancy. *Acetaminophen is preferred.*
3. Peptic ulcer.

**Over Dose & toxicity of Aspirin:**

1. *Serious intoxication occurs when the amount ingested exceeds 150-175 mg/kg* (gastric lavage is devised).

2. Hyperthermia is treated with a topical sponges or ice patches.

3. Also, maintain high urine volume & treat acid base abnormality.

4. In severe toxic reaction, ventilatory assisstant may be recommended. *NaHCO₃* infusion may be employed infusion to alkalinize urine & ↑ secretion of salicylates.
Drag interaction:
1. Drugs enhance salicylate intoxication as acetazolamid and NH₄Cl.
2. Alcohol increase GIT bleeding induced by aspirin.
3. Aspirin displace some drugs from protein binding sites: tolbamate, phenytoin, clorpropamide, NSAIDs, methotrexate, probenecid) and thus ↑ their free amount → ↑ their effects.
4. Aspirin ↓ activity of spironolactone and intensify the effects of heparin.
5. Aspirin competes with penicillin G for renal tubular secretion and inhibits uricosuric effect of sulphinpyrazon and probenecid.

Newer NSAIDs
Adverse effects of Aspirin have led to search for alternative compounds. In 1971 Ibuprofen and several other aspirin-like drugs were introduced later.
Chemistry: they are grouped in several classes, which are chemically diverse and broad variety in their Kinetics & properties

Dynamics:
1. Their anti-inflammatory activity is similar to aspirin in mechanism (i.e. by inhibition of PGs synthesis).
2. inflammation is reduced by ↓ release of mediators produced by granulocytes, basophils & mast cells.
3. they ↓ sensitivity of vessels to bradykinin and histamine.
4. All are analgesics, anti-inflammatory, antipyretics and all inhibit platelet aggregation.
5. All are gastric irritants, but less than aspirin.
6. Nephrotoxicity is observed for all of them.
7. Affect lymphokin production from T- lymphocytes and reverse vasodilation.
8. Thy inhibit prothrombin synthesis.

Ibuprofen: $t_{1/2} = 2$ hrs
• An analgesic, but inferior as anti-inflammatory agent $t_{1/2}$.
• Ibuprofen, when used in 2–4 gm/day, it equals 4 gm of aspirin as anti-inflammatory, but causes less gastric irritation.
• Metabolized by liver & abut 10% of it is excreted in urine unchanged.
• GIT irritation & bleeding occurs, but less than Aspirin.
• Contraindicated in patients with nasal polyps (because it affect airways) angioedema and bronchospastic reactivity of aspirin.
• GIT symptoms:
  rash, dizziness, headache, anxiety and fluid retention also reported.
• Interaction with anti-coagulants is uncommon.
• It also cause serious hemolytic effect granulocytosis, aplastic anemia, effects on kidney: renal failure, nephritis, nephrotic syndrome.

**Naproxen:** $t_{1/2} = 13$ hrs
• Binds to plasma protein, $t_{1/2} = 13$ hrs.
• Antacids delay its absorption.
• Excreted in urine as inactive glucuronid metabolites.
  • Competes with aspirin for plasma protein binding sites & it prolong prothrombin time.
• Average doses for inflammatory arthritis is 375 mg twice a day.

**Fenoprofen:** $t_{1/2} = 2$ hrs (needs multiple dosing)
• Dose for inflammatory arthritis = 600-800 mg 4 times daily.

*Adverse effects for naproxen and fenoprofen are similar to these of Ibuprofen.*

**Indomethacin:** $t_{1/2} = 2$ hrs
• more toxic than aspirin.
• more effective than aspirin and other NSAIDs.
• the most potent inhibitor of PGs synthesis especially (in vitro).
• well absorbed orally, high bound to plasma proteins, metabolized in liver and excreted unchanged or as inactive metabolites (excreted in bile & in urine).

• Clinical uses:
  - not suggested for general use as analgesic except for the treatment of patent ductus arteriosus.
  - should not be used in children.
  - useful in acute gouty arthritis, ankylosing spondylitis & osteoarthritis.
    In acute gout, it is replaces (colchicin) as the initial medication.

• Adverse Effects:
  1. produce high incidence of dose-related toxic effect.
  2. At higher dose, 30% of patients have reactions requiring discontinuation of therapy.
  3. GIT effect are abdominal pain, diarrhea, GIT hemorrhage.
  4. Severe headache is experience in 20-25 % of patients (may be with confusion, dizziness & depression).
  5. Hemolytic reactions are noted (thrombocytopenia & aplastic anemia).
  6. Coronary vasoconstrictiton also demonstrated.
  7. Hyprekalemia is also reported due to inhibition of PGs & its effects on kidneys.

Etodolac:
• Similar to the effects of other NSAIDs, GIT problems are less common.
- **Adverse effect:** fluid retention, abnormal kidney and liver functions are reported.
- It may increase serum level & adverse effect of digoxin, lithium, methotrexate, and enhance nephrotoxicity of cyclosporines.

**Diclofenac:**
- Approved for *long term treatment of osteoarthritis, ankylosing spondylitis & rheumatoid arthritis*
- More potent than indomethacin or naproxen.
- It accumulates in synovial fluid so cause healing of arthritis.
- Eliminated by urine.
- Toxicity: similar to other NSAIDs.
- GIT problems are common & it causes rise in hepatic enzymes level.

**Ketorolac:**
- Its action is similar to other NSAIDs, it is given *orally & IM in treatment of postoperative pain* and given *topically in treatment of allergic conjunctivitis*.
- It is metabolized by liver and eliminated in urine.
- Side effect: like other NSAIDs.

**Nebumeton:** as potent as aspirin in treating adult or juvenile rheumatoid arthritis or osteoarthritis with few side effect.

**Sulindac:**
- It is a prodrug effective only after conversion to sulfide by liver enzyme. Excreted in bile and then reabsorbed from intestine.
- The enterohepatic cycling prolongs its duration of action up to 16 hrs.
- Indication and adverse effect are similar to other NSAIDs.
- The dose for inflammatory arthritis = 200 mg twice daily (bid).

**Mefenamic Acid (ponstan):**
- It has analgesics properties.
It is less effective than aspirin as anti-inflammatory agent.
It is more toxic, not to be used for longer than 1 week & never used in children below 12 years.

Meclofenate: $t_{1/2} = 2$ hrs
- It reaches peak plasma conc. in 30–60 min after administration.
- Excreted in urine.
- It has similar adverse effect to other NSAIDs, with no advantage over time.
  - It enhances effects of oral anti-coagulants.
  - Contraindicated in pregnancy.
  - Dose for inflammatory arthritis = 200-400 mg/day divided into 4 doses (qid).

Tolmetin: $t_{1/2} = 1$ hr
- Similar to aspirin as anti-inflammatory agent.
- Adult dose is 400 mg, 4 times daily (qid).

Piroxicam: $t_{1/2} = 24$ hrs
- Long $t_{1/2} = 24$ hrs.
- Because of long $t_{1/2}$, it is used once a day.
- Rapidly absorbed from stomach & reaches 80% of peak plasma conc. in 1 hr.
- Used for rheumatoid disease and musculoskeletal disorders.
- Adverse effect, as GIT effects, occur in 20% of patients, (headache and rash).

Diflunisal: $t_{1/2} = 8-12$ hrs
- Like aspirin, it has analgesic & anti-inflammatory effects.
- It is indicated in pain & osteoarthritis.
- Adverse effects: similar to other NSAIDs.

COX-2 Selective inhibitors:
• **Coxibs** were developed to *inhibit prostacyclin synthesis* at site of inflammation without affecting the action of the constitutively active "housekeeping" COX-1 isoenzyme found in GIT, kidneys and platelets.

• **COXIBs selectively bind to and block the active site of the COX-2 enzymes much more effectively than that of COX-1.**

• Coxibs have analgesic, antipyretic and anti-inflammatory effects (have fewer GIT side effect).

• **They have NO effect on platelets aggregation.**

• Because COX-2 is constitutively active within the kidney, COX-2 inhibitors cause renal toxicities similar to traditional NSAIDs.

• Also, it has been found that a higher incidence or cardiovascular thrombotic events associated with COX-2 inhibitors (rofecoxib).

**Celecoxib:**

- *highly selective COX-2 inhibitor (10-20 times more selective for COX-2 than COX-1).*
  - It has a $t_{1/2}$ of 11 hrs and 27% of its dose excreted in urine (unchanged).
  - It is effective as the NSAIDs in rheumatoid arthritis and osteoarthritis (cause fewer endoscopic ulcer than other NSAIDs).
  - It may cause rashes (salfomamide).

**Etoricoxib:**

- A second generation COX-2 selective inhibitor with the highest selectivity ratio of any Coxib for inhibition of COX-2 relative to COX-1.
  - It is extensively metabolized by hepatic P450 enzymes and excretion is renal ($t_{1/2} = 22$ hrs).
  - It is used for the treatment of signs and symptoms of osteoarthritis, gouty arthritis, relief of acute musculoskeletal pain.

**Meloxicam:**
• This agent shown to inhibit COX-2 more than COX-1 (especially at lower doses).
  • it is not as selective as other coxibs, it is used for the treatment of most rheumatic diseases.
  • its use is associated with fewer clinical GIT symptoms & complications than piroxicam, diclofenac and naproxen.
  • $t_{1/2} = 20$ hrs.

Rofecoxib:
• A potent, selective COX-2 inhibitor, it is approved for the treatment of osteoarthritis and rheumatoid arthritis.
• it is an analgesic and antipyretic, it has no effect on platelets aggregation and small effect on GIT PGs.
  • At high dose, it causes edema and hypertension (occasional).
  • Other toxicities, similar to other coxibs.
  • $t_{1/2} = 17$ hrs.

Valdecoxib:
• A new, highly selective COX-2 inhibitor.
• $t_{1/2} = 8-11$ hrs and 90% eliminated unchanged by kidney.
• GI and other toxicities are similar to other coxibs with no effect on platelets (bleeding time)
  • In treatment of dysmenorrhea, it is as effective as non selective NSAIDs for this indication.

Non-Narcotic Analgesics
They have little or even no anti-inflammatory effect (unlike NSAIDs).
They have therapeutic advantages over narcotic analgesics (not causing dependence or tolerance).
These are Acetaminophen & phenacetin.

**Acetaminophen:**

**Mechanism of action:**
- Act by inhibiting PG synthesis in the CNS (this explains its anti-pyretic and analgesic properties).
- It has less effects on COX enzyme in peripheral tissue and this accounts for is weak anti-inflammatory effect.
- It doesn’t affect platelet function or increase blood clotting time & also lacks side effect of aspirin & doesn’t cause treatogenicity (i.e. it doesn’t increase bleeding time so producing no effect on bleeding time).

### Major Differences between and Aspirin and Acetaminophen:

<table>
<thead>
<tr>
<th>feature</th>
<th>Aspirin</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of inhibition</strong></td>
<td>peripherally</td>
<td>centrally</td>
</tr>
<tr>
<td><strong>COX inhibition</strong></td>
<td>irreversible</td>
<td>reversible</td>
</tr>
<tr>
<td><strong>Effect on inflammation</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Effect on platelet agg.</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Effect on bleeding time</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Side effects (SE)</strong></td>
<td>too many</td>
<td>Few and in ↑ dose</td>
</tr>
</tbody>
</table>

### Uses:
1. Suitable substitute for aspirin as antipyretic and analgesic especially in patients with gastric problems and prolongation of bleeding time.
2. It is the drugs of choice (as analgesic & antipyretic) in children with viral infection or chicken pox.
3. It doesn’t antagonize uricosuric agents probenecid and may be used in gouty patients using probenecid.

Kinetics:
- Rapidly absorbed from GIT, 1st pass metabolism occurs in luminal cells of the intestine and hepatocytes.
- Conjugated in liver and a portion is hydroxylated to N-acetyl benzoquinemine (NABQI) which is highly reactive & dangerous metabolite with sulfhydryl group of glutathione forming non toxic substance.
- Excreted in urine.

Adverse Effects:
1) At normal therapeutic doses, are nearly without side effects.
2) Skin rash and minor allergic reaction occur rarely.
3) Renal tubular necrosis and hypoglycemic coma are rare complication with prolonged large dose therapy.
4) With large doses, the available glutathione in the liver is depleted and NABQI reacts with sulfhydryl (SH) groups of hepatic proteins forming covalent bonds → leading to hepatic necrosis and very serious life-threatening condition can result.
5) Also renal tubular necrosis may occur.
Metabolism & Excretion of Acetaminophen:

- Sulfate → Acetaminophen → Glucuronide

- Glutathion

- Toxic intermediate
  - Therapeutic dose: Mercapturic (non-toxic)
  - Toxic dose: Macromolecular Cell death

- Cytochrome P_{450} (mixed oxidase function)

- Nucleophilic Hepatic cell proteins

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**THIS LECTURE WAS REVISED BY DR. AHMED HIMSELF, EDITED BY QATO0000B**