NSAIDs, Antirheumatic drugs, Drugs used in Gout, Non-Opioid analgesics

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Classification

Non-selective COX inhibitors

- Aspirin
- Ibuprofen
- Naproxen
- Flurbiprofen
- Mephenamic acid
- Diclofenac
- Aceclofenac
- Piroxicam, Tenoxicam
- Indomethacin
- Phenylbutazone

Preferential COX-2 inhibitors

- Nimesulide
- Meloxicam
- Nabumetone

Classification

Selective COX-2 Inhibitors

- Celecoxib
- Etoricoxib
- Rofecoxib
- Valdecoxib

Analgesics, antipyretics, poor antiinflammatory

- Paracetamol
- Nefopam
- Metamizol

Non-Acetylated Salicylates

- Magnesium choline salicylate
- Sodium salicylate
- Salicylsalicylate
  - Effective anti-inflammatory
  - Less effective analgesics
  - Less effective COX inhibitors
  - Preferable in patients with asthma, bleeding tendencies, renal dysfunction

NSAIDs

- **Pk.**
  - Well absorbed
  - Food does not change their bioavailability
  - Highly metabolized
  - Renal excretion
  - Enterohepatic circulation
  - Highly protein bound

NSAIDs

- **Pd:**
  - Selective COX-2 inhibitors do not affect platelet function at usual doses
  - Selective and preferential COX-2 inhibitors are less gastric irritants
  - Nephrotoxicity, Hepatotoxicity

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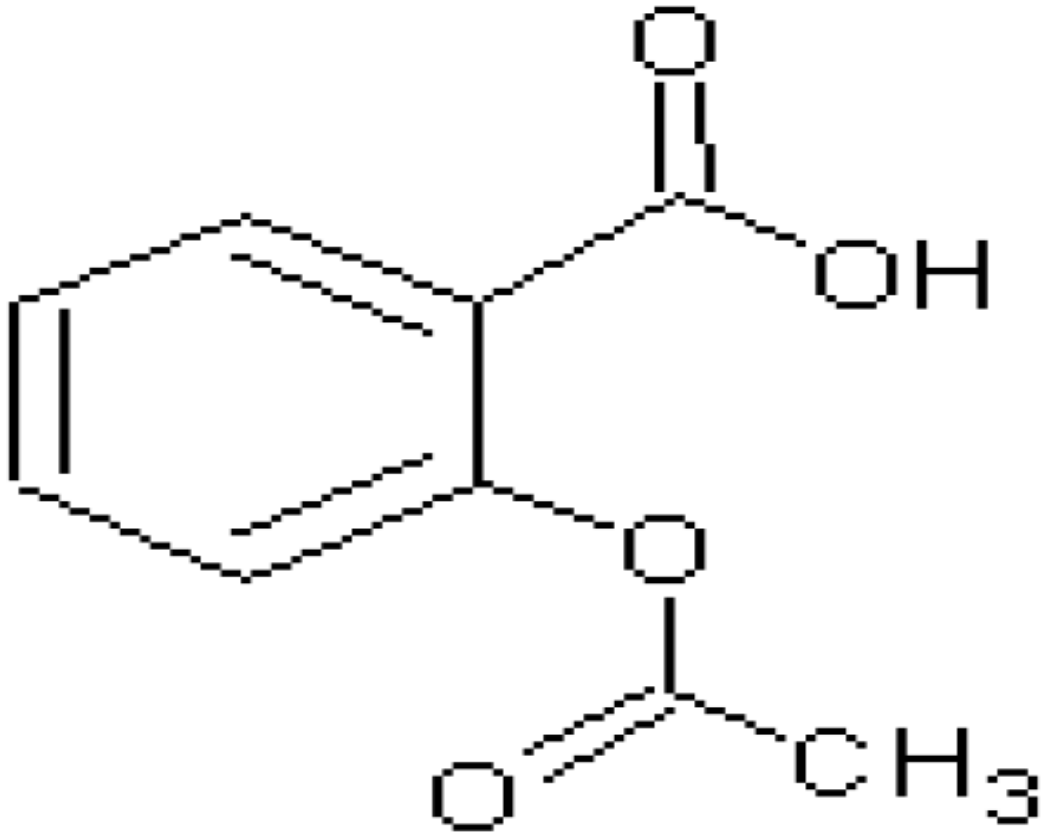
Aspirin (Salicylate)

- Acetylsalicylic acid; ASA
- Hydrolysed rapidly to acetic acid and salicylate
- T1/2= 15 mins
- **MOA:**
- <u>Anti-inflammatory:</u>
  - Irreversibly inhibits COX and platelet aggregation
  - Inhibits chemotaxis of leucocytes & macrophages



Aspirin

Acetylsalicylic Acid

$C_9H_8O_4$

Aspirin

- Analgesic effects:
  - Through effects on inflammation
  - Inhibits pain stimuli at subcortical site
- Antipyretic effect:
  - Inhibition of COX in CNS and IL-1 (released from macrophages during episodes of inflammation

Aspirin

- Antiplatelet effect:
  - Lasts 8-10 days (Life of platelet)
- Mild to moderate pain
  - In combination with opioids for severe pain (anti-inflammatory effects)
  - In high dose for rheumatic fever, rheumatoid arthritis, inflammatory joint conditions

Aspirin

- Other effects:
  - Decreases incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction
- ADRs:
  - Gastric ulcers
  - Less frequently: hepatotoxicity, asthma, rashes, renal toxicity

Aspirin

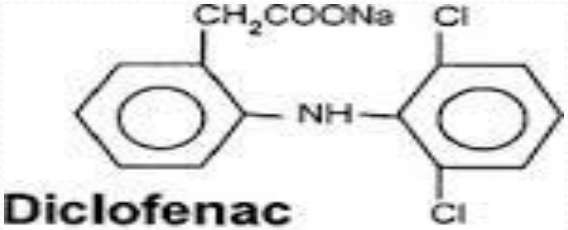
- Salicylism with higher doses:
  - Vomiting, tinnitus, decreased hearing, vertigo
  - Reversible on reducing dose
  - Still higher dose: Hyperpnea; through direct effect on medulla
- At toxic doses:
  - respiratory alkalosis followed by metabolic acidosis
  - Cardiotoxicity
  - Glucose intolerance

Aspirin

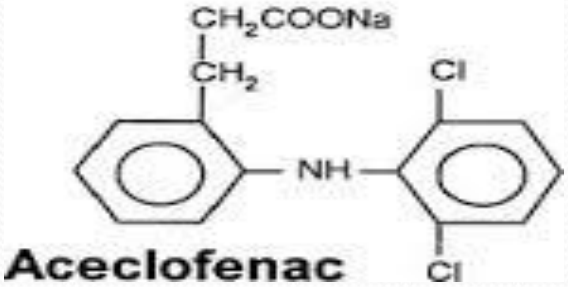
- Treatment of overdosage:
  - Gastric lavage, alkaline high urine output, ventilatory assistance, hyperthermia & electrolyte abnormalities should be treated

Diclofenac (Arylalkanoic acid)

- T1/2= 1 hour
- ADRs:
  - GIT distress
  - Occult GIT bleeding
  - Gastric ulceration
- Ophthalmic preparation for ophthalmic inflammation
- Also as oral, IM, rectal suppository



Diclofenac



Aceclofenac

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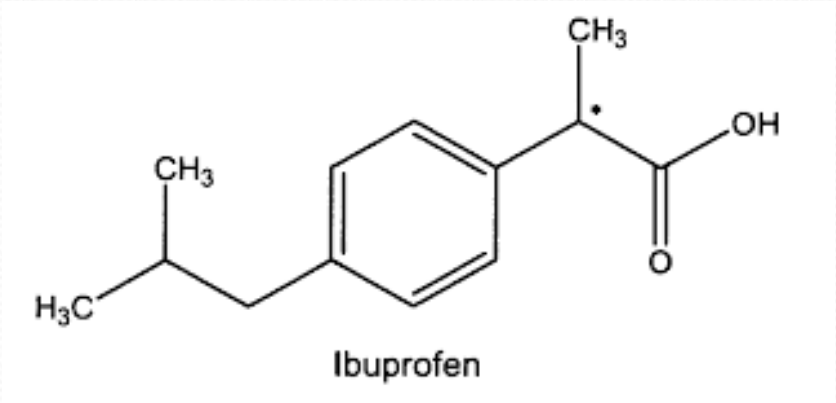
Ibuprofen (Arylpropionic acid)

- Lower doses prescribed: Analgesic effect seen, not anti-inflammatory
- Available as gel & topical cream preparations
- ADRs:
  - GIT irritation, rash, pruritus, tinnitus, dizziness, headache, fluid retention
  - Nephrotic syndrome, renal failure

Ibuprofen

- CI:
  - Nasal polyps, angioedema, bronchospastic activity to aspirin
- DI:
  - Concomitant administration antagonizes the irreversible platelet inhibition by aspirin



Ibuprofen

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Indomethacin (Arylalkanoic acid)

- Inhibits Phospholipase A and C
- Reduces neutrophil migration, decreases T cell and B cell proliferation
- Probenecid prolongs indomethacin's half life
- Uses:
  - Gout, ankylosing spondylitis, patent ductus arteriosus, ophthalmic preparation, oral rinse, epidural

Indomethacin

- ADRs:
  - GIT disturbances
  - Headache, dizziness, confusion, depression
  - Psychosis, hallucinations
  - Aplastic anemia, thrombocytopenia
  - Hyperkalemia (↓ synthesis of PG in kidneys)
- C.I:
  - As for Ibuprofen

Ketoprofen

- Inhibits both cyclo-oxygenase and Lipo-oxygenase
- But still not superior to other NSAIDs

Mefenamic acid (Fenamate)

- Inhibit both COX and PLA2
- Enhances the effect of anticoagulants
- C.I: in pregnancy
- Efficacy and safety not established in children
- More toxic than aspirin
- Less efficacious

Nabumetone (Naphthylalkanones)

- Only non-acid NSAID
- T1/2= > 24hrs
- Expensive
- No enterohepatic circulation
- Less damaging to stomach
- Reported to cause pseudoporphyria, photosensitvity in some

Piroxicam (Enolic acid)

- Also inhibits chemotaxis, decreases oxygen radical production
- For usual rheumatic indications
- Peptic ulcer and bleeding risk higher than with other NSAIDs

Sulindac

- Indications and ADRs similar to other NSAIDs
- In addition to rheumatic disease indications, familial intestinal polyposis, may inhibit development of colon, breast and prostate cancer
- Reoxidized to inactive prodrug in the kidney
- Hence inhibit renal COX less
- Stevens-Johnson syndrome, thrombocytopenia, agranulocytosis, hepatitis reported

Overall ADRs

- In renal insufficiency: non-acetylated NSAIDs are best
- Diclofenac and sulindac are associated with more liver function abnormalities
- COX-2 inhibitors safer for patients at risk of GIT bleeding
- In patients with GIT bleeding: prefer COX-2 inhibitors or non-selective plus omeprazole or misoprostol

COX-2 inhibitors

- "Good PGs and Bad PGs"
- COX-1: PGs for maintenance and protection of GIT
- COX-1 is dominant in GIT
- COX-2: PGs for inflammation and pain
- Constitutively expressed in certain areas of brain and kidney
- Increased risk of artherogenesis and stroke were seen with selective COX-2 inhibitors

COXIBs

- Rofecoxib out of market since September 2004
- Valdecoxib out of market since April 2005
- Celecoxib sold with warning

❖ Read on Paracetamol

THANKS

Additional Notes to guide Reading

- NSAIDs do not affect the tenderness induced by direct application of the PGs
- Block the sensitization mechn induced by TNFa, IL, Bradykinin and other analgesic substances.
- Therefore more effective against inflammation associated pain.

Notes

- Anti pyretic:
- NSAIDs reduce temperature by their action on pyrogens (IL, TNF a, Interferons which induce PGE2 in the hypothalamus) and not PGE2.

- PGs are only one of the mediators of inflammation. Inhibition of COX does not depress the production of other mediators like LTs, PAF, Cytokines.

Notes

- Inflammation is a s a result of collective participation of a large number of vasoactive chemtactic and proliferative factors at different stages.
- These may be targets for anti-inflammatory action.
- Activated endothelial cells express adhesion molecules (ECAM-1, ICAM-1) on their surface.
- These play a role in directing circulatory leucocytes to site of inflammation.

Notes

- Inflammatory cells express selectins and integrins. Certain NSAIDs work by additional mechanism of inhibiting expression and activity of some of these molecules and generation of superoxide free radicals.
- Stabilization of leucocyte lysosomal membrane and antagonism of certain action of kinnins may contribute