NSAIDs

- NSAIDs means "**N**on **S**teroidal **A**nti-**I**nflammatory **D**rugs"
- Nonnarcotic/ nonopioid analgesics.
- Analgesic, antipyretic and anti-inflammatory actions.
- Compared to morphine, they are weaker analgesics do not depress CNS and have no abuse liability.
- primarily on peripheral pain mechanism.
- Nomenclature NSAIDs was given to this class of drug to distinguish them from the anti inflammatory activity of glucocorticoids.

A. Nonselective COX inhibitors (Conventional NSAIDs)

1. Salicylates: Aspirin
2. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.
3. Indole derivatives: Indomethacin
4. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
5. Anthranilic acid derivative: Mephenamic acid.
6. Aryl Acetic acid derivatives: Diclofenac
7. Oxicam derivatives: piroxicam, Tenoxicam.
8. Pyrrolo-Pyrrole derivative: Ketorolac

B. Preferential COX-2 inhibitors

Nimesulide, Meloxicam, Nabumetone,

C. Selective COX-2 inhibitors

Celecoxib, Rofecoxib, Vadeecoxib, Etoricoxib

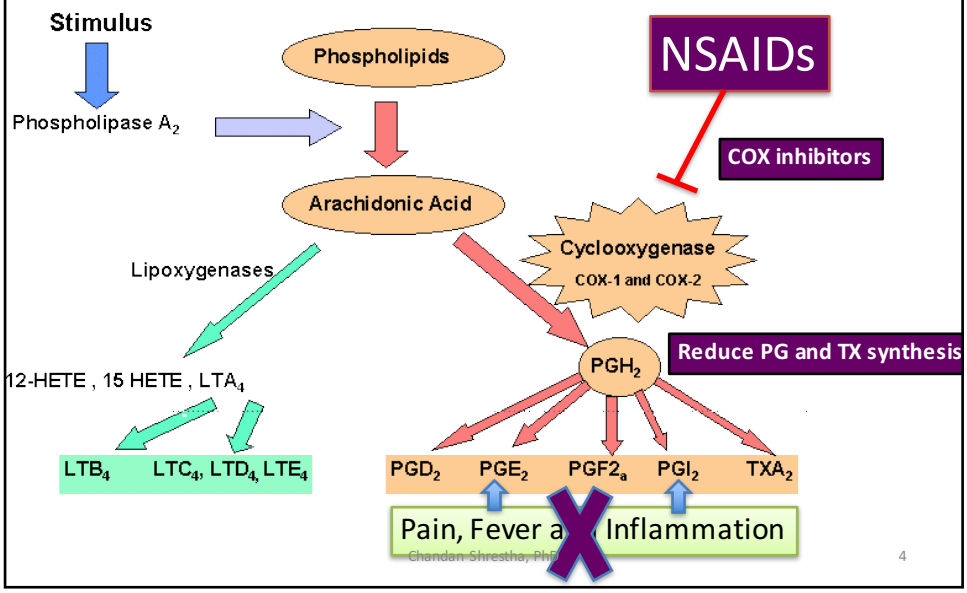
D. Analgesic-antipyretics with poor antiinfammatory action

1. Paraaminophenol derivative: Paracetamol (Acetaminophen)
2. Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone
3. Benzoxazocin derivative: Nefopam

Mechanism of Action

- The major mechanism by which the NSAIDs elicit their therapeutics effects (antipyretics, analgesic and anti-inflammatory activities) is inhibition of prostaglandin synthesis.
- NSAIDs competitively inhibit cyclooxygenase (COX) enzyme, the enzyme responsible for biosynthesis of prostaglandins from arachidonic acid.
- Aspirin causes irreversible inhibition of COX enzyme. Rest of the NSAIDS cause reversible inhibition of COX enzyme.

Mechanism of Action



Two Isoform of COX

COX 1
Physiologically expressed
Maintains the normal function (Homeostasis)
Expressed in Platelets, GIT
Inhibition is undesirable

COX-2
Induced in pathological states
Physiologically expressed in kidney, brain.
Inhibition is desirable

NON SPECIFIC NSAIDs produces bleeding tendency and peptic ulcer

Beneficial and toxicities due to PG synthesis inhibition

Beneficial actions due to PG Synthesis inhibition
- Analgesia
- Antipyresis
- Antiinflammatory
- Antithrombotic

Shared toxicities due to PG synthesis inhibition
- Gastric mucosal damage
- Bleeding: Inhibition of platelet function
- Limitation of renal blood flow: Na^+ and water retention
- Delay / prolongation of labour
- Asthma & anaphylactoid reactions

Adverse effects of NSAIDs

Gastrointestinal
Gastric irritation, erosions, peptic ulceration, gastric bleeding

Renal
Na+ and water retention , chronic renal failure, interstitial nephritis papillary necrosis (rare)

Hepatic
Raised transaminases, hepatic failure (rare)

CNS
mental confusion, behavioral disturbances, seizure precipitation

Haematological
Bleeding, thrombocytopenia, haemolytic anaemia, agranulocytosis

Others
Asthma exacerbation, skin rashes, pruritis, angioedema

ASPIRIN

- Aspirin is prototype drug
- Is a acetylsalicylic acid which is rapidly converted to salicylic acid (responsible for most the actions)
- The other non selective NSAIDs vary mainly in their potency, analgesic, ant inflammatory effects and duration of action.

Pharmacological Actions of Aspirin

Analgesic	Respiration
Antipyretic	Acid-base and electrolyte balance
Anti-inflammatory	GIT
Anti-platelets	CVS
Metabolic	Urate excretion

Antiinflammatory

- Observed at high doses.
- By inhibition of PG & other mediators synthesis, T-cell modulation & inhibiting chemotaxis

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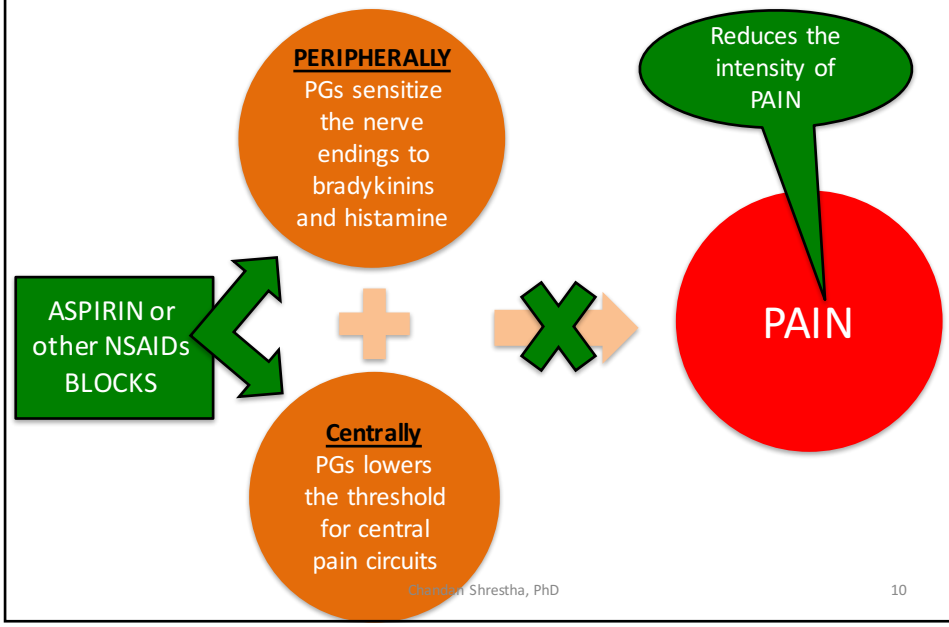
Analgesic



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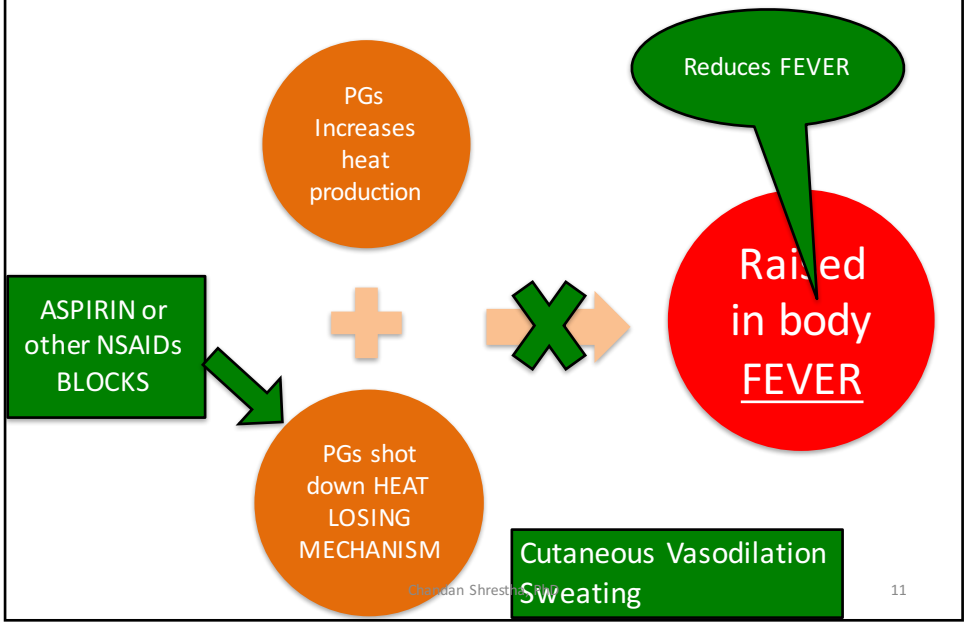
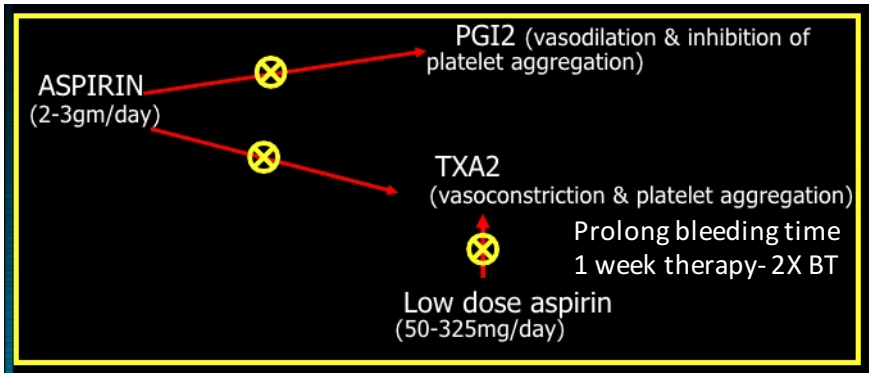
Antipyretic

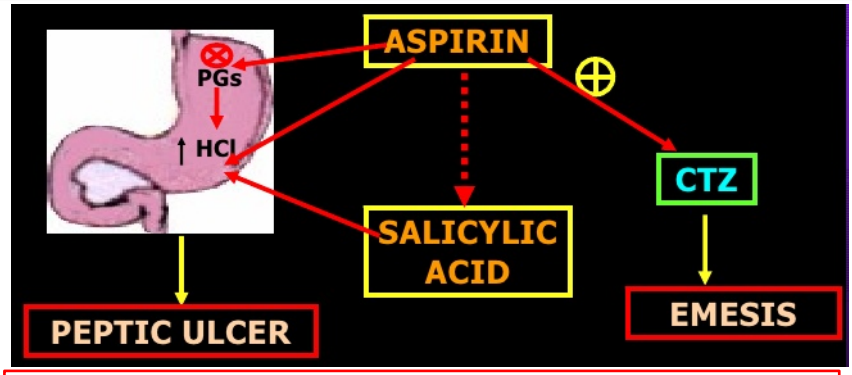


Antiplatelet



Decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction and thrombosis after coronary artery bypass grafting.

Gastrointestinal



Minimized by taking plenty of water or after Foods (not in empty stomach)
monitor bleeding complication
H2 blocker or proton pump inhibitor
Buffered aspirin
Enteric coated tablet

Side effects

Occur at analgesic dose (0.3-1.5g/d).

Nausea, vomiting, epigastric distress, increased occult blood loss in stools.

The most important adverse effect is gastric mucosal damage and peptic ulceration.

Ulcerogenic effect is major drawback of NSAIDS which is minimized by taking after food or or taken with H2 blockers or use of selective cox 2 inhibitors.

Hypersensitivity: Skin rashes, urticaria, broncheospasm (asthma), anaphylactic reaction

Antiinflammatory doses (3-6g/d)

Produce the syndrome *salicylism*.

The symptoms include headache, tinnitus, vertigo, reversible impairment of hearing, excitement and mental confusion, hyperventilation and electrolyte imbalance.

The symptoms are reversible on stoppage of therapy.

Can cause elevation of serum transaminase indicating liver damage.

Acute salicylate poisoning

- More common in children.
- Fatal dose in adult is estimated to be 15-30g. Lower in children.
- Serious toxicity is seen at serum salicylate levels >50mg/dl.
- Common manifestations are vomiting, dehydration, electrolyte imbalance, acidotic breathing, hyper/hypoglyceamia, petechial hemorrhages, restlessness, confusion, coma, convulsions, cardiovascular collapse, hyperpyrexia and death

Treatment

- Gastric lavage (to remove unabsorbed drug) followed by administration of activated charcoal
- I/V sodium bicarbonate to treat metabolic acidosis. It also alkalinizes the urine and enhances renal excretion of salicylates
- Fluid and electrolyte and acid base balance restoration
- Hemodailysis in severe cases
- Vit k and blood transfusion is given if there is bleeding

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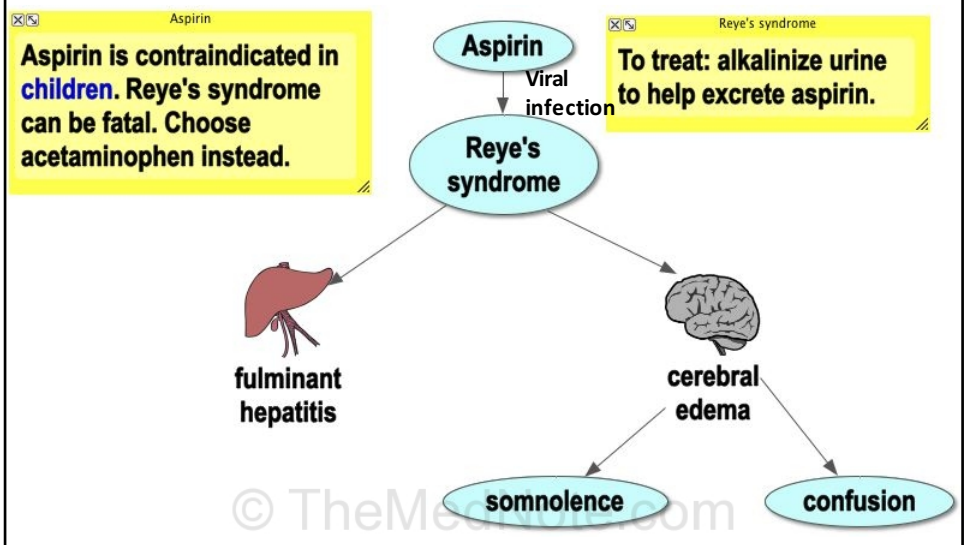
REYES SYNDROME



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Clinical Uses of Aspirin

ANALGESIC

ANTIPYRETIC
(PCM)

ANTIINFLAMMATORY
Rheumatic arthritis
Acute rheumatic fever

ANTI-PLATELET
Unstable Angina
Transient ischemic attack

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Nursing Consideration

- *GI upset*: not to take on empty stomach; after food
- *GI bleeding*: 3-7ml blood loss in stools---→black stool (melena)(Haematochezia: fresh blood in stool)

  Contraindicated in patient having peptic ulcer
- *Anti-platelet action*: Monitor bleeding complication

  Contraindicated in patient with Hemophilia
- **Monitor of hearing loss /tinnnitus (salicylate toxicity)**
- **COX inhibitor- Contraindicated in patient having asthma.**
- *RYES Syndrome*: not for the children (5 months -15 years)
- *Pregnancy*: **postpartum hemorrhage; delay of labor**

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Indomethacin

Extra MOAs, Extra uses, Extra adverse

- Nonselective reversible COX-inhibitor, Potent PGs-Inhibitors
- Potent anti-inflammatory; also Potent & promptly acting analgesic-antipyretic
- *Inhibit phospholipase-A & C; Inhibits migration of neutrophils in inflamed area*
- Use: rheumatic arthritis resistant to aspirin, acute gout
- *ADR: high incidence of (50%) CNS & GIT side effects. Increase bleeding due to decrease platelet aggregability.*
- Dose: 50mg tid

Ibuprofen

- Nonselective reversible COX-inhibitor
- Moderate anti-inflammatory
- Better tolerated than aspirin
- *Can be used in children*
- Dose:400-600mg tid

Mephenamic acid

- Nonselective reversible COX-inhibitor
- *Central as well as peripheral analgesic.*
- Useful in dysmenorrhea, joint & soft tissue pain
- *Diarrhea is most common adverse*
- Dose:250-500mg tid

Diclofenac

- Nonselective reversible COX-inhibitor
- Potent anti-inflammatory
- ADR: mild ADRs. Epigastric pain, nausea, headache, dizziness, rashes. Kidney damage is rare
- More hepatotoxic
- Use: most extensively used NSAIDs. Rheumatoid, and osteo-arthritis, ankylosing spondylitis, renal colic, posttraumatic and post-operative inflammatory condition.
- Dose: 50-100mg bid

Piroxicam

- Nonselective reversible COX-inhibitor
- Long acting potent anti-inflammatory
- Use: rheumatoid and osteo-arthritis
- GIT side effects pronounced (20%)
- Dose: 20 OD

Ketorolac

- Nonselective reversible COX-inhibitor
- *Potent analgesic; modest anti-inflammatory agent*
- *Equally effective as morphine but produce analgesia with out respiratory depression, hypotension & dependence*
- ADR: nausea, abdominal pain, loose stools, pain in injection site
- Used in renal colic, postoperative & cancer pain.
- Dose: 50-100mg bid

Preferential COX-2 inhibitors

Nimesulide

- Preferential COX2-inhibitor
- Weaker inhibitor of PGs synthesis.
- Antiinflammatory action may be exerted by other mechanism eg *reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNFα release*.
- ADRs Less than other NSAIDs.
- Useful in short lasting inflammatory pain e.g. sports injury sinusitis, bursitis, low backache, dysmenorrhea.
- Patient with history of asthma or intolerance to aspirin and other NSAIDs
- Dose:100mg bid

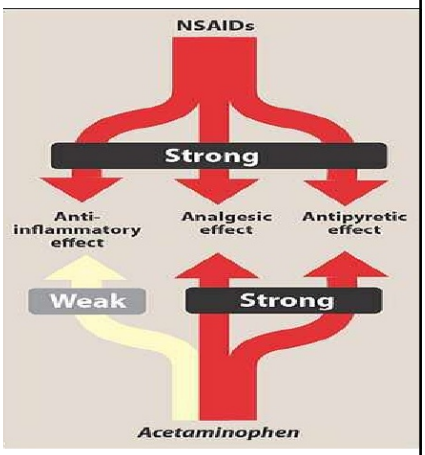
Selective COX2-inhibitor

- Potent anti-inflammatory, analgesic and antipyretic
- No antiplatelet actions.
- Use as other NSAIDs
- ADR : GIT side effects less; Nephrotoxic, Cardiotoxic
- Celecoxibs: 50mg-200/day
- Rofecoxib: 12.5-25 mg OD
- Etoricoxib

↑ risk of cardiovascular adverse events with COX 2 inhibitors
Higher BP, incidence of myocardial infarction, stroke

Paracetamol (Acetaminophen)

- Reversible non selective COX inhibitor
- Inhibits COX in the brain (Analgesic and Antipyretic effects).
- Less effect on peripheral tissues (Weak anti-inflammatory actions)
- Advantages: **No**
  - ✓ GI irritation,
  - ✓ peptic ulcer,
  - ✓ acid-base electrolyte imbalance,
  - ✓ anti-platelet action (do not prolong bleeding time) and
  - ✓ uricosuric effect



USE

Antipyretic: reduce body temperature during fever

Analgesic: to relieve headache, toothache, musculoskeletal pain, dysmenorrhea

Preferred analgesic and antipyretic in patients with *peptic ulcer, hemophilia, bronchial asthma and children.*

ADR: Safe and well tolerated. Nausea and rashes occur occasionally. Rarely produces hepatic toxicity.

Acute Paracetamol Poisoning

Paracetamol overdose

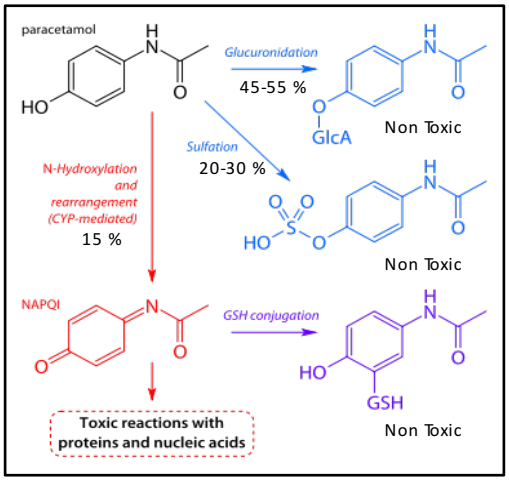
- Ingestion of >10g of paracetamol may be fatal
- May be lower in chronic alcoholics or subjects with underlying liver disease.

Clinical features

In severe poisoning

- Up to 24 hours - none or nausea and vomiting
- > 24 hours - nausea and vomiting, right upper quadrant pain, jaundice, encephalopathy

Mechanism of Toxicity



N-acetyl-p-benzoquinone imine

Treatment

Gastric lavage. **Activated charcoal** is given orally to prevent further absorption.

Specific antidote (N-acetylcysteine)

- Replenished the glutathione store of liver and prevents binding of the toxic metabolite to other cellular constituents.
- 150 mg/kg should be infused iv over 15 min, followed by same dose iv over the next 20 hr.

OR

- 75 mg/kg given orally every 4-6 h for 2-3 days.