NSAIDs

NSAIDs have following group of drugs

- Analgesic
- Antipyretic
- Antiinflammatory

Classification

A. Nonselective COX inhibitors (traditional NSAIDs)

1. Salicylates: Aspirin
2. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. Fenamate : Mephenamic acid
4. Enolic acid derivative: Piroxicam, Tenoxicam.
5. Acetic acid derivative: Ketorolac, indomethacin, nabumentone.
6. Pyrazolone derivative: phenylbutazone, Oxyphenbutazone

B. Preferential COX-2 inhibitors

Nimesulide, Meloxicam, Nabumeton, Diclofenac, Aceclofenac

C. Selective COX-2 inhibitors

Celecoxib, Etoricoxib, Parecoxib.

D. Analgesic-antipyratics with poor antiinflammatory action

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

Mechanism of action of NSAIDs

1. Antiinflammatory effect
   - Due to the inhibition of the enzymes that produce prostaglandin H2 synthase (cyclooxygenase, or COX), which converts arachidonic acid to **prostaglandins**, and to **TXA2** and **prostacyclin.**

- Aspirin irreversibly inactivates COX-1 and COX-2 by acetylation of a specific serine residue.
- This distinguishes it from other NSAIDs, which reversibly inhibit COX-1 and COX-2.

2. Analgesic effect

A. The analgesic effect of NSAIDs is thought to be related to:
   - the peripheral inhibition of prostaglandin production
   - may also be due to the inhibition of pain stimuli at a subcortical site.

B. NSAIDs prevent the potentiating action of prostaglandins on endogenous mediators of peripheral nerve stimulation (e.g., bradykinin).

3. Antipyretic effect

- The antipyretic effect of NSAIDs is believed to be related to:
  - inhibition of production of prostaglandins induced by interleukin-1 (IL-1) and interleukin-6 (IL-6) in the hypothalamus
  - the "resetting" of the thermoregulatory system, leading to vasodilatation and increased heat loss.

NSAIDs and Prostaglandin (PG) synthesis inhibition

- NSAIDs blocked PG generation.
- Prostaglandins, prostacyclin (PGI2), and thromboxane A2(TXA2) are produced from arachidonic acid by the enzyme cyclooxygenase.
- Cyclooxygenase (COX) exists in COX-1 and COX-2 isoforms.
- COX -3 has recently been identified

- Cyclooxygenase (COX) is found bound to the endoplasmatic reticulum. It exists in 3 isoforms:
- COX-1 (constitutive) acts in physiological conditions.
- COX-2 (inducible) is induced in inflammatory cells by pathological stimulus.
- COX-3 (in brain).

Actions of prostaglandins

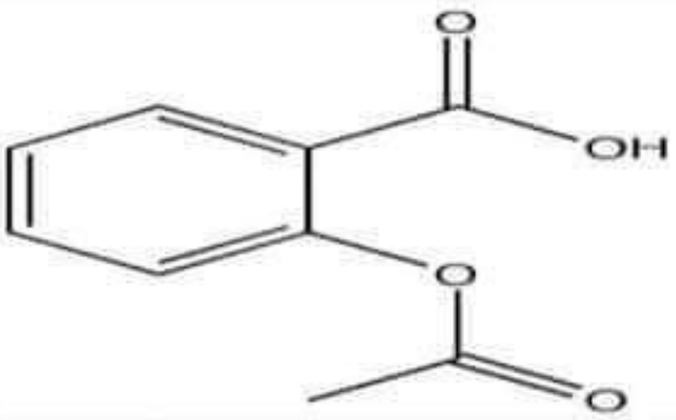
Beneficial actions	Shared toxicities
Analgesia	Gastric mucosal damage
Antipyretics	Bleeding (inhibition of platelet function
Anti inflammatory	Na and water retention
Antithrombotic	Delay/prolongation of labor
Closure of ductus arteriosus in newborn	Asthma and anaphylactoid reactions in susceptible individuals

Nonselective COX inhibitor

Salicylates

Aspirin:

- Aspirin is Acetylsalicylic acid converts to salicylic acid in body, responsible for action.



Aspirin

(acetylsalicylic acid)

Pharmacological actions of aspirin

Analgesic, antipyretic, antiinflammatory

- Aspirin is a weaker analgesic
- **Aspirin 600 mg < Codeine 60 mg**
- Relieves inflammation, tissue injury, connective tissue and integumental pain.
- The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings.
- No sedation
- Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss, but does not decrease heat production.
- Antiinflammatory action is exerted at high doses (3-6 g/ day or 100 mg/kg/ day)

Metabolic effects:

- Significant only at antiinflammatory doses
- Cellular metabolism is increased (skeletal muscles) increased heat production.
- There is increased utilization of glucose blood sugar may decrease (especially in diabetics) and liver glycogen is depleted.
- Chronic use of large doses cause negative N2 balance by increased conversion of protein to carbohydrate.
- Plasma free fatty acid and cholesterol levels are reduced.

Respiration:

- Effects are dose dependent.

- At antiinflammatory doses, respiration is stimulated by peripheral (increased C02 production) and central (increased sensitivity of respiratory centre to C02) actions.

- Hyperventilation is prominent in salicylate poisoning. Further rise in salicylate level causes respiratory depression; death is due to respiratory failure.

Acid-base and electrolyte balance:

- Antiinflammatory doses
- Initially, respiratory stimulation predominates and tends to wash out Co_2 despite increased production. respiratory alkalosis, which is compensated by increased renal excretion of HCO_3^-; (with accompanying Na+, K+ and water).
- Still higher doses cause respiratory depression with Co2 retention, while excess Co_2 production continues.... respiratory acidosis .

CVS:

- Aspirin has no direct effect in therapeutic doses.
- Larger doses increase cardiac output to meet increased peripheral O_2 demand and causes direct vasodilatation.
- Toxic doses depress , vasomotor centre: BP may fall. Because of increased cardiac work as well as Na+ and water retention.

GIT:

- Aspirin and released salicylic acid irritate gastric mucosa, cause epigastric distress, nausea and vomiting.
- It also stimulates CTZ.

Urate excretion:

- Aspirin in high dose reduces renal tubular excretion of urate

Blood:

- Aspirin, even in small doses, irreversibly inhibits TXA2 synthesis by platelets. Thus, it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value.
- long-term intake of large dose decreases synthesis of clotting factors in liver and predisposes to bleeding; can be prevented by prophylactic vit K therapy.

Pharmacokinetics

- Aspirin is absorbed from the stomach and small intestines.
- Its poor water solubility is the limiting factor in absorption: microfining the drug particles and inclusion of an alkali (solubility is more at higher pH) enhances absorption.
- Aspirin is rapidly deacetylated in the gut wall, liver, plasma and other tissues.

- It slowly enters brain but freely crosses placenta.
- The metabolites are excreted by glomerular filtration as well as tubular secretion.

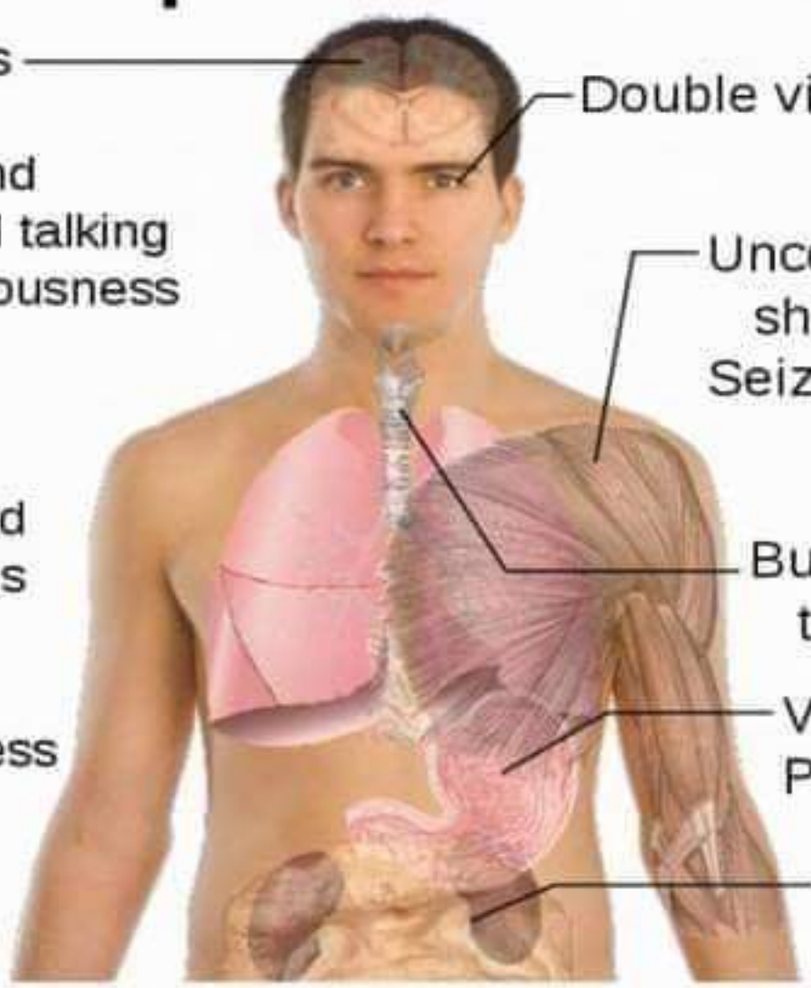
Uses of Aspirin

- As analgesic for headache, backache, pulled muscle, toothache, neuralgias.
- As antipyretic in fever of any origin in the same doses as for analglesia. However, *paracetamol and metamizole are safer*, and generally preferred.
- Acute rheumatic fever. *Aspirin is the first drug of choice.*
- Rheumatoid arthritis. Aspirin a dose of 3 to 5 g/24 h *after meal* is effective in most cases. the new NSAIDs (diclofenac, ibuprofen, etc.) in depot form are preferred.

- An association between salicylate therapy and "Reye's syndrome", *a rare form of hepatic encephalopathy seen in children, having viral infection* (varicella, influenza), has been noted.
- *Aspirin should not be given to children under 15years* unless specifically indicated, e.g. for juvenile arthritis (paracetamol is preferred).
- Postmyocardial infarction and poststroke patients: By inhibiting platelet aggregation in low doses (100 mg daily) Aspirin decreases the incidence of reinfarction.

Symptoms of

Aspirin overdose



Adverse effects

1. Gastrointestinal effects

- most common adverse effects of high-dose aspirin use (70% of patients):
  - nausea
  - vomiting
  - diarrhea or constipation
  - dyspepsia (impaired digestion)
  - epigastric pain
  - bleeding, and ulceration (primarily gastric).

- The gastrointestinal effects may contraindicate **aspirin** use in patients with an active ulcer.

- Decrease gastric irritation by:
  - Substitution of enteric-coated or timed-release preparations, or
  - the use of **nonacetylated salicylates**, may decrease gastric irritation.

Hypersensitivity (intolerance)

- Hypersensitivity is relatively uncommon with the use of aspirin (0.3% of patients); hypersensitivity results in:
  - rash
  - bronchospasm
  - rhinitis
  - Edema, or
  - an anaphylactic reaction with shock, which may be life threatening.

- The incidence of intolerance is highest in patients with asthma, nasal polyps, recurrent rhinitis, or urticaria.
- Aspirin should be avoided in such patients.

- **Cross-hypersensitivity** may exist:
  - to other NSAIDs
  - to the yellow dye tartrazine, which is used in many pharmaceutical preparations.
- Hypersensitivity is not associated with:
  - sodium salicylate or
  - magnesium salicylate.

- **Renal:** Na and water retention, chronic renal failure, nephropathy, papillary necrosis
- **CVS:** Rise in BP, risk of myocardial infacrtion

- **Hepatic:** raised transminases, hepatic failure.
- **CNS:** Headache, mental confusion, vertigo, behavioural disturbances, seizure precipitation
- **Haematological :** Bleeding, thrombocytopenia, heamolytic anaemia, agranulcytosis
- **Other:** asthma, rhinitis, nasal polyposis, skin rashes, pruritis, angioedema

- The use of aspirin and other salicylates to control fever during viral infections (influenza and chickenpox) in children and adolescents is associated with an increased incidence of Reye's syndrome, an illness characterized by vomiting, hepatic disturbances, and encephalopathy that has a 35% mortality rate.
- Acetaminophen is recommended as a substitute for children with fever of unknown etiology.

Drug interactions

Pharmacodynamic		Pharmacokinetic	
Diuretics	: ↓ diuresis	Oral anticoagulants Sulfonylureas Phenytoin Valproate	Metabolism inhibited; competition for plasma protein binding
β blocker	: ↓ antihypertensive effect		
ACE inhibitors	: ↓ antihypertensive effect		
Anticoagulants	: ↑ risk of g.i. bleed		
Sulfonylureas	: ↑ risk of hypoglycaemia	Digoxin Lithium Aminoglycosides Methotrexate	↓ Renal excretion of interacting drug
Alcohol	: ↑ risk of g.i. bleed		
Cyclosporine	: ↑ nephrotoxicity		
Corticosteroids	: ↑ risk of g.i. bleed		
Selective serotonin reuptake inhibitors	: ↑ risk of g.i. bleed		

PROPIONIC ACID DERIVATIVES

- Ibuprofen was the first member
- The analgesic, antipyretic and antiinflammatory efficacy is rated somewhat lower than high dose of aspirin.
- All inhibit PG synthesis, naproxen being the most potent; but their *in vitro* potency tor this action does not closely parallel *in vitro* antiinflammatory potency.
- Inhibition of platelet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

- Ibuprofen:
- In doses of 2.4 g daily it is equivalent to 4 g of Aspirin in anti-inflammatory effect.
- Oral ibuprofen is often prescribed *in lower doses* (< 2.4 g/d), at which it *has analgesic but not antiinflammatory efficacy*. It is available in low dose forms under several trade names (e. g. *Nurofen® – film-tabl. 400 mg).*
- A liquid gel preparation of ibuprofen provides prompt relief in postsurgical dental pain.
- In comparison with indometacin, ibuprofen decreases urine output less and also causes less fluid retention.
- It is effective in closing ductus arteriosus in preterm infants, with much the same efficacy as indometacin.

- Flurbiprofen:
- Its (S)(-) enantiomer inhibits COX nonselectively, but it has been shown in rat tissue to also affect TNF-α and NO synthesis.
- Hepatic metabolism is extensive. It does demonstrate enterohepatic circulation.
- The efficacy of flurbiprofen at dosages of 200–400 mg/d is comparable to that of Aspirin and other NSAIDs for patients with rheumatoid arthritis, gout, and osteoarthritis.
- Flurbiprofen i.v. is effective for perioperative analgesia in minor ear, neck, and nose surgery and in lozenge form for sore throat.

Adverse effect

- Ibuprofen and all its congeners are better tolerated than aspirin.
- Side effects are milder and their incidence is lower.
- Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects.
- Gastric erosion and blood loss are rare.
- CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression.
- Rashes, itching and other hypersensitivity phenomena are infrequent.
- They are not to be prescribed to pregnant woman and should be avoided in peptic ulcer patient.

Pharmacokinetic and interactions

- Well absorbed orally.

- Highly bounded to the plasma protein (90-99%).
- Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided.
- Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.
- All enter brain, synovial fluid and cross placenta.
- They are largely metabolized in liver by hydroxylation and glucuronide conjugation
- Excreted in urine as well as bile.

Uses

- Ibuprofen is used as a simple analgesic, and antipyretic in the same way as low dose of aspirin.
- It is particularly effective in dysmenorrhoea. In which the action is clearly due to PG synthesis inhibition.
- It is available as an over-the-counter drug.
- Used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders.
- Soft tissue injuries, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation.

Anthranilic acid derivative

- **Mephenamic acid:**
- An analgesic, antipyretic and weaker antiinflammatory drug, which inhibits COX as well as antagonises certain actions of PGs.
- Mephenamic acid exerts peripheral as well central analgesic action.

Adverse effects:

- Diarrhoea is the most important dose-related side effect. Epigastric distress is complained.
- Skin rashes, dizziness and other CNS manifestations have occurred.
- Haemolytic anaemia is a rare but serious complication.

Pharmacokinetics:

- Oral absorption is slow but almost complete. It is highly bound to plasma proteins-displacement interactions can occur; partly metabolized and excreted in urine as well as bile. Plasma t1/2 is 2-4 hours.

Uses:

- Mephenamic acid is indicated primarily as analgesic in muscle, joint and soft tissue pain.
- It is quite effective in dysmenorrhoea.
- It may be useful in some cases of rheumatoid and osteoarthritis.

Aryl-acetic acid derivatives

Diclofenac:

- An analgesic-antipyretic antiinflammatory drug, similar in efficacy to naproxen. It inhibits PG synthesis and is somewhat COX-2 selective.
- The antiplatelet action is short lasting. Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.

Adverse effects

- mild epigastric pain, nausea, headache, dizziness, rashes. Gastric ulceration and bleeding are less common.
- Reversible elevation of serum aminotransferases has been reported more commonly

Uses:

- Decreases upper GI ulceration but may result in diarrhoea.
- Rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, post-traumatic and postoperative inflammatory conditions-affords quick relief of pain and wound edema.

Oxicam derivatives

- Piroxicam:
- It is a long-acting potent NSAID with antiinflammatory potency similar to indomethacin and good analgesic-antipyretic action.
- It is a reversible inhibitor of COX;
- lowers PG concentration in synovial fluid and
- Inhibits platelet aggregation-prolonging bleeding time.
- In addition, it decreases the production of IgM rheumatoid factor and leucocyte chemotaxis.

Pharmacokinetics:

- It is rapidly and completely absorbed
- 99% plasma protein bound;
- Hydroxylation and glucuronide conjugation;
- Excreted in urine and bile;
- Plasma t1/2 is long nearly 2 days.

Adverse effects:

- The g.i. side effects are more than ibuprofen,
- less ulcerogenic than indomethacin or phenylbutazone;
- less faecal blood loss than aspirin.
- Rashes and pruritus are seen in < 1% patients. Edema and reversible azotaemia have been observed.
- Tenoxicam:
- A congener of piroxicam with similar properties and uses.

Pyrrolo-pyrrole derivative

Ketorolac:

- A novel NSAID with potent analgesic and modest antiinflammatory activity.
- In postoperative pain it has equalled the efficacy of morphine
- It inhibits PG synthesis and relieves pain by a peripheral mechanism.
- Rapidly absorbed after oral and i.m. administration.
- It is highly plasma protein bound and 60% excreted unchanged in urine.
- Major metabolic pathway is glucuronidation.
- plasma t1/2 is 5-7 hours.

Adverse effects:

- Nausea, abdominal pain,
- Dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness,
- Nervousness, pruritus, pain at injection site, rise in serum transaminase and fluid retention have been noted.

Use:

- Ketorolac is frequently used in postoperative, dental and acute musculoskeletal pain
- It may also be used for renal colic,
- Migraine and pain due to bony metastasis.

Indole derivative

Indomethacin:

- It is a potent antiinflammatory drug with prompt antipyretic action.
- Indomethacin relieves only inflammatory or tissue injury related pain.
- It is a highly potent inhibitor of PG synthesis and suppresses neutrophil motility.

Pharmacokinetics:

- Indomethacin is well absorbed orally
- It is 90% bound to plasma proteins, partly metabolized in liver to inactive products and excreted by kidney.
- Plasma t1/2 is 2-5 hours.

Adverse effect:

- A high incidence (up to 50%) of GI and CNS side effects is produced: GI bleeding, diarrhoea, frontal headache, mental confusion, etc.
- It is contraindicated in machinery operators,
- Drivers, psychiatric patients, epileptics, kidney
- Disease, pregnant women and in children.

PREFERENTIAL COX-2 INHIBITORS

Nimesulide:

- weak inhibitor of PG synthesis and COX-2 selectivity.
- Antiinflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNFa release, free radical scavanging, inhibition of metalloproteinase activity in cartilage.

- The analgesic, antipyretic and antiinflammatory activity of nimesulide has been rated comparable to other NSAIDs.

- It has been used primarily for **short-lasting painful** inflammatory conditions like sports injuries, sinusitis and other ear-nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and for fever.
- **Adverse effects** of nimesulide are gastrointestinal (epigastralgia, heart burn, nausea, loose motions), dermatological (rash, pruritus) and central (dizziness).

SELECTIVE COX-2 INHIBITORS

- They cause **little gastric mucosal damage;** occurrence of peptic ulcer and ulcer bleeds is clearly lower than with traditional NSAIDs.
- They do not depress TXA2 Production by platelets (COX-I dependent);
- Do not inhibit platelet aggregation or prolong bleeding time
- Reduce PGI2 production by vascular endothelium.
- It has been concluded that selective COX-2 inhibitors should be used only in patients at high risk of peptic ulcer, perforation or bleeds.

- If selected, they should be administered in the lowest dose for the shortest period of time.
- Avoided in patients with ischaemic heart disease/ hypertension/ cardiac failure/ cerebrovascular disease.

Celecoxib:

- It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential.
- Comparative trials in rheumatoid arthritis have found it to be as effective as naproxen or diclofenac, without affecting COX- 1 activity in gastroduodenal mucosa .

- Platelet aggregation in response to collagen exposure remained intact in celecoxib recipients and serum TXB2 levels were not reduced.
- Though tolerability of celecoxib is better than traditional NSAIDs, still abdominal pain, dyspepsia and mild diarrhoea are the common side effects.
- Rashes, edema and a small rise in BP have also been noted.

- Celecoxib is slowly absorbed,

- 97% plasma protein bound and metabolized primarily by CYP2C9 with a t1/2 of 10 hours.
- It is approved for use in osteo- and rheumatoid arthritis in a dose of 100-200 mg BD.

PARA AMINO PHENOL DERIVATIVES

PARACETAMOL (acetaminophen)

Phenacetin introduced in 1887 used as analgesic antipyretic

Banned because it was implicated in analgesic abuse nephropathy

Pracetamol the active metabolite of phenacetin introduced in last century and come in common use in 1950

Pharmacological actions

- Central analgesic action like aspirin (raise pain threshold)
- Weak peripheral anti-inflammatory component
- Analgesic action of aspirin and paracetamol is additive
- Poor inhibitor of PG in peripheral tissues
- Active on COX in brain
- Inability to inhibit the peroxides which are generated at sites of inflammation (poor anti-inflammatory)
- Ability of paracetamol to inhibit the COX in dog brain also account for analgesic and antipyretic

- In contrast to aspirin. Pracetamol doesnot stimulate respiration or affect acid base balance
- Does not increase cellular metabolism
- No effect on CVS
- Gastric irritation is insignificant
- Mucosal erosion and bleeding occur rarely only in overdose
- Doesn't effect platelet function or clotting factors and it is not uricosuric

Pharmacokinetics

- Well absorbed orally
- Only 1/4th is protein bound in plasma
- Uniformly distributed in the body
- Conjugation metabolism with glucuronic acid and sulfate
- Conjugates are rapidly excreted rapidly in urine
- Plasma t1/2 is 2-3hours
- Oral dose last for 5 hours

Adverse effects

- Isolated antipyretic doses paracetamol is safe and tolerated
- Nauses , vomiting and leukopenia (rare)
- Acute paracetamol poisoning: small children (conjugation poor) large dose >150mg/kg or >10g in a adult) serious toxicity can occur, >250mg /kg fatal
- Abdominal pain, liver tenderness
- Centrilobular hepatic necrosis, renal tubular necrosis and hypoglycemia to coma
- Jaundice starts after 2 days
- Hepatic failure and death next

Uses:

- Common over the counter drugs
- Headache, mild migraine, musculoskeletal pain, dysmenorrhea
- Ineffective in inflammation present in rheumatoid arthritis
- First choice analgesic for osteoarthritis
- Best drug for antipyretic
- Can be give to ulcer patients
- No metabolic effects
- No prolonged bleeding time
- No acid base disturbance
- No hypersentivity

Given to aspirin contraindicated patients

Thank you