Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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NSAIDs

- Also known **as Non-Narcotic or Non-Opioid analgesics ..**differs from Morphine

- Is Nonsteroidal **because** it differs from corticosteroids like Prednisolone & others in terms of mechanism of action, adverse effects & uses.

- NSAIDs are considered **as Aspirin-like drugs because** Aspirin is the Prototype in this group.

NSAIDs - History

- **1829 – Leroux used Bark of Willow in pure form (Salin) à** Demonstrated Antipyretic Effect.
- Salin à **Hydrolysed toà Glucose + Salicylic acid à Salicylic alcohol à Salicylic acid.**
- **1875 –** Sodium salicylate was used as antipyretic, as uricosuric in Gout & in Rheumatic fever.
- Hoffmann à **synthesized Acetyl salicylic acid**
- **1899 – Dreser** à introduced à Acetyl salicylic acid as **à Aspirin**
- **Later on à newer Non-selective COX-inhibitors like Paracetamol (Acetaminophen), Indomethacin** & then Selective COX-2 inhibitors like Celecoxib, **Rofecoxib**, **Etoricoxib** were introduced.

NSAIDs – Classification

1) **Non-selective COX (cyclooxygenase) Inhibitors :-**

i) **Salicylates :** Aspirin
ii) **Proprionic acid derivatives :** Ibuprofen, Flurbiprofen, Ketoprofen & Naproxen
iii) **Acetic acid derivatives :** Diclofenac, Aceclofenac
iv) **Fenamic acid derivatives :** Mefenamic acid
v) **Pyrrolo-pyrrole derivatives :** Ketorolac, Etodolac
vi) **Oxicam derivatives :** Piroxicam
vii) **Indole derivatives :** Indomethacin

2) **Preferred COX-2 inhibitors :** Nimesulide, Meloxicam

3) **Highly Selective COX-2 inhibitors :** Etoricoxib, Rofecoxib

4) **Analgesic, Antipyretic with poor Antiinflammatory effect :** Paracetamol.

NSAIDs – Mechanism of Action

- **Two Pathways :- Cyclooxygenase (COX) & Lipooxygenase (LOX)**

- **2 - Isoforms of COX : COX-1 & COX-2**

- **COX-1 à is Constitutive à Found in Blood vessels, Stomach & Kidneys à Have protective effects like prevents bleeding, GI ulcers & renal failure.**
- **Blocking of COX-1 pathway à loses protective effects and produce bleeding from blood vessels & tissues, GI ulcers & CRF.**

- **COX-2 à is Inducible à Responsible for production of mediators of inflammation à Induces Inflammation & Pain.**
- **Blocking COX-2 pathway à Relieves pain & Inflammation.**

NSAIDs – Mechanism of Action

Membrane Phospholipids

↓

Arachidonic acid

Cyclo-oxygenase
(Cox -1,COX-2) Pathway

↓

PGG2

↓

PGH2

↓ PGs synthetase

↓ **(--) NSAIDs Inhibits**

(PGF2α, PGD2, PGE2)

↓ **(Prostaglandins)**

PGI synthetase

↓

PGI2 (Prostacyclin) synthesis

Lipo-oxygenase (LOP) Pathway

↓

Hydroperoxides

↓

(LTs Inhibitors)

↓ (--)

Leukotrienes (LTs) synthesis

TXA synthetase

↓

TXA2 (Thromboxane) synthesis

NSAIDs – Mechanism of Action

- **Indomethacin à** inhibits Phosphodiesterase à ↑ intracellular cAMP conc.à stabilizes lysosomal membranes in polymorpho -nuclear leukocytes à prevents release of inflammatory enzymes.

- **Aspirin à** inhibits PGs synthesis & activation of T-lymphocytes à Inhibits release of Inflammatory mediators.

- **Diclofenac, Indomethacin à** Inhibits COX & LOX pathways à inhibits synthesis of PGs, TXA2, LTs.

ASPIRIN & NSAIDs - Actions

- Has analgesic, antiinflammatory & antipyretic actions

1) **Analgesic effect :-** Relieves Musculoskeletal pain, dysmenorrhoea & inflammatory pain by inhibiting PGs & TXA2 synthesis. Increases pain threshold level by acting at subcortical level. No sedation, tolerance, dependence.
2) **Antiinflammatory effect :-** **NSAIDS à** Suppresses signs & symptoms of inflammation, pain, tenderness, swelling, vasodilatation & leukocytes infiltration. **NSAIDs à** inhibits PGs synthesis at injury site à inhibits mediators like Histamine, Bradykinin, Serotonin à Inhibits adherence of Granulocytes to damaged vasculature. **NSAIDs à** also modulates T-cell function, Stabilizes lysosomal membrane & Inhibits chemotaxis. **Aspirin à** 4-6 Gm / Day has antiinflammatory effect.
3) **Antipyretic effect :-** **ASPIRIN & NSAIDs à** Inhibits PGs synthesis in Hypothalamus à Resets hypothalamic thermostat & reduce elevated body temperature to normal during fever. Also promote heat loss by causing cutaneous vasodilatation & sweating.

ASPIRIN & NSAIDs - Actions

4) Antiplatelet (Antithrombotic) effect : -

ASPIRIN (Low Dose 50-325 mg/day) à

irreversibly inhibits platelet TXA2 synthesis à produces antiplatelet effectà lasts for 8-10 days i.e life span of platelets. Withdraw Aspirin 1 week before any planned surgery to reduce risk of profuse bleeding during surgery.

ASPIRIN (at high dose 2-3 G/Day) à inhibits PGI2 & TXA2 synthesis à Hence losses beneficial effects of PGI2.

ASPIRIN & NSAIDs - Actions

Inhibits (--) PGI2 (PGI2 causes vasodilatation & inhibits platelet aggregation)

ASPIRIN (2-3 G/Day)

Inhibits (--) TXA2 (TXA2 causes vasoconstriction & promotes platelet aggregation)

Inhibits (--) ↑

ASPIRIN – Low Dose (50-325 mg/Day)

ASPIRIN & NSAIDS - Actions

5) GIT effect :-

Aspirin à Inhibits PGs in Gastric Mucosa à ↑ HCL production

↓

Loss of Protective action à Gastric irritation , peptic ulcer

Aspirin à Acidic pH of stomach à Exists in unionized form à Enters mucosal cells à ph 7.1 à Ionized & become indiffusible à Active ulcers, Erosive gastritis & haemorrhage.

ASPIRIN & NSAIDs - Actions

6) Acid – Base and Electrolytes Imbalance : -

Aspirin à In Therapeutic Dose à Causes Respiratory alkalosis à compensated by excretion of alkaline urine

(Compensated respiratory alkalosis).

Aspirin à In Toxic Doses à Depresses respiratory centre à leads to respiratory alkalosis à later on produces

(Uncompensated metabolic alkalosis).

ASPIRIN & NSAIDs - Actions

7) CVS effect :- Aspirin & NSAIDs à produces sodium & water retention on prolonged use à Precipitates CCF in pts with poor cardiac reserves.

NSAIDs à Blunts anti-hypertensives drugs effect when given together.

8) Urate Excretion :-

Aspirin à In Therapeutic doses à inhibits urate secretion in renal tubules à increases plasma urate levels.

Aspirin à In High doses à inhibits reabsorption of uric acid in the renal tubules à produces uricosuric effect.

ASPIRIN Pharmacokinetics

ASPIRINà Orally completely absorbed. Highly bound to plasma proteins. Well distributed in body. Metabolized in liver by Glycine & Glucuronyl conjugation. Follows saturation kinetics.

ASPIRIN à At Low doses à follows First order elimination kinetics à after saturation of metabolizing enzymes à follows Zero – order elimination kinetics à **Increase in dosage** à increases plasma concentration disproportionately by increasing plasma half-life of Aspirin à Resulting into severe toxicityà Alkalinization of urine à increases rate of elimination of Aspirin.

ASPIRIN

- **Dosage Regimen for Aspirin :-**

1) **Analgesic Dose :-** 2-3 g/ day in divided doses
2) **Antiinflammatory Dose :-** 4-6 G/Day in divided doses
3) **Antiplatelet dose :- (Low Dose):-** 50-325 mg /day.

ASPIRIN & NSAIDs – Adverse effects

1) **GIT :-** Nausea, vomiting, gastric irritation, dyspepsia, epigastric pain, gastric mucosa erosion, ulceration & GI bleeding. Ulcerogenic effects can be revented by :-

i) Taking Aspirin, NSAIDs after food

ii) Taking Buffered aspirin (aspirin with antacud preparation)

iii) Under cover of Proton pump inhibitors, H-2 Blockers

iv) Give COX-2 inhibitors instead of Aspirin or NSAIDs.

2) Hypersensitivity reactions :- Rashes, urticaria, rhinitis, bronchospasm, angioedema.

3) Hemolytic anaemia :- In G6PD defeciency.

4)Hypoprothrombinaemia & Bleeding :- Prolonged use of aspirinà interfers with vit-K action in liver à decreasing clotting factors synthesis à producing hypoprothombinaemia à causing bleeding. Treated with Vit-K supplementation.

ASPIRIN & NSAIDs - Adverse effectsActions

5) **Rey's Syndrome :-** Use of Aspirin in children with Viral feverà Causes hepatic damage à Fatty infiltration & hepatic encephalopathy. Aspirin is C/I in children with viral fever.

6) **Pregnancy :-** Inhibits PGs synthesis à delays onset of labour à increases chances of postpartum haemorrhage.

7) **In New Born :-** Aspirin or Indomethacin à Inhibits PGs synthesisà produces premature closure of ductus Arteriosus.

8) **Analgesic Nephropathy :-** Chronic use of NSAID's à causes slow progressive renal failure which is reversible on stoppage.

Acute (Salicylate) ASPIRIN POISONING

- More in children
- Fatal in adults at doses > 20-30 G
- **Pl level > 50-75 mg/dl** in serious toxicity
- **Features of Acute Aspirin Toxicity** are :-
- Vomiting, dehydration, electrolyte imbalance leading to respiratory alkalosis (in adults) or respiratory acidosis (in children), petechial haemorrhage, hypoglycaemia, high fever, delirium, convulsions, coma and respiratory failure.

Acute (Salicylate) ASPIRIN POISONING - TREATMENT

1) Gastric lavage with activated charcoal
2) Alkalinization of urine by Sodium Bicarbonate – to correct acidosis
3) Reducing fever – cold sponging with ice or antipyretic drugs like Paracetamol
4) To correct electrolyte imbalance
5) IV Glucose to correct hypoglycaemia
6) Vitamin K inj. IV if bleeding occurs
7) Haemodialysis if Pl. salicylate level >90 mg/dl.

ASPIRIN - Precautions & Contraindications

1) C/I in peptic ulcer (Aggravate ulcer & cause bleeding)
2) C/I in Infants & children suffering from viral fever (chicken pox, influenza, juvenile rheumatoid arthritis etc)
3) C/I in Pts with Bronchial asthma (precipitates aspirin – induced asthma)
4) C/I in G-5-PD deficiency – cause hemolysis
5) C/I in Pts with poor cardiac reserve & increase in circulatory volume – may precipitate heart failure, hypertension because Aspirin & NSAIDs increases circulatory volume.
6) Bleeding disorders as aspirin may cause bleeding
7) Discontinue aspirin 7-10 days before planned surgery to avoid increase risk of bleeding due to prolongation of BT snd clotting time with Aspirin.
8) Aspirin may cause hepatic necrosis in chronic liver disease & renal damage.

ASPIRIN - Precautions & Contraindications

9) May precipitate Gout attack at 2 g/ day dose

10) Administered during pregnancy, Aspirin à cause low birth weight babies.

11) Aspirin administered during labour à may cause delayed in labour, more post-partum blood loss & early closure of patent ductus arteriosus.

12) However, Aspirin or Indomethacin is used in cases of failure of closure of patent ductus arteriosus within time in new born babies.

Aspirin – Drug Interactions

1) **Aspirin à** causes displacement of Naproxen, warfarin, phenytoin, methotrexate , tobutamide from its plasma protein binding sites à increases toxicity of displaced drugs.
2) **Aspirin à** blocks effect of uricosuric drug Probenecid by competing with it.
3) **Aspirin à** reduces diuretic of Furosemide, Thiazides & Spironolactone
4) **Antacids (Mg-Al) à** increases clearance of Aspirin by making urine alkaline.

Clinical Uses of Aspirin & NSAIDs

1) **As Anti-inflammatory in Rheumatoid arthritis (RA), Osteoarthritis (OA), Spondylitis, Tendinitis & Bursitis (3-5 G/Day):-**

- **In Rheumatoid Arthritis (RA) à Aspirin à** reduces joint swelling & tenderness, reduces pain, reduces duration of morning stiffness & increases grip strength.

- **In Ankylosing spondylitis à Aspirin à** relieves pain, reduces inflammation and stiffness.

- **In Osteoarthritis (OA) à Paracetamol is preferred over Aspirin à Because there in no Inflammation in OA.**

Clinical Uses of Aspirin & NSAIDs

2) As Analgesic & Antipyretic : -

- **As Analgesic à Aspirin à used for Headache including mild migraine, muscle pain (myalgia), toothache, neuralgias, dysmenorrhoea (↑ed PGs conc in endometrial tissues) etc. (Dose : 300-600 mg TDS)**

- **As Antipyretic in fever, but Paracetamol preferred over Aspirin, because Aspirin may cause Rey's syndrome in children if given to treat viral fever.**

Clinical Uses of Aspirin & NSAIDs

3) Rheumatic Fever :-

Aspirin (Dose : 100 mg/kg/Day in D.D) (Pl. conc 15-30 mg %) à Reduce to 50 mg/kg /day for 2-3 weeks & gradually discontinue over 2-3 weeks.

Aspirin à effective in Rheumatic Fever à because of its Antiinflammatory action by blocking PGs synthesis à by Cellular & Immunological mechanisms à i.e. by inhibiting antibody production, antigen induced histamine release, antigen antibody aggregation, non-specific stabilization of capillary permeability during immunological insult.

Clinical Uses of Aspirin & NSAIDs

4) Post –MI, Unstable angina, Post-stroke (Cerebral infarction) :-

Aspirin (5-325 mg / day) à produces antiplatelet action by inhibiting TXA2 synthesis in Platelets à prevents arterial thrombosis & subsequent events.

5) Closure of Patent Ductus Arteriosus (PDA) :- In infants with failure to close ductus arteriosus within time, Aspirin à helps in closure of PDA to avoid surgery.

6) Prevention of Colon cancer :- Aspirin à prevents colon cancer if used prophylactically à by inhibiting COX-2 which is expressed in high amount in colon tumours.

7) Flushing & Pruritus due to Niacin :- Aspirin (300mg OD) à prevents release of PGD2 due to Niacin (5-6 G/Day) à prevents and relieve intense flushing & pruritus.

Clinical Uses of Aspirin & NSAIDs

8) Cough due to ACE – inhibitors

9) Systemic Mastocytosis : Aspirin or Ketoprofen + H1 & H2 Blockers à prevents excess release of PGD2 from mast cells & Bone Marrow à prevents vasodilatation & Hypotension associated with Mastocytosis.

10) Topical uses of Salicylic acid :-

i) Methyl salicylate (Oil of Wintergreen) à As counterirritant in muscle & joint pain as liniment or ointment.

ii) Keratolytic agent in corn

iii) In epidermophytosis – Salicylic acid + Benzoic acid

iv) As sunscreen lotion (absorbs UVB radiation) – Trolamine salicylate used topically.

11) Pregnancy induced Hypertension – Low dose aspirin used.

12) To prevent progression of cataract & Alzheimer disease.

13) Familial Adenomatous Polyposis (FAP) :- Aspirin prevents colon cancer in old age in Pts inherited FAP in adolescence.