PC
Pharmacology Concepts
By Rajesh Choudhary

NSAIDs Pharmacology

Website

Videos

Pharmacology 2 | U2

NSAIDs | Anti Inflammatory, Analgesics, Antipyratics

Phospholipid
↓ PL-A_2

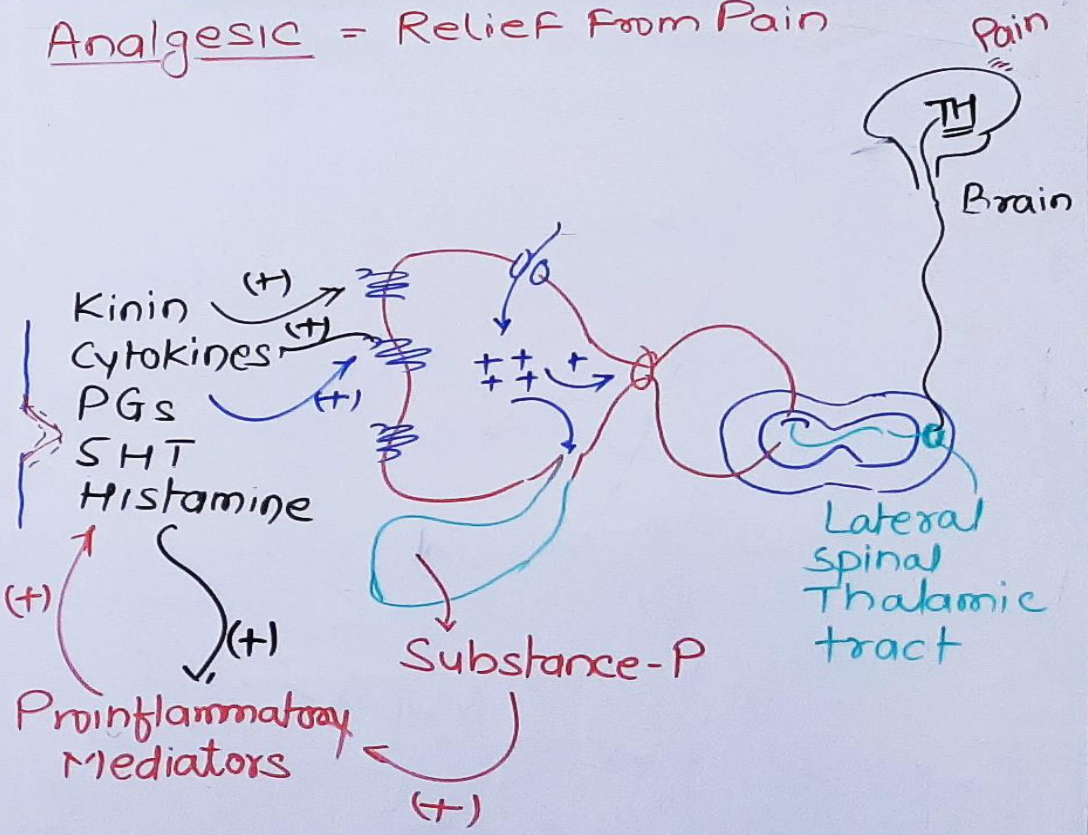
Corticosteroids

Arachidonic Acid

Cytokines
Carcinogen
Interleukin
TNFα
(+)

COX-I (Constitutive)	NSAIDs	COX II (Inducible)
↓ PGs (PGs, PGI_2, TX_A)		PGs (PGE_2, PGI_2)
↓↓ "Housekeeping Functn"		↓ "Inflammatory & Neoplasia"
↓ GI - Cytoprotective Role – ↑Mucus & ↓ HCl		Macrophages → Inf. Res. "Inflammatn, Pain, Fever"
Kidney - Cytoprotective Vasodilation		Kidney - Vasodilation & ↑Salt/water excretn
Platelet (TXA_2) - Aggregation		Female - Induce Labour
		Brain/spinal cord - Nociceptn Physiological Pain
Ketorolac, Flubiprofen, ketoprofen, Indomethacin low dose Aspirin		Celecoxib, Etoricoxib, Parecoxib Nimesulide, Diclofenac

Analgesic = Relief From Pain



More Effective against Inflam. pain

Peripheral & centrally

NSAIDs | Anti Inflammatory, Analgesics, Antipyratics

= Corticosteroids

↓ PL-A_2

Arachidonic Acid

Cox-I (Constitutive) → PGs (PGs, PGI_2, TXA_2) → "Housekeeping Funct"

- GI - Cytoprotective Role - ↑Mucus & ↓ HCl
- kidney - Cytoprotective Vasodilation
- Platelet (TXA_2) - Aggregation

NSAIDs

(+) Cytokines, Carcinogen, Interleukin, TNFα

Cox II (Inducible) → PGs (PGE_2, PGI_2) → "Inflammatory & Neoplasia"

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① Analgesic = Relief From Pain
② Antipyretic – ↓ body temp in Fever
③ Anti inflammatory → ↓ Inflammation

Side Effects

① GI – ↓ PGE_2, PGI_2 → GI bleeding, Ulcer, dyspepsia, Nauseq

② ↓ TXA_2 – Antiplatelet effects (Aspirin) → ↑ bleeding time

③ Kidney – ↓ PGE_2, PGI_2 → Kidney injury, Fluid Retention

④ delayed labour

⑤ Selective Cox-2 – ↑ TXA_2 Vasoconstrictn, Ischemic Heart disease

PHARMACOLOGY of ASPIRIN

PHARMACOKINETICS :-

Abs.- in stomach & intestine, Poor water soluble (limiting factor for Abs), microfining & addⁿ of alkali enhance it absorptⁿ. Higher pH – Ionization

Metabolism – Rapidly deacetylated in Gut wall, liver, plasma & release Salicylic ā #

Distributⁿ - 80% PB Vd - 0.17 L/kg. easily cross # placenta, slowly in Brain

Eliminatⁿ – Exc. through G.F & T.S after Conjugatⁿ with glycine & Glycuroni acid

ADR = ① At Analgesic dose - "GIT (Ulcer) #

② Hypersensetivity & Idiosyncrasy = Allergy
- Rashes, Urtecaria, Asthma, Anaphylactic reactⁿ Rhinorrhoea, angiodema

③ At inflammatory dose - "Salicylism Syndrome"
↳ Dizziness, tinitis, vertigo, impairment on hearing & vison, electrolyte imbalance, Hyperventilation
↳ child → liver damage
↳ "Reye's Syndrome" - hepatic encephalopathy

④ Acute Salicylate Poisoning - more common in children in adult (15-30g)

*Treatment = IV Fluids (Na^+ K^+ HCO_3^-), glucose, vit K

Uses - ① Analgesic, Antipyretic
② Acute Rheumatic fever – 4-5 g/day
③ Rheumatoid arthritis - 3-5 g/day
④ Osteoarthritis
⑥ Postmyocardial infarctn - 75-150 mg/day
#

Interactions

① Aspirin – displace the warfarin, Sulfonylurea phenytoin, MTX from its PB site

② – ↓ T.S. of uric acid (at analgesic dose)

③ Aspirin – ↓ Diuretic actⁿ of furesemide, Thiazide, etc. due to compete with Active transport system in T.S.

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PROPIONIC ACID DERIVATIVES NSAIDs

Ibuprofen	400-600 mg	2-4 h
Naproxen	250 mg	12-16 h
Ketoprofen	50-100 mg	2-3 h
Flubiprofen	50-100 mg	4-6 h

P'DYNAMIC/MOA ⇒ Inhibit COX → ↓ PGs Synthesis
→ ↓ PGs mediated - Inflammatn, Pain & Fever

All NSAIDs have similar Mode of Action

Ibuprofen introduced in 1969 as a better tolerated alternative aspirin

Naproxan is being most potent to inhibit COX, in vitro ≈ in vivo anti inflammatory property

Platelet aggregation - short lasting with Ibuprofen
long-lasting with Naproxan

ADR :- mild side effects as compared to Aspirin
GI discomfort, nausea, vomiting. Ulcer (long term)
CNS - dizziness, tinitis, blurred vision
Allergy infrequent, However precipitate Aspirin induced asthma

CI = Ulcers & Pregnancy

P'KINETIC = Orally active, 90-99% PB.
Not clinically significant Displacement occurs thus no need to dose alteratn of oral antihyperglycemic & oral anticoagulant drugs
Cross BBB & Placenta
Metabolised in liver by hydroxylation & Glucoronide conjugatn & Exc. through Urine & Bile

Uses ① Antipyretic & Analgesic
② Pain management in Rheumatoid arthritis, Osteoarthritis, musculoskeletal disorder
③ Indicated for Soft-tissue injury, Fractures, high fever, tooth extraction

* Ibuprofen → weaker antiinflammatory
• Naproxen → stronger antiinflammatory S(−) enantiomer ↓ leucocyte migration
→ more valuable in acute Gout 750mg → 250mg
→ may cause GI bleeding due to ↓ platelet aggration

Ketoprofen - ↓ COX & LOX, Similar Antiinflammatory effects as Ibuprofen but having more side effects

Flubiprofen - antiinflammatory action & Side effects both are more than Ibuprofen.
used in occular inflammation

NSAIDs

Mephenamic Acid → # Anthranilic ā derivative, (Fenamate) → Analgesic, Antipyretic & weaker anti-inflammatory drugs. ⇒ ↓ PGs Synthesis

P'kinetic – oral active, High PB, Partially metabolised & excreted through urine & bile, $t_{1/2}$ = 2-4h.

ADR – # Diarrhoea is common - dose-related
↳ GI distress, CNS manifastation may occur
↳ Haemolytic Anaemia - Rare but serious

Use – Analgesic – Muscle, Joint, Soft Tissue pain

ĒNOLIC Ā DERIVATIVES (Oxicams)

PEROXICAM :– Long-acting potent anti inflammatory similar as Indomethacin and good analgesic-antipyretic action.

MOA – Non Selective reversible COX inhibitor
↓↓ PG Synthesis & ↓ Platelet aggration
↓ ROS production & ↓ IgM Rheumatoid Factor
↓ Leucocyte chemotaxis

P'kinetics – Rapidly oral Absorption, (99% PB)

Metabolised in liver by Hydroxylation & Glucuro-nide conjugatn. Exc. through urine & bile
Enterohepatic Circulation
$t_{1/2}$: 2 days. Dose - 10-20 mg BD → OD

ADR :–
GI Side effect > Ibuprofen, < Indomethacin
Allergy ~ 1% patient
Edema & Revesible Azotaemia occurs

Uses =
Rheumatoid, Osteoarthritis, Spondylitis due to long-term anti inflammatory but not 1st choice due to toxicity
It can be also used in Acute gout, musculoskeletal injury & dentistry

PYRAZOLONES – Antipyrin (Phenazone) & Amidopyrin (Aminopyrin) = Banned Globally due to higher incidence of Agranulocytosis
Propyphenazone – Still available in "India"

NSAIDs

Acetic Acid Derivatives

KETOROLAC – "Aryl Acetic Acid"

↳ Potent analgesic & Modest anti-inflammatory
↳ In postoperative pain management ≈ Morphin

MOA → –X– COX → ↓ PG Synthesis → ↓ Pain

P'kinetic :→ Orally active, im., high PB, 60% exc unchanged through urine, Metabolised in Liver by Glucuronid conj., t1/2: 5-7 h

ADR: # GI → Nausea, Abdominal pain, dyspepsia, loos stool, Ulceration,
CNS – Headach, Diziness, Nervousness
↑ Serum Transaminase & Fluid Retention

USES :– # Postoperative, Dental, musculoskeletal pain (15-30 mg, im, every 4-6 h → 90 mg/day max)
Renal Colic, Migrane - pain management
Topical - noninfective ocular condition

Not Recommended = > 5 days, preanesthetic medicatn

INDOMETHACIN :– # "Indole Acetic acid"

↳ Potent antiinflammatory & prompt antipyretic
↳ It relieves only inflamm. & tissue injury related pain

MOA – ↓PG Synthesis, ↓ neutrophil motility & in toxic dose it uncouples oxidative P° as Aspirin

P'kinetic – oral active, PB = 90%, Partially metabolised by Liver & excrete through urine, t1/2 = 2-5 hours

ADR – * 50 % incidence of GI & CNS side effects
GI – Irritation, Nausea, diarrhoea, anoroxia, GI bleeding, ulceratn
CNS – Confusion, hallucinatn, Dizziness, depression, psychosis
others – Leukopenia, Allergy, bleeding,

Contraindicatn – Machinery operator, Driver, psychotic, kidney patients

USES – Reserve for antiinflammatory
→ Spondylitis, Arthopathies, arthritis, Gout, Rheumatoid arthritis
Bartter's Syndrome

PREFERENTIAL COX-2 INHIBITORS

NIMESULIDE ⇒ Weak inhibitor of COX-1 mediated PGs Syn. & Moderately COX-II Selective

Anti inflamatory Act^n ⇒ ↓COX-II, ↓ROS, ↓PAF Syn. ↓TNFα release, ↓Metelloproteinase activity in cartilage

Uses - short-lasting painfull inflammatory Cond^n like sport injury, dysmenorrhoea etc

P'kinetics – Oral Active, 99% PB, Metabolised by liver & Exc. through urine, $t_{1/2}$ 2-5 h)

ADR – ① GI - Epigastralgia, Acidity, Loosmotion

② Allergy - Rash, pruritis

③ CNS - Diziness, Somnolence

④ Instances of "Fluminant Hepatic Failure",

* withdrawn or Banned → Spain, Singapore, Ireland, Turkey.

Contraindicated in children in many contries including "India"

DICLOFENAC = Anti inflammatory, Analgesics, Antipyretic - Similar to Neproxam

MOA = ↓COX-II mainly, ↓ ROS, ↓chemotaxis of Neutrophil

P'kinetic – Oral Active, 99% PB, Metabolised in liver, excreted through Urine & Bile, $t_{1/2}$: 2h

* Good Tissue permiability & conc. in synovial fluids & maintained 3 times longer than plasma → ↑ action in Joint

USES - Rheumatoid Arthritis, Osteoarthritis, toothach, dysmenorrhoea, Spondylitis etc.

ADR - Mild Epigastric Pain, nausea, Ulceration, nausea, Diziness, Rashes – less common

It may enhance the risk of Heart attack, and stroke due to lake of antiplatelet activity

↑ Seram Amino-transferase – Liver toxicity

↓Renal blood Flow, ↓GFR at higher Dose

ACCLOFENAC – chondroprotective property due to ↑ Glycosaminoglycan Synthesis

PARACETAMOL (ACETAMINOPHEN)

↳ Para-Amino Phenol Derivative
↳ Deethylated active metabolite of Phenacetin

C_2H_5O- Phenacetin

PCM
Acetaminophen

MOA:- 1. Central Analgesic Action – Similar to Aspirin, Increase the pain threshold

2. Antipyretic :- ↓ COX-3 in the Brain that could account for its Analgesic-Antipyretic action

However it unables to ↓ COX in presence of peroxides, which generated at inflam-matory site (Absent in brain). So shows very poor Antiinflammatory action.

In Contrast to Aspirin, PCM does not →
- ✓ ↳ Stimulate Respiration
- ✓ ↳ Acid-base balance
- ✓ ↳ Cellular metabolism
- ✓ ↳ CVS
- ✓ ↳ platelet

Little effect on GI irritation and bleeding

P'KINETICS – Orally Active, PB 25%, well Δ uniform distribution in the body, metabolized by conju-gation with glycuronic acid Δ Sulfate. Excrete through urine. $t_{1/2}$ = 2-3h

ADR – # Liver toxicity at high dose

N-Acetyl-p-benzoquinone imine (NABQI) reactive metabolite which damage Liver

* Toxicity appears at – > 10g/day or > 150 mg/kg/day

Fetal Action = > 250 mg/kg/day

Others → Nausea, Vomiting, Abdominal Pain

Hepatic Necrosis → Renal Tubular Necrosis → Hypoglycemia → "Coma"

Antidote - N-Acetylcysteine #

Use - ↳ Fever
↳ Mild Pain Management

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