NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Sources:

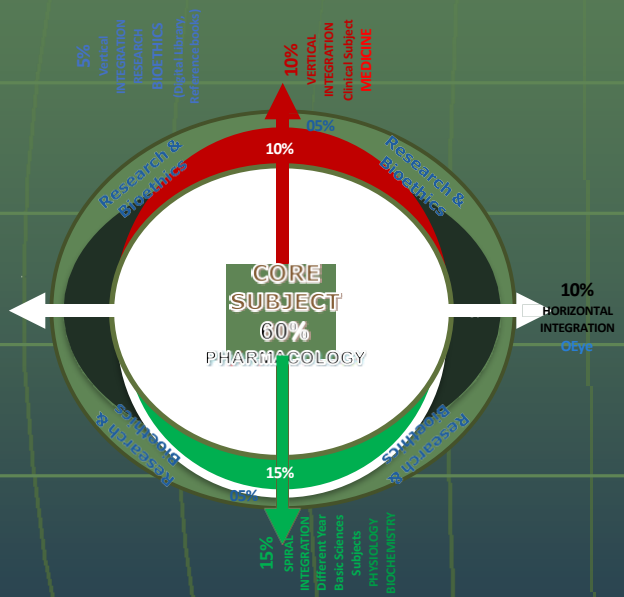
Bertram G. katzung Basic & Clinical Pharmacology 15th Edition

Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



4rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Eye • Pathology
Vertical Integration – 10%	
Clinical Subjects	• Medicine • Surgery
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Research & Bioethics, Digital library – 05%	

Learning Objectives

- ✓ At the end of the lecture, students should be able to:
- Classify NSAIDs
- Describe the mechanism of action of NSAIDS.
- Describe the shared toxicities of NSAIDs.
- Differentiate between non selective COX inhibitors and selective COX-2 inhibitors

ANTI INFLAMMATORY

Used in treatment of musculoskeletal disorders, such as:

Rheumatoid arthritis

Acute rheumatic fever: Aspirin used for both its antipyretic & anti-inflammatory effects

Osteoarthritis

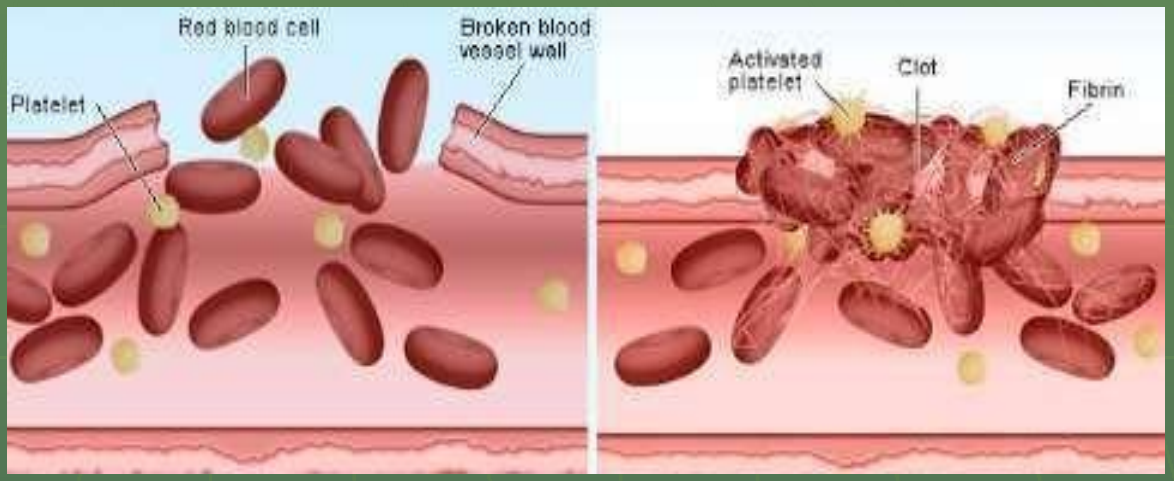
Ankylosing spondylitis

Gout

ANTIPYRETIC

- Hypothalamus regulates set point at which body temperature is maintained
- Fever after infection & tissue injury, leads to formation of cytokines (IL-1β, IL-6, TNF-α,) which ↑es synthesis of PGs → triggers hypothalamus to elevate body temp. by promoting an increase in heat generation & decrease in heat loss
- NSAIDs & aspirin suppress this response by inhibiting PGE2 synthesis
- NSAIDs & aspirin reduce all fevers but not effective in raised body temperature due to exercise

PLATELETS



TXA2 stimulates platelet aggregation

PGI2 inhibits platelet aggregation

SYSTEMIC MASTOCYTOSIS

A condition associated with excessive formation of mast cells in bone marrow, RES, GIT, bones & skin Large amount of PGD_2 released from mast cells which causes severe episodes of vasodilatation, flushing & hypotension, this PGD_2 effect is resistant to antihistamines

Aspirin or ketoprofen are useful in this condition

NIACIN TOLERABILITY

- Large doses of niacin (antihyperlipidemic dg) causes intense flushing by release of PGD_2 from skin
- This can be inhibited by use with aspirin

BARTTER´S SYNDROME

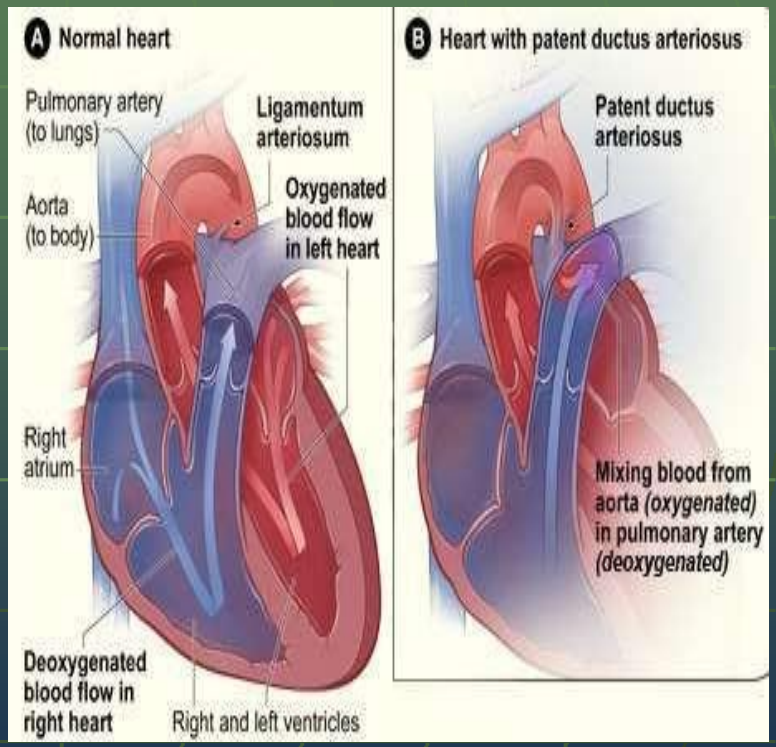
- Rare disorder, caused by functional mutation in $Na^+/K^+/2Cl^-$ cotransporter in ascending limb of LOH
- Characterized by hypokalemia, hypochloremic metabolic alkalosis with normal B.P & hyperplasia of JG apparatus
- Renal COX-2 is induced, synthesis of PGE_2 is increased
- Treatment with indomethacin along with K^+ repletion shows improvement in symptoms

CANCER CHEMOPREVENTION

- Frequent use of aspirin & other NSAIDs decrease risk of colon cancer about 50% when taken for 5 yrs. or longer

CLOSURE OF PDA

- Ductus arteriosus is a shunt connecting pulmonary artery to the aortic arch
- Patency is maintained by local PGE2 and PGI2
- Closes at birth
- ***Indomethacin,*** ibuprofen, aspirin & other NSAIDs, used in neonates to close inappropriately patent ductus



(No NSAIDs in late pregnancy – premature closure)

TOPICAL USES:

- ***SALICYLIC ACID***, irritant to skin & mucosa & destroy epithelial cells, so used for treatment of warts, corns, fungal infections & eczematous dermatitis
- ***METHYL SALICYLATE (oil of wintergreen)*** used as counter-irritant for relief of mild musculoskeletal pain
- ***MESALAMINE (5-aminosalicylic acid)*** used locally in inflammatory bowel disease

COMMON & SHARED ADVERSE EFFECTS OF NSAIDs

CNS: Headache, tinnitus, vertigo, confusion, dizziness, hyperventilation(salicylates)

CVS: Fluid retention, edema, HTN, MI, thrombosis & stroke (except with low dose aspirin)

Hematologic: Rarely thrombocytopenia, neutropenia or even aplastic anemia

Hepatic : Abnormal LFTs, rarely liver failure

Hypersensitivity: Urticaria, flushing, asthma, hypotension

Uterus: Prolongation of gestation, inhibition of labor

Vascular: Closure of ductus arteriosus

CORE SUBJECT

REYE´S SNDROME

- Is a severe & fatal disease, associated with use of aspirin & other salicylates if given in children & young adults less than 20years with fever associated with viral illness
- Characterized by acute onset of encephalopathy, liver dysfunction, fatty infiltration of liver & other viscera
- ***Acetaminophen not associated with Reye´s syndrome***, drug of choice as antipyretic in children & teens

Contraindications / Precautions for Aspirin

- Peptic ulcer
- Hemophilia
- Aspirin hypersensitivity
- Children with a viral illness
- Chronic liver disease
- Aspirin should be stopped one week before elective surgery
- Avoid high doses in G-6-PD deficient
- Avoid in pregnancy & lactation

ASPIRIN TOXICITY

SALICYLISM: usually occurs with repeated administration of large doses. Characteristic findings include:

----Headache, mental confusion, lassitude & drowsiness

----Tinnitus & difficulty in hearing

----Hyperthermia, sweating, thirst, hyperventilation, vomiting & diarrhea

Bronchospasm in 'aspirin-sensitive' asthmatics

MANAGEMENT OF ASPIRIN / SALICYLATE OVERDOSE TOXICITY / POISONING

1. Gastric Lavage
2. Activated Charcoal
3. Correct electrolyte, fluid & acid base balance
4. Diazepam I/V - convulsions
5. Promote excretion of salicylates by $NaHCO_3$ I/V to alkalinize urine
6. Hemodialysis in pt. with severe acidosis & coma

DRUG INTERACTIONS

- **Corticosteroids & other NSAIDs:** ↑ GIT A/E
- **With ACE inhibitors:** ↓ Antihypertensive effect
- **With Warfarin or Heparin :** ↑ GIT bleed
- **With Probenecid & Sufinpyrazone**
- Aspirin antagonizes uricosuric action of probenecid & sufinpyrazone , as it inhibits tubular secretion of uric acid (in low doses—< 2g/d)

PARACETAMOL / ACETOAMINOPHEN

- Acetaminophen, active metabolite of phenacetin
- Effective alternative to aspirin as analgesic & antipyretic but much weaker anti-inflammatory effects
- It may act through inhibition of a central nervous system-specific cyclo-oxygenase (COX) isoform COX-3
- Inhibition of PGs synthesis in brain, accounting for its analgesic & antipyretic activity

PHARMACOLOGICAL ACTIONS

- Analgesic , antipyretic effects similar to aspirin
- Weak anti-inflammatory effects (weak COX-1 & COX-2 inhibitor in peripheral tissues)
- Low incidence of GI side effects
- No effect on CVS & respiratory system
- No effect on platelet aggregation or coagulation
- No effect on uric acid excretion

THERAPEUTIC USES

Used as analgesic & antipyretic particularly for pts. in whom aspirin is contraindicated (e.g., in patients with peptic ulcer or hemophilia) & when anti-inflammatory action of aspirin is not required

TOXICITY

- In therapeutic doses 90-95% metabolized to inactive glucuronide & sulfate conjugates →excreted in urine
- 5-10 % metabolized to highly reactive **N- acetyl-p-benzoquinoneimine(NAPQI)** which detoxified by conjugation with glutathione & gets eliminated
- In large doses, glucuronide & sulfate conjugation capacity saturated, more **NAPQI** formed, hepatic glutathione depleted & **NAPQI** binds covalently to proteins in liver cells & renal tubules causing hepatic & renal tubular necrosis

ANTIDOTE – *Cysteamine & N-Acetylcysteine* (NAC)

- Administration of NAC within 8-16hrs, provide SH-groups to neutralize toxic metabolite
- Administration of GSH, not effective because it does not cross cell membrane readily

COX-2 INHIBITORS/COXIBs

CELECOXIB, ETORICOXIB, PARECOXIB

VALDECOXCIB, ROFECOXIB, LUMIRACOXIB

- Potent anti-inflammatory
- Antipyretic & analgesic
- Lower incidence of gastric upset

(Recommended in patients with a history of gastric ulceration)

- No effect on platelet aggregation
- Have no inhibitory effect on COX-1 so can be given in hemophilic patients & in patients with gastric ulcer
- ***Increased CV risk*** (↑ incidence of MI, stroke & thrombosis), as they inhibit PGI2 synthesis in vasculature
- Should not be used in patients with ischemic heart disease or stroke

RESEARCH

- Guirguis-Blake JM, Evans CV, Perdue LA, Bean SI, Senger CA. Aspirin use to prevent cardiovascular disease and colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. Jama. 2022 Apr 26;327(16):1585-97.

- Dear JW, Bateman DN. Developing new antidotes for poisons with existing effective treatments: a case study of fomepizole in paracetamol poisoning. Clinical toxicology. 2023 Sep 22:1-3.

FAMILY MEDICINE

- Wallis KA, Elley CR, Moyes SA, Lee A, Hikaka JF, Kerse NM. Safer Prescribing and Care for the Elderly (SPACE): a cluster randomised controlled trial in general practice. BJGP open. 2022 Mar 1;6(1).

ARTIFICIAL INTELLIGENCE

- Ravikumar, C., Sanganal, J.S., Shridhar, N.B., Sunilchandra, U. and andMoonoshree Sarma, R.S., 2023. An overview of NSAID loaded nanomaterials.

BIOETHICS

- Johnson CF, Maskrey M, MacBride-Stewart S, Lees A, Macdonald H, Thompson A. New ways of working releasing general practitioner capacity with pharmacy prescribing support: a cost-consequence analysis. Family Practice. 2022 Aug 1;39(4):648-55.


THANK
YOU!