Steroids ⊖ Cell-membrane phospholipids (A.A is a part of phospho)

activated by Chemical, mechanical or physical stimuli or by inflammation (mediator (5a) → Phospholip-ases ⇓

Arachidonic Acid (released from phospholipid).

- edema
- phagocytosis
- mucus secretion

COX-1 & COX-2 inhibitors (Aspirin & indomethacin inhibit).

⊖ Cyclooxygenase - enzyme.

Other homo- A.A 5-hydroperoxide

5-Lipoxygenase - Enzyme → metabolite

5-HPETE (intermediate) → 5HETE → cause Chemotaxis ↑ causes

12-Lipoxygenase

PGH2 → PGI2, PGD2, PGE2, PGF2α, TXA2 — precursors for other biolog. signif. molecules

Endothelial cells contain Prostacyclin synthetase → Prostacyclin (PGI2) → causes vasodila., inhibit platelets aggregation

Thromboxane A2 (TXA2) [Platelets contain Thromboxane synthetase] → cause vasoconstri., promote platelets aggregation, bronchoconstriction

1st step in LT synth → LTA_4 → LTB4 (produced by Neutro & macr...

LTA_4 → LTC4 → LTD4 → LTE4 (produced in mast cells) → Bronchospasm, ↑s vascular Permeability

Once leukocyte, reach tissue they change the A.A metabo... from LT to lipoxins.

anti-inflamm mediators.

Lipoxin A4 (LXA4)

Lipoxin B4 (LXB4)

- inhibit Neutrophil's adhesion and chemotaxis.
- endogenous antagonist of leukotrien...

major metabolite in mast cells → PGD2

PGF2α, PGE2 ← augment pain sensitivity and increase cytokines to cause fever

all are PG-

vasodilation, increased vascular Permeability ⇓ Potentiate edema

★ COX-I

- responsible for physiologic produc. of prostanoids (Tx and PGI, PA).
- It is constitutive enzyme that regulate normal cellular proces. e.g gastric cytoprotective effect, vascular homeostasis, platele. aggre & reproduc. & kidney junctions

∴ "Both've different binding site shape"

COX-II

- cause elevated production of prostanoi... that occur at site of inflamm.
- COX-II is constitutive enzyme expressed in brain, Kidney & bone, expression at other sites ↑s during state of chronic inflamm.
- Its expression is induced by TNFα and IL-1.
- Inhibited by Glucocorticoids

INFLAMMATION → meaning burning

- It is a defensive host response to foreign invaders and necrotic tissues
BUT, itself capable of causing tissue damage.

Main components
- Vascular reaction
- cellular response

Both activated by mediators derived from plasma protein & various cells.

Cardinal signs
- Calor (heat)
- Rubor (redness)
- Tumor (swelling)
- dolor (pain)
- functio laesa (loss of function)

Youtube channel
PHARMACO-STUDY

STEPS (5) & OUTCOMES

1- Recognition of injurious agent
2- Recruitment of leukocytes
3- Removal of the agent
4- Regulation (control of response)
5- Resolution (Repair).

Outcomes (either)
- elimination of noxious stimulus → followed by decline of rex and repair of damaged tissues.
- Persistent injury → Chronic inflamm

STIMULI FOR ACUTE INFLAMMATION

(1) Infections
- Bacteria
- viral
- fungi

(2) Trauma (blunt & penetrating)
- injury by blunt surface (NOT sharp) or object as a result of acceleration, compression or shearing force.
- injury caused by sharp objects that penetrate into skin into deeper tissues

(3) Chemicals
- Thermal injury (burns)
- Frostbite (injury by freezing)
- irradiations

(4) Tissue Necrosis
- From any cause
- MI (myocardial)
- physical & chemical injury

(5) Foreign bodies
- Splinter (Fragment of a large object eg wood)
- Dirt
- suture
- crystal deposit

(6) Immune Reaction. (Hyper-sensitivity rex)
- against environmental subs
- against self tissue.

*- FEATURES:-

	ACUTE	CHRONIC
1) ONSET	Fast (min → hrs)	slow: days.
2) cellular infiltrate	mainly neutrophils	monocytes/macro & lymphs.
3) Tissue injury, fibrosis	mild & self limited	severe & progressive.
4) Local & systemic signs	prominent	less: may be swollen

∴ neutrop./macroph are the phagocytes

* - Severe acute inflamm = fulminant. A.C.

* - Acute | Stage | sub acute | Chronic

Recognition of Microbes, Necrotic cells & Foreign subs.

PATTERN-RECOGNITION RECEPTORS

Toll-like receptors

- Microbial sensors
- Name for founding member called Toll, discovered in Drosophilla.
- The 10 mammalian TLRs, which recognise the products of bacteria (Endotoxin & DNA), viruses (double stran. RNA) and other pathogen

Are located in plasma membrane & endosomes
(collection of intracellular sorting organelles in eukaryotic cells)

* RECOGNITION ⇨ Activate Transcription Factors

That stimulate production of membr. protein

These proteins include:
- → mediator of inflamm. (e.g. cytokines, ① Killing ② Protective immune response)
- → antiviral cytokines
- → That stimulate lymphocyte activation

* - Natural Killer cell recognize virally infected cells

INFIAMMASOME

- multiprotein - cytoplasmic complex

1. recognizes the products of dead cells (e.g uric acid, extracellor ATP, crystals and some microbial products)
2. Trigger the activation of enzyme CASPASE-I

cleave precursor form of inflamma. Cytokine Interleukin-1β (IL-1B) into active form (Imp mediator of leukocyte recruit. in acute inflamm. response)

3. leukocyte phagocytose & destroy the dead cells.

* **GOUT**:- Caused by deposition of urate crystals — which're ingested by phagocytes and activate inflammasome → IL-1 rise → acute inflamma.

- Thus — IL1 antagonist → effective Treatment incase of resistance to conventional anti-inflamm. Therapy

* **Atherosclerosis**:- cholesterol crystals & free Fatty Acids also activate inflammasome — suggest that IL-1 play role in common diseases like atherosclerosis → Thus its antagonist is effective in their treatment

EVENTS OF ACUTE INFLAMMATION

Rapidly deliver leukocytes & plasma Proteins to site of injury

Vascular changes

Transient vasoconstriction (few seconds) → arteriolar vasodilation → ↑Blood flow → redness (Rubor) (erythema), warmth (calor)

Induce by chemical mediators (histamin)

Inflammation → Microvascular permeability ↑se → Protein rich fluid move into extravascular tissues → blood concentra in vessel ↑ses → ↑viscosity → ↓/slow circulation (stasis)

Histamin, Kinins & other mediators that produce gap b/w endothelial cells → (exudate (Protein rich fluid) accumulate in tissues)

Also causes edema

Leukocytes (neutrophils) accumulate at site along vascular endothelial surface a process called migration.

Cellular Events:- (leukocytes Recruitment & Activation)

Endothelial cells (activated by cytokines & other mediator) EXPRESS — adhesion molecules → leukocytes attach → Begin Rolling → Adhesion → leukocytes sense change in movement as they begone to roll due to expression of selectin, they also express "integrins" on their surface

By selectin receptors

E-selectin — express on endothe.

P — express on endothelium & platelets

L — on leukocytes

These integrins binds to their receptors on endothelium (TNF & IL-1 ↑se receptors for integrins)

After being arrested on endothe leukocyte migrate through intracellular junction by sequezing process called Diapedesis

Transmigration or migration is driven by chemokines produc in EC tissues

After Passing through endothelium, leukocyte secrete collagenases which enable them to pass through basement memb.

leukocytes reaches the site of action by chemotaxis stimulus from

- Bac. products: N-formyl methionine terminal
- cytokines
- complement system C5
- leukotriene-B4 (LTB4)

leukocyte eliminate microbes & dead cell by phagocytosis, followed by their destruction in phagolysosomes (Fusion of phagosome & Lysosome (contain digestive enzy))

Destruction is caused by free radicals (ROS, NO) generated in activated leuko. and Lyso. enzymes.

These enzy may release in EC environment → capable of damaging normal tissues

These enzy and ROS

CLINICAL EXAMPLES OF Leukocyte-INDUCED INJURY.

* DISORDER	CELL & MOL. INVOLVED IN INJURY
∘ Acute	
- ARDS (acute respir. distress syndrome)	neutrophils
- Acute Transplant rejection	Lymphocyte s antibodies & complement
- Asthma	Eosinophils; IgE antibodies
- Glomerulonephritis	Antibodies & complement; Neuto, monocytes
- Septic shock	Cytokines.
∘ Chronic	
- R.A	Lymphocytes, macrop. antibodies
- Asthma	Eosinophils; IgE antibodies
- Atherosclerosis	Macro and lympho.
- chronic transplant rejec.	Lympho, macro, cytokines.
- pulmonary fibrosis	Macrop; fibroblasts

CELL-DERIVED MEDIATORS

- **Vasoactive Amine** → Histamin, serotonin → vasodilation & ↑se Vasculaepermeab.
- **Arachidonic Acid Metabolites** → • Products from arachidonic acid metabo. affect variety of biolo. Processes including INFLAMMATION AND HEMOSTASIS
- **Cytokines** → usually act at short range → • leukocyte recruit • and migration ⇒ IL-1, IL-6 TNF and chemokines.
- **ROS** → • microbial killing • tissue injury
- **NO** → vasodilation
- eosin → Lysosomal enzym

- AA. metab also called Eicosanoids becoz derived from 20-C F.A; Greek eicosa = 20
- Their synthesis ↑ at site of inflamm. response, and agents that inhibit their synthesis also diminish inflammation
- Leukocytes, M.C, endothelial cells and platelets ⇒ are major source of A.A metabo

ACTION

- Vasodilation
- vasoconstriction
- ↑se vascular permeab.
- Chemotaxis, Leukocyte adhesion

EICOSANOIDS

PGI$_2$ (Prostacyclin), PGE$_1$, PGE$_2$, PGD$_2$
Thromboxane A$_2$, LTC$_4$, D$_4$, E$_4$
LTC$_4$, D$_4$ E$_4$
LTB$_4$, Hydroxyeicosatetraenoic acid (HETE)

* ACTIONS OF PRINCIPLE MEDIATORS OF INFLAMMATION

* Mediator	Source	ACTION
(cell-derived)		
1) Histamine	Mast cells, Basophil, platelet (resident cell of connective tissue – contain histamin & heparin rich granules)	• vasodilation, ↑se vascular permeabi. • endothelial activation
2) Serotonin	Platelets	vasoconstriction
3) Prostaglandi	Mast cell, leuko.	vasodilation, pain, fever
4) Leukotrienes	M.C, leukocytes	↑se permeab, chemotaxis, leuko adhesion + activation
5) Platelet-Activa. Factor	Leukocy, M.C	vasodilation, ↑permeabili, chemotaxis, leukocy (adhes + activ), degranulation (Platelet release inflammatory molecules)
6) Reactive-O_2-spece	Leukocytes	oxidative burst.
7) Nitric oxide	Endothelium, macrophages	killing of microbe & tissue damag. vascular smooth muscle relaxa., killing of microbes.
8) CYTOkines (TNF, IL-1, IL-6)	macro, endothelial cells, mast cells	Local: endothelial activation (express adhesion mol) Systemic: fever, metabolic abnor. Hypotension (shock)
9) Chemokines	leukocy, Activated macroph.	chemotaxis, leukocy. activati
PLASMA-PROTEIN-DERIVED	(Activated when microbe enter blood)	
1) complement	plasma (Produce in liver)	• Leukocyte chemotaxis & activa. • Direct target killing (MAC) ⇓ membrane attack complex or terminal complement complex ⇓ complex of protein formed on cell mem due to host complement activa • vasodilation
2) kinins	plasma (liver)	↑se v. permeab., smooth muscle contraction vasodilation, pain
3) Proteases Activated during coagulation	//	Endothelial activ, Leukocyte recruitment

Hemocytoblast →
- → proerythroblast →→ erythrocytes (RBCs)
- → Myeloblast →→ Basophils, Eosinophils, Neutrophils (granulocytes)
- → Lymphoblast → Lymphocytes → T → (CD4+) Helper-T cell, (CD8+) cytotoxic-T cell; B → plasma → antibody cell (agranulocytes)
- → Monoblast → Monocytes → Macrophages
- → Megakaryoblast →→ Thrombocytes

PROSTAGLANDINS

modulating pain, inflamm. and fever | role in acid secretion & mucus production in GIT | Uterine contraction | renal Blood flow

*-ALPROSTADIL:- it is PGI_1

that naturally produced in tissues such as seminal vesicles and cavernous tissues (refer to blood-filled spaces lined by endothel & surrounded by smooth muscle — present in erectile tissue of penis & clitoris (part of female genital)], in placenta and ductus arteriosus of fetus (artery that connect aorta & pulmonary artery)

↓

The ductus arteriosus serve as a temp shunt b/w pulm. artery & aorta. In fetus the blood is oxygenated in placenta before being returned to body. The lungs are filled ē amniotic fluid and therefore can't use to oxygenate the blood.

⇨ Alprostadil is use to treat erectile dysfunction & to keep the ductus arteriosus open in neonates ē congenital Heart condition until surgery is possible. (↳ vasodilation)

*-LUBIPROSTONE:

PGE_1 Derivative

- use to treat constipation (chronic-idiopathic), opoid-induced-constip. and IBS ē constipation.
- N/D - S.E
- N ↓se if taken ē food.

MoA:- Stimulate Typ-2 Cl^- channel = ↑Cl^- ion in intestinal lumen.

*-Misoprostol:- PGE_1 analog

- use to protect the mucosal lining of stomach during chronic NSAID treatment

MOA → ↓se chance of NSAID induce ulcers.

↓ interact ē PG receptor on parietal cells → ↓se acid secreti

↓ GI cytoprotective effect as → ↓ it stimulate mucus pro

Brand name: Cytotec

∴ combination product → Diclofenac + misoprostol

OFF-Label: For labor induction, as it interact ē PG recep on uterine

(PG) Diarr & abdo. pain.

R.A, O.A in pt ē risk of develop ulcer.

PG $F_{2\alpha}$-Analogs:

Bimatoprost, latanoprost, Tafluprost and Travoprost — indicated for "open-angle glaucoma" (↓ IOP)

- Adm. as oph soln - OD. "being Hypotensive"
- as effective as Timolol.

*-Bimatoprost — ↑ses eyelash prominence, length and darkness

↓ MoA • ↑se hair growth cycle.

↓ so approved for Eye lash hypotrichosis

↓ Inadeq. amount of eyelash.

S.E = blurred vision, iris color change (↑se brown pigm.) ocular irritation.

*-PROSTACYCLIN (PGI_2) Analog

- Epoprostenol (pharmaceutical form of naturally occu)
- Iloprost & Treprostinil — Synthetic
- indicated for treat. of pulmonary arterial HT
- All are short-$t_{1/2}$ agent
- Epo & treprost — continuous IV infu.
- Trep — also as oral or IV or S/C.
- Ilo — Inhalation — can cause bronchesp and cough.

Others S.E of all of them → Dizzy, Headache, faintness, flushing

ACETAMINOPHEN

- NOT an NSAID – due to weak anti-inflam effect (due to peripheral inactiy)
- More action on COX-3 (blockade) → antipyretic
- N-acetyl-P-aminophenol or (APAP)

MOA

- Sensitize pain receptor & raise threshold level → Below TH, impulse doesn't generate
- inhibit PG syntheses in Brain → antipyretic, analgesic.

Therapeutic USES – avail as 325 & 500mg

Also avail as 650mg caplet (Prolong release)

- mild → moderate pain
- ↓se fever
- post-immun pyrexia in infants
- DOC in children ē viral infection or chickenpox (Due to Reye synd. ē Aspirin rex).

Acc. to American college of Rheumatology → It is 1st-line agent for osteoarthri. of knee & hip, NOT use for Swelling and Stiffness related to R.A (as anti-inf is less).

Acute migraine

Now FDA has reduce this to 3250mg and even lower for alcoholics.

→ Adults (analgesic or antipyretic) → 500 – 1000mg TID – max 4000
- Osteoarth → 1000mg QID

NMT 10days for pain
NMT 3 days for fever.

⇒ children 325mg q 4-6 hr as needed. – max 1600mg

(5day pain) NMT → 1day for Sore throat
(3 day for fever)

KINECTICS

- rapidly abs. from GIT
- 1st-pass metab. occur in luminal cell of intestine & hepatocytes
- Excreted in urine
- Avail as IV & rectal formulations

IN Liver Acetaminophen

- A portion Hydroxylated → NAPQI (N-acetyl P-benzoquinone imine) → This highly reactive specie react ē sulfhydral gp of Glutathione ⇒ Non-toxic metabo
- Conjugated to form inactive glucuronide or sulfated metab.

PRECAUTIONS & INTERACTIONS

- ē large dose, liver glutathione become depleted and NAPQI react ē SHgp of liver proteins → Hepatic necrosis – (N-AC; contain SHgp is use as antidote).
- pt ē active alcoholism, hepatic disease or viral hepatit are at risk from chronic adm.
- Toxicity → 5g or more / or MT 1 month
  → Acute dose of 10g or more.

Acetam inhibit metabo. of Zidovudine → ↑se zidovu & Acetam. Toxicity.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

ASPIRIN & OTHER NSAIDS

- it is weak organic acid — that irreversibly acetylates COX.
- Other NSAIDS — REVERSIBLE INHIBITORS of COX.

MOA — NSAIDS includ. Aspirin has 3 MOA

Anti-inflamm.
- cyclooxygenase inhibition ↓ (X) Prostaglandins.
- They inhibit inflamm. in arthritis BUT neither arrest progression NOR induce remission.

Analgesic
- ↓ PGE2 synthesis ↓ (−) → Nerve ending doesn't get sensitize to the action of bradykinin, histam & other mediator.
- COX-2 inhibition (which release during inflamm).

Antipyretic
infection, hypersensitivity, malignancy or inflammati ↓ WBCs activated ↓ Release fever producing agents pyrogens eg cytokines ↓ which stimulate PGE2 synth ↓ which elevate set point of Hypothalamic Thermoregul. centre

"Rapid ↓ of body temp. of febrile Pt. by using heat dissipation as a result of Peripheal vasod. & sweating"

∴ NSAIDS have no effect on normal body temp.

Other MOA (Aspirin only: NOT other salicylate)

Anti-platelets
Aspirin → irreversibly inhibit COX in platelets ↓ which prevent formation of aggregating agent Thromboxane A2.

PPB = 80–90%.

Anti-Thrombotic — at high doses ↑se CVS events
At low doses
- Inhibit TxA2 ↓ blocking platelets aggreg. agent TXA2
- Small effect on prostacyclin ↓ so preserve the action of aggregation inhibit (PGI2)

Aspirin-THERAPEUTIC USES

Analgesic/Antiinflamm
- relieve mild → moderate pain. at low doses
- High doses — antiinflamm

e.g
2 (325mg) QID — analgesia
12–20 tab. (325 mg) per day — inflam+ analge.

Antipyretic
- Aspir, Ibupr. Nap. may be used to treat fever.
- Ar. → in pt < 20yr ē viral infection (such as chickenpox or influenza) to prevent Reye Syndrom (that cause fulminating hepatitis ē cerebral edema → often death).

CVS-Applic.
- ↓se risk of stroke in women & MI in men
- men & women who has previous MI, Angina, coronary artery bypass surgery → candidates for Aspirin

EXTERNAL APPLIC.

Salicylic acid

used TOpically to treat acne, corns (build up of hard skin near a bony area of toe or b/w toes – caused by pressure from shoe or friction) calluses (build up of hard skin – usually underside of foot) and warts (is a small growth ē rough texture that can appear anywhere on body – looks like small cauliflower or hard blister)

Methyl salicylates (oil of wintergreen)

As cutaneous counterirritant in liniments such as arthritis creams & sports rubs.

∴ Dose for analgesic or antipyresis = 325–650mg q 4hr OR, 650–1000mg q 6hr.
max = 4g/day for NMT 10 day for pain or 3 day for fever.

KINECTICS – Aspirin.

After oral,

- Rapidly deacetylated by esterases in body → produce salicylates.
  - unionized salicy absorb. from upper small intestine (at higher pH)
- CROSS – BBB and placenta except (Diflunisal)
- Convert to water soluble conjug. by liver
  - first order elimin ē $t_{1/2}$ 3.5hrs
- Anti-inflt. doses (NMT 4g/day) → Hepatic metabo. pathway saturated
  - ← zero-order elimi
  - $t_{1/2}$ 15hr or more
- Being organic acid – affect uric acid secretion.
  - AV. → gout or pt taking probenecid
- They inhibit PG synthesis BUT NOT LT system
- So, should be use ē caution in asthmatic pt, as ↓ PG syn. may cause ↑se shift toward leukotriene synthesis.

PRECAUTIONS

- **Hypersensitivity**
  - occur in 0.5% population
  - Cross-reactivity = ē >90% of NSAID and 5% ē Acetaminophin.
- **PG**
  - ↓RBF → edema in some PTs
  - caution requir ē High doses during last trimester
    - BEcos
      - Potential bleeding risk
      - Prolonging or complicating delivery
- **GI disturbances**
  - enteric coated dosages and by taking salicyl. ē food or large doses of antacids can prevent GI disturb.
- **CNS disturb.**
  - Tinnitus
  - Dizziness
  - Headache
- **Salicylism**
  - Salicylate toxicity occur at anti-inflam. doses, in addition to CNS disturbances resp alkalosis, Nausea, Hyperthermia, confusion & convulsions may occur

(A) → ē bleeding disorder or peptic ulcer.

Pt < 20yr ē viral infec

Interactions

- anticoagul. Ej thrombolytic agents
- ↑se effect of hypoglycemics (anti-diab)
- ↓ Zidovudine metabo
- ē caffeine, ana effect ↑ses.

NSAIDS

- Currently Ibuprofen & Naproxen are only NSAIDS – given over prescript
- NSAID → • mild – moderate pain and • use inflammation
- Acetaminophen – initial treatment for osteoarthritis becoz of its safety profile – But NSAIDS – more effective for pain & inflamm.

COMMON NSAIDS, USES

Diclofenac = Doc in joint pains

Naproxen

Inhibit COX-1 & COX-II

- may inhibit chemotaxis, activity of lymphocy. and cytokine (anti-inf. effect).

★ ONSET: 30 tamin

USES: pain, R.A, O.A,
- Ankylosing Spondylitis (long term inflamm of joints & spine including pelvis)
- Dysmenorrhea
- Acute Gout

(Take ē food or 8-12 oz of H_2O to avoid GIT effect)

(CI) ē ketorolac, Aspirin

ADR: Abdominal pain, constip., Nausea, edema, GI bleeding.

For analgesia in adults: 220 mg q 8-12 hrs (max 660/day)

RA = 1100 mg/day (Divide q 8-12 hr)

★ Ibuprofen

- MOA & onset same as Naproxen

USES: pain, fever
- Dysmenorrhea
- O.A., R.A
- Dental pain.
- Acute migraine
- JIA in children
- Pain & inflam due to musculoskeletal disorders.
- Headache
- Symp of cold & influenza.
- pain & inflam. due to soft-tissue injuries
- Post-Immunization Pyrexia in infants.
- post operati
- Pain = 200-400 mg q 4-6 hr divide
- Arth = 3200 mg/day

- Dental procedures
- Pain & inflam. in musculoskeletal disorder.
- Acute migraine

Mefenamic Acid

- MOA - same
- ONSET - rapid

USES:
- pain
- primary Dysmenor. (Adm. ē onset of bleeding & pain).
- Musculo-Skeletal disorders
- R.A, O.A
- Migraine.
- Toothache
- menorrhagia (bleeding nt 7 days or heavy bleed.)
- Pain & inflamm. in Juvenile Idiopathic Arthritis in child. (JIA)

intolerant to other (autoimmune disorder affect joints and other tissue. <16 yrs) NSAIDS.

★ Diclofenac Na

- K⁺ salt → rapid action than Na⁺ salt

USES:
- PEI in m.s disorder
- Acute gout
- JIA in child
- post-oper. pain

DIC-K⁺ use
- First 3 same as above
- Migraine
- fever in ear, nose or throat infection.

★ INDOMET-ACIN

- For moderate to severe pain due to inflamm in rheumatic & m.s disord
- Acute gout
- Dysmenorrhe

Precautions & Interactions

- CI = pt ē bleeding disorder or peptic ulcer.
- use ē extreme caution in last trimester of pg due to risk of premature closure of ductus arteriosus
- cause GI distu, so take ē food or large amount of antacid. (Ibuprofen is prefer over Aspirin, as it cause fewer GI disturb)
- Renal toxicity – (chronic adm) – may occur esp in Nephrosyn, Hyperkalem, bleeding cases
- Risk of CVS toxicity, Although risk is low, Ibuprofen more risky than naproxen.
- NSAID ↑ effect of anti-coagu & thrombolytics
- ↑se effect of Anti-diabet (at anti-inf doses)
- ↑se adrs of GI reaction resulting from chronic alcohol or Salicylate use.
- caffein + Ibupro = ↑analgesi
- Hypersentiv to Aspirin can occur ē NSAIDS.
- Avoid NSAIDS in combination.