Anti-inflammatory analgesic drugs

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Pharmacology for Dentistry

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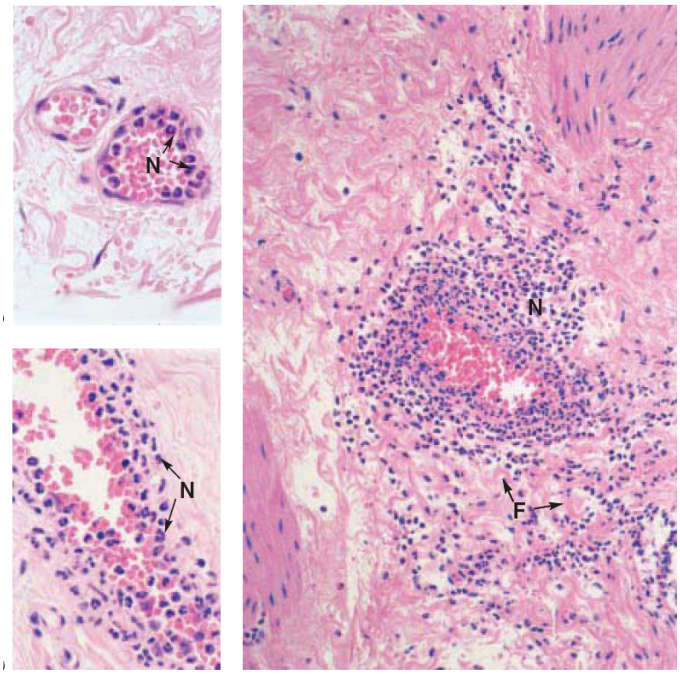
Assigned reading:

Pharmacology and Therapeutics for Dentistry, 5th edition, Yagiela et al

Chapter 21: pages 331-364



Inflammation

- Complex reaction of innate immune system
  - Occurs in vascularized tissues
  - Accumulation and activation of leukocytes and plasma proteins
- Triggered by infection, toxin exposure, or cell injury
- Vascular changes promote leukocyte recruitment
- Local adaptive immune responses amplify the inflammatory response

Three phases to inflammation

1. Acute inflammation
   autocoids, innate immune responses
2. Immune response (subacute inflammation)
   adaptive immune response
   induction and effector phases
3. Chronic inflammation

Inflammatory response

I. **Acute inflammation** (initial response to tissue injury induced by a pathogen or noxious substance)

1. Chemical mediators or autacoids (Bradykinin, serotonin, Histamine, NO, prostaglandins, leukotrienes, ILs)
2. Vascular system (flow and permeability changes)
3. Migration of blood cells, chemotaxis (neutrophils, mast cells, NK)
4. Innate immune response ("first line of defense")
5. Adaptive immune response
6. Time course is minutes to hours

Autocoids mediate initial response to tissue injury

Serotonin: ↑ vascular permeability, some effect on vasodilation

Histamine: ↑ vasodilation and vascular permeability

Bradykinin: ↑ vasodilation, vascular permeability and pain

Prostaglandins: ↑ vasodilation; ↑ bloodflow; ↑redness, edema and heat; ↑vascular permeability; ↑chemotaxis and ↑ migration of WBC; ↑ pain

Leukotrienes: ↑ vascular permeability and chemotaxis

II. Immune response or subacute inflammation (immune competent cell activation)

1. Innate and adaptive responses to antigen

   innate: recognition by tissue MØ of specific pathogen-associated molecular patterns (PAMPs)

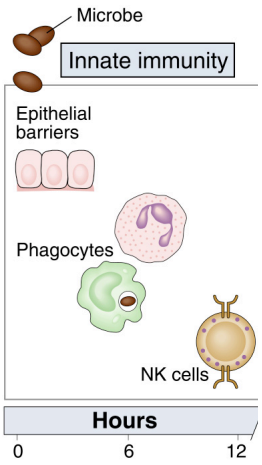
   adaptive: induction and effector phase of both cell mediated and humoral mediated response

2. Can be beneficial and/or destructive

   hypersensitivity reactions

   autoimmune diseases

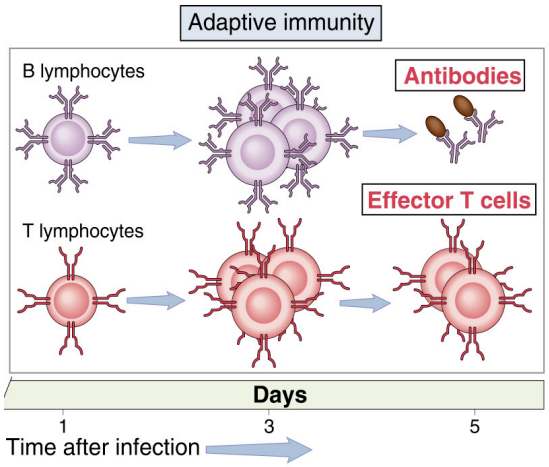
Innate immunity



- Natural or native immunity
- Rapid response to microbes
- Physical and chemical barriers
- Phagocytic cells (neutrophils and macrophages) and NK cells
- Blood proteins (complement system) and other mediators
- Cytokines: secreted proteins that regulate and control cells of the immune system
- Increase in vascular permeability

Adaptive Immunity

- Specific or acquired immunity
- Exquisite specificity for a large diversity of distinct foreign antigens
- Memory and robust response to 2nd exposure
- Lymphocytes and their products (T and B cells)



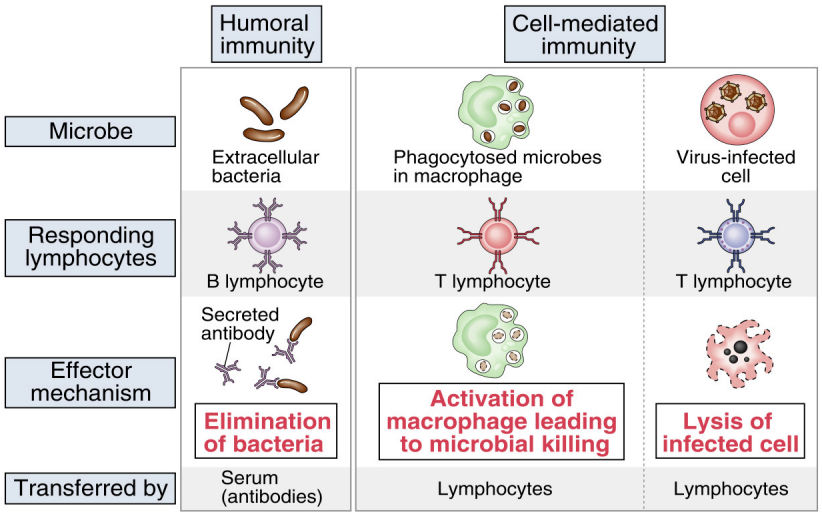
Immune System

Innate Immunity	Adaptive Immunity
Rapid kinetics	Slower kinetics
Nonspecific response	Specific response
Baseline response	Increase response with repeat exposure
Mediated by phagocytes, physical and chemical barriers, blood proteins	Mediated by lymphocytes and their products (B and T cells)

Humoral and Cell-mediated Adaptive Immune Responses

1) Humoral: mediated by B-cell secreted Abs
   - ✓ Extracellular microbes and their toxins
   - ✓ Specific effector functions (promote phagocytosis or granule release)
2) Cell-mediated: mediated by T-cells
   - ✓ Intracellular microbes (inaccessible to Abs) including viruses
   - ✓ Destruction of intracellular microbe or lysis of infected cells

Humoral and Cell-mediated Immunity



Innate Immunity

Adaptive Immunity

III. Chronic inflammation

- Vascular system (flow and permeability changes)
- Migration of blood cells (infiltrate of lymphocytes & monocytes)
- Chemical mediators (chemokines, cytokines, Igs, coagulation
- Adaptive immune response
- Time course is weeks to years
- Tissue proliferation and destruction

Two sides of the Inflammatory Response

- **Protective:** controls infection and promotes tissue repair
- **Destructive:** causes tissue damage, necrosis, and disease

Clinical features of inflammation

- Tumor (edema/swelling)
- Rubor (redness)
- Calor (heat/fever)
- Dolor (pain)
- Loss of function

These features are due to an inflammatory response and the products of a number of cell types including activated mast cells, leukocytes, macrophages, eosinophils, endothelial cells, platelets, et al.

Inflammatory Mediators/Signaling Molecules

(see Table 21-1 and Box 21-1)

1. Arachidonic acid derivatives: prostaglandins, thromboxanes & leukotrines
2. Bradykinin: vasoactive plasma peptides formed from kinnogens; vasodilator, ⇧ vascular permeability & pain
3. Cytokines: IL-1 and TNFα released from tissue macrophages and see ⇧vascular permeability and ⇧ adhesion molecule expression
4. Chemokines: chemoattractants, IL-8, RANTES, MCP-1
5. Complement: activated by Ab-Ag complexes, LPS or endotoxin, lyse bacteria, ⇧ EC permeability, opsonization
6. Clotting mediators: activated by platelets or collagen, Hageman/Factor XII

Inflammatory Mediators (con't)

7. Thromboxanes: (platelets aggregation & vasoconstriction
8. Histamine: IgE mediated or complement [C3a and C5a] mediated release from mast cells and basophils, vasodilator, ⇧ permeability of capillaries
9. Serotonin: vasoconstrictor released by mast cells
10. Angiogenic factors: VEGF, FGF
11. Platelet activating factor: (from platelets, EC, macrophages & mast cells; vasodilator, stimulates prostaglandin syn.)
12. Nitric oxide: (NO) released from EC and causes smooth muscles to relax and ⇧ vasodilation and PGs syn.
13. Pathogen produced: (bacterial LPS, OMP, fMLP)

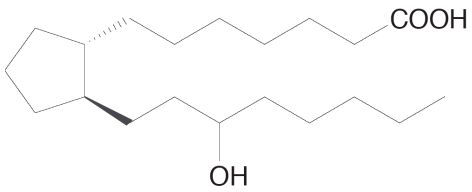
Therapeutic strategies

- ⇩ pain and arrest tissue damage
- 3 main classes of drugs to ⇩ pain
  - NSAIDs: ⇩pain and ⇩inflammation
  - Glucocorticoids: inhibition of induction of the cyclooxygenases (but toxicity asso. with chronic corticosteriod use, so used only for acute episodes)
  - SAARDs (slow acting antirheumatic drugs) or DMARDs (disease modifying antirheumatic drugs) but these are also very toxic
- NSAIDs are the drug of choice

Nonsteroidal anti-inflammatory drugs (NSAIDS)

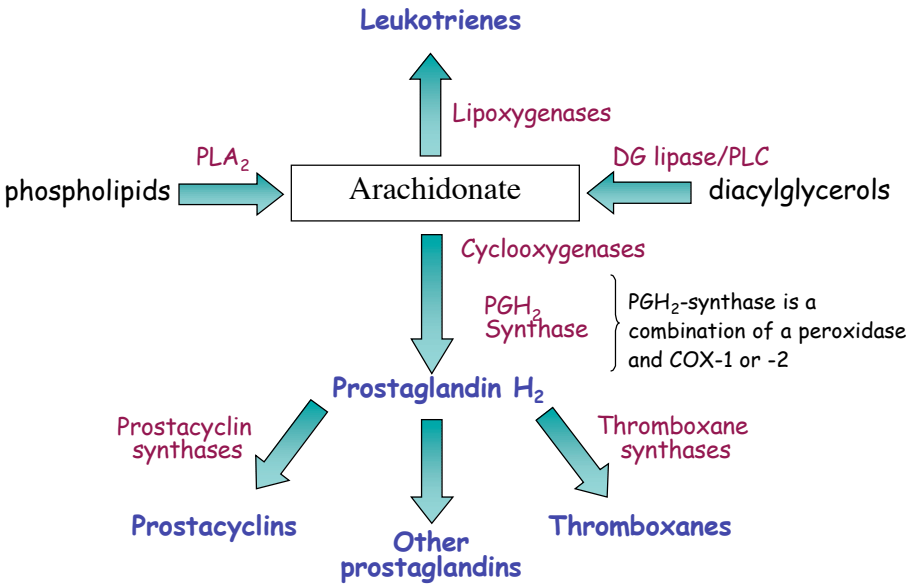
- One of the most widely used therapeutic agents (Rx and non-Rx forms)
- Inhibit arachidonate cyclooxygenase and thus inhibit production of prostaglandins (PG) and thromboxanes (TX)
  - 3 types of cyclooxygenase enzymes: COX-1, COX-2 & COX-3
    - COX-1: wide spread constitutive enzyme and important in tissue homeostasis
    - COX-2: induced in inflammatory cells by IL-1 and TNF-α
    - COX-3: a splice variant of COX-1 (also referred to as COX-1b or-1v)
  - NSAIDS generally inhibit both isoenzymes, thus :
    - COX-1 inhibition: GI distress
    - COX-2 inhibition: anti-inflammatory effect
  - Goal is to develop NSAIDS with a selective action on COX-2

Arachidonic acid (AA)



- AA gives rise to PGs, thrombaxanes and leukotrienes
- Phospholipase A_2 (PLA_2) and phospholipase C (PLC) generate AA from phospholipids and diacylglycerols
- fatty acid cyclooxygenases (COX-1 and COX-2) initiate the biosynthesis of the PGs and TXs (prostanoids)
- various lipoxygenases give rise to the leukotrienes and lipoxins (inhibitors of lipoxygenase are potential anti-asthmatic drugs

Arachidonate is the precursor of eicosanoids



Beneficial Effects of PG's

GI Tract: PGE_2, PGI_2 and prostacyclins

- Maintenance of microvascular integrity
- Enhanced blood flow through mucosa
- Protection of gastric mucosa
  - Stimulate mucous production
  - Secretion of phospholipids and surfactants
  - ⇩ gastric acid secretion and ⇧intestinal fluid secretion

Endothelium: PGD_2 and PGI_2

- Vasodilation and ⇩platelet aggregation

Kidney: PGI_2

- Renin release
- ⇩ reabsorption of Na+ and Cl-

Role of prostanoids in inflammation

- PGE_2 & PGI_2 released by EC and inflammatory cells; PGD_2 released by mast cells; monocytes and macrophages release PGE_2 and TXA_2
- Vasodilation, ⇧blood flow and redness
- Synergize with histamine and bradykinin to ⇧ vascular permeability, fever and pain
- PGE_2 are implicated in the production of fever with high concentrations in the CNS fluid

Cyclooxygenase isoenzymes

- **COX-1:** constitutively expressed; upregulated in some cancers and has a role in tumorigenesis
- **COX-2:** undetectable in normal tissue; inducible in cells associated with inflammation
- **COX-3:** splice variant of COX-1

Classical NSAIDS inhibit both COX-1 and COX-2 and are associated with adverse effects of peptic ulceration and dyspepsia

Newer NSAIDS selectively inhibit COX-2, fewer gastric side effects but reported increase risk for heart attack, stroke and thrombosis due to a relative ⇧ in TX

3 main pharmacologic effects of NSAIDS

- **Antipyretic** (lowering of an elevated temperature)
  - Inhibition of PG production in hypothalamus (contains center for normal body temperature regulation) and "reset" temperature
  - During inflam. rx, see ⇧IL-1 ⇨ ⇧PGE ⇨ ⇧temp.
  - COX-2: induced by IL-1 in EC and ⇧ PGE
- **Analgesic effect** (reduction of pain assoc. with inflammatory rx.)
  - ⇩ PGs that sensitize receptors to inflam. mediators
  - Work in combination with opioids and can ⇩ required opioid dose
  - Reduce vasodilator effect of PGs on cerebral vasculature, thus ⇩ pain associated with headache
- **Anti-inflammatory** (modification of the reaction)
  - Due to action of COX-2 (NSAIDS ⇩ PGs and TX syn in inflam. cells)
  - ⇩ vasodilation, cell adhesion and migration, stablizes lysosomes
  - ⇩ vascular permeability and thus ⇩ edema

NSAIDS: Chemistry and Pharmacokinetics

- Weak organic acids that are well absorbed
- Metabolized by Phase I and Phase II mechanisms or by Phase II alone
- Utilize CYP3A or CYP2C family of P450 enzymes in the liver
- Final renal excretion but also biliary excretion and re-absorption (excreted unchanged or as H_20 soluble metabolites)
- Protein bound, usually to albumin (drug interactions?)
- All can be found in synovial fluid after repeated dosing

NSAIDS: Pharmacodynamics

- ⇩ PGs biosynthesis
- Can also ⇩chemotaxis, ⇩ IL-1 production, ⇩production of free radicals & superoxide, and disrupt calcium mediated intracellular events
- Most inhibit both COX-1 and COX-2 pathways but selective COX-2 inhibitors are available
- Some inhibit platelet cyclooxygenase
- Some inhibit lipoxygenase or leukotriene synthesis
- ⇩ release of mediators from granulocytes, mast cells, basophils, and some T-cells
- Can cause gastric irritation, nephrotoxicity and hepatotoxicity

NSAIDs: common unwanted effects

1. GI disturbances: Due to inhibition of COX-1 and its protective effect on gastric mucosa; effects include dyspepsia, diarrhea, nausea, vomiting, gastric bleeding and ulcers. Fewer GI problems associated with selective COX-2 inhibition.

2. Skin reactions: mild rashes and photosensitivity reactions. Most common with Mefenamic acid and Sulindac.

3. Renal effects: Rare in healthy pts. but in susceptible pts. see reversible renal insufficiency due to noradrenaline or angiotension mediated vasoconstriction and lack of compensatory PG mediated vasodilation. Analgesic nephropathy occurs in 0.5-1.0% of the chonic high dose NSAID users.

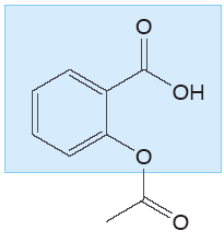
4. Bronchospasm: in 'aspirin-sensitive' asthmatics.

5. Prolong bleeding: inhibition of platelet function.

6. Reye's syndrome: NSAIDs given to children with viral infections, can result in death if not treated aggressively.

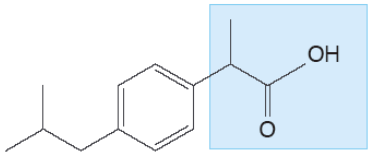
Non-selective COX inhibitors

Salicylate class



Aspirin

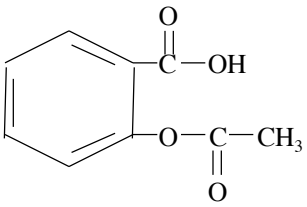
Propionic acid class



Ibuprofen

Advil, Motrin

Aspirin (acetylsalicylic acid; ASA)



- Weak organic acid
- pK_a=3.5
- Prototype NSAID
- Inhibits both COX-1 and COX-2
- Rapidly absorbed from stomach and upper SI (peak plasma level in 1-2 hrs)
- 75% metabolized in the liver
- Rapidly hydrolyzed to acetic acid and salicylate by esterases
- Elimination follows 1st order kinetics with low doses ($t_{1/2}$=4 hr) and saturation kinetics at high doses resulting in ⇧ $t_{1/2}$ of 12-16 hours
- Binding to albumin is saturable

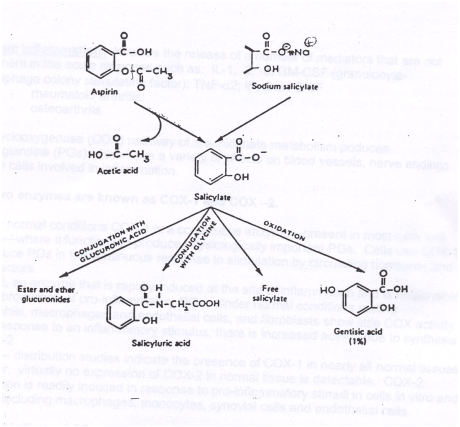
Aspirin: anti-inflammatory effects

- Non-selective inhibitor of COX-1 and -2 (thus even at low dose, an effective inhibitor of platelet aggregation)
- Due to its effect on the synthesis of eicosanoid and kallikrein mediators, aspirin inhibits leukocyte adhesion and migration into sites of inflammation.
- Reduces pain that is mild to moderate by acting both peripherally and at a subcortical site
- Reduces fever by ⇩ IL-1 production and CNS inhibition; ⇩ temperature associated with vasodilation and sweating

Aspirin dosage

- **Antipyretic or analgesic dose:** 650-1000 mg every 4 hours for adults and 50-75 mg/kg/d in divided doses for children
- **Anti-inflammatory dose:** 3.2-5 gm/day for adults and 50-75 mg/kg/d for children
- Due to the long $t_{1/2}$ of the active metabolite (salicylates), frequent doses are not required when daily dose is > 4 gm. Normally TID with meals.

Metabolism of salicylates



- **Low dose** (600mg):
  Elimination is first-order
  Serum $t_{1/2}$ is 3-5 hours
  Urinary excretion of unchanged drug <2%
- **High dose** (>600 mg or 4g/day)
  Elimination is saturation
  Serum $t_{1/2}$ is 12-15 hrs

75% metabolized in the liver

Clinical uses

- Often used to ⇩ mild to moderate pain
- Used in combo with other mild analgesics
- Combined with opioids for CA pain, synergistic enhancement of analgesia
- High doses used in TX of rheumatoid arthritis, rheumatic fever and other joint disorders
- Low dose aspirin is effective in prevention of transient ischemic attacks, unstable angina, coronary artery thrombosis with MI, and thrombosis after coronary artery bypass grafting
- Long term, low dose and ⇩ incidence of colon CA
- ⇩ risk of Alzheimer's disease

Unwanted effects

- Therapeutic doses can cause gastric bleeding
- Salicylism with repeated high dose ingestion (ringing or buzzing in the ears (tinnitus), vertigo, nausea, vomiting, hyperventilation
- Avoid use in children due to correlation with onset of Reye's syndrome (postviral encephalitis)
- Salicylate poisoning:
  High doses alter acid-base and electrolyte balance due to alterations in oxidative phosphorylation ⇨ ⇧O_2 consumption and ⇧ CO_2 production ⇨hyperventilation ⇨ ⇧ bicarb excretion.
  Higher doses can cause ⇩of respiratory center ⇨ ⇧ plasma CO_2 resulting in uncompensated respiratory acidosis.
  Toxic doses cause disruption of normal hemostasis and effect on platelet aggregation plus CNS effects including coma and respiratory depression.

Contraindications

- Patients at risk for bleeding disorders (due to anti-platelet effect)
- Patients on anticoagulant therapy
- Drug interactions due to NSAIDS ability to displace other drugs from plasma albumin
- Adverse effect on GI tract (multiple sources)
- Can block the effect of several antihypertensive drugs including diuretics, ACE inhibitors and β-Adrenoceptor blockers)
- Low dose aspirin reduces urate excretion so don't use in gout

Implications for Dentistry

- Acute pain control (pulpitis, abscesses, post oral surgery) very effective at 650 mg dose and more effective than 60 mg of codeine (fig. 21-7)
- Chronic pain associated with TMJ due to trauma, malocclusion, osteoarthritis

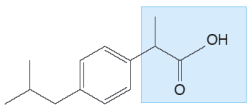
Dental considerations

- Avoid prescribing buffered-aspirin if patient is on low Na diet
- increased risk of bleeding
- avoid prescribing if patient is taking lithium or methotrexate
- low doses ⇩ urate excretion, so do not use in gout

Ibuprofen

Motrin, Advil

Propionic acid class

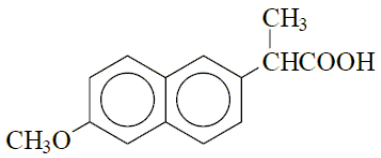


Ibuprofen

- Both OTC and Rx (dose varies from 200-400 mg)
- $T_{1/2}$ of 2 hours, duration of action 4-8 hrs
- Lower incident of side effects vs. aspirin (less GI ADR when used at low doses)
- Recommended anti-inflammatory dose is 600 mg QID
- Use for osteoarthritis, rheumatoid arthritis, fever, toothaches, postop pain control, sports injuries
- Chronic use can result in nausea, dyspepsia, GI ulceration, ⇧ liver enzymes, headache, hypertension
- Hepatic metabolism and renal excretion

Napoxen

Aleve



- Propionic acid derivative, thus same indications as Ibuprofen, $T_{1/2}$ of ~ 13 hrs
- available as both the free acid and sodium salt
- sodium salt form is more rapidly absorbed from GI tract
- OTC is 220 mg and recommended daily dose of 660 mg
- more irritating to GI tract than Ibuprofen
- renal clearance
- highly bound to plasma albumin
- FDA has issued warming of ⇧ risk of heart attack

COX-2 selective inhibitors

Coxibs=Cyclooxygenase-2 inhibitors
Hydrophobic sulfonic acid derivatives

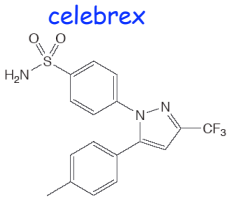
✓Reduce inflammation and pain while minimizing the undesired GI adverse effects

✓⇧ BP if given with antihyper-tensive drugs

✓Larger than non-selective COX inhibitors, and thus are too bulky to access the smaller hydrophobic channel of COX-1

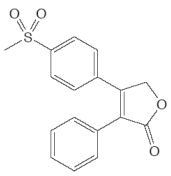
✓Potential CV side effects

celebrex



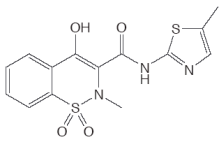
Celecoxib

vioxx



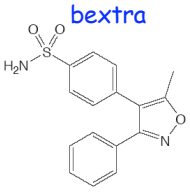
Rofecoxib

mobic



Meloxicam

bextra



Valdecoxib

COX-2 selective inhibitors (con't)

- **Celecoxib (Celebrex):** ⇩ inflammation & pain with minimal GI ADR and reduced effect on platelet aggregation, 375 times more effective for COX-2 than COX-1
- Used in Tx of osteo- and rheumatoid arthritis, acute pain, menstrual cramps, post dental or orthopedic surgery
- Contains a sulfonamide moiety so may cause allergic Rx
- Recommended dose 100-200 mg BID, oral
- Bioavailability is about 36%
- Elimination-$T_{1/2}$ is 11 hours, hepatic metabolism (p450 2C9) and excreted in the urine

COX-2 selective inhibitors (con't)

•**Rofecoxib (Vioxx):** withdrawn from the market in 2004 due to concerned about⇧ risk of stroke and heart attack

•**Valdecoxib (Bextra):** use in Tx of osteo- and rheumatoid arthritis

•Rx only, dose is 10-30 mg daily, peak plasma levels in ~3 hr.

•Hepatic metabolism and excreted via the urine

•**Meloxicam (Mobic):** use for relief of signs and symptoms associated with osteoarthritis

•Rx only, dose is 15 mg daily

•Max. plasma levels in 4-5 hrs, $T_{1/2}$ is 15-20 hrs, excretion of metabolites in both feces and urine

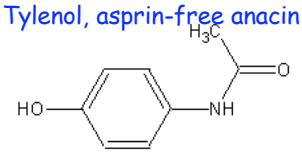
COX-2 inhibitors: Implications for Dentistry

- role of COX-2 inhibitors in acute postsurgical dental needs additional studies
- potential role in long-term treatment of localized TMJ inflammation or other oral facial pain syndromes due to enhanced GI safety
- indications for use as preemptive analgesic before a dental surgical procedure due to long duration of effect and lack of antiplatelet action
- desirable due to once a day dosing

?? COX-3 selective inhibitors ??

- has no anti-inflammatory activity, used for mild to moderate pain and fever, when NSAIDs are not well tolerated
- Peroxides produced during an inflam. rx, result in inhibition of acetaminophen
- Peak plasma levels in 30-60 minutes, $T_{1/2}$ is 2-4 hrs, metabolized in the liver
- Acts mainly in the CNS and but also on peripheral nerves
- Dose 650 mg QID, not to exceed 4 gm/day
- Toxic dose (15g): vomiting, nausea, and potential fatal liver and kidney necrosis
- Highly toxic liver metabolite can be neutralized with sulfhydryl groups derived from Acetylcysteine

Tylenol, asprin-free anacin



Paracetamol (acetaminophen)

Paracetamol is not considered an NSAID as it has no anti-inflammatory activity

Drugs used in gout

- Gout: ⇧plasma [urate] due to either overproduction or ⇩excretion of purines; results in deposition of sodium urate crystals in the synovial tissues; very painful intermittent attacks of acute arthritis.

- Drugs used to treat gout:
  - Allopurinol inhibits uric acid synthesis by inhibiting xanthine oxidase; drug of choice for long term use
  - Probenecid ⇧ uric acid excretion
  - Colchicine ⇩ leukocyte migration into joints; binds to tubulin resulting in depolymerization of micro tubules and interference with cell motility
  - NSAIDs have anti-inflammatory effects and ⇩ pain
- Unwanted effects of anti-gout drugs:
  - GI disturbances, vomiting
  - Skin rash
  - Can trigger acute attacks of gout at initiation of therapy

Drugs used in the treatment of gout

Acute Attack:

NSAIDs: reduce pain due to anti-inflammatory action

Colchicine: decreases leukocyte migration into joints

Prophylaxis:

allopurinol: reduces uric acid production

probenecid: increases uric acid excretion

Do not use drugs for prophylaxis until the acute attack has been resolved!!

Antirheumatoid drugs

- Rheumatoid disease is the most common chronic inflammatory condition. Rheumatoid arthritic (RA) joint changes (autoimmune rx?) include inflammation, synovium proliferation and erosion of bone and cartilage.
- Can result in severe disability
- Pathogenesis: involves IL-1 and TNFα
- Treat with DMARDs, NSAIDs, immunosuppressants, glucocorticoids and anticytokine drugs
- NSAIDs do **not** retard the progress of the disease, they just reduce the symptoms.
- DMARDs may halt or reverse the underlying disease

Antirheumatoid drugs

- **DMARDS** (Disease modifying antirheumatoid drugs): include a variety of agents from different structural families and with different mechanisms of action
  - **Methotrexate:** folic acid antagonist with cytotoxic and immuno-suppressive activity. First-choice Tx as to a more rapid onset and fewer adverse effects
  - **Chloroquine:** 4-aminoquinoline drug used for the prevention and Tx of malaria; causes remission of RA but does not retard progression of bone erosion. Use with other anti-inflam agents for pain relief. ~50% of patients benefit from Tx. Can cause ocular toxicity
  - **Sulfasalazine:** produces remission of active RA. Acts by scavenging toxic oxygen metabolites produced by neutrophils. It is a combination of sulfonamide with a salicylate and is split into its component parts by bacteria in the colon. The released 5-aminosalicylic acid is the radical scavenger. GI distress is common side effect.
  - **Gold compounds:** mechanism of inflammation suppression is not known. Inhibition of PG syn, suppress cellular immune response, inactivates complement pathways and decrease phagocytic activity

Antirheumatoid drugs (con't)

- **Anticytokine therapy:** TNFα blockers and directed towards specific aspects of RA. Also used in Crohn's disease
  - **Infliximab**: used in anticytokine therapy and is a humanized mAb against TNFα. Used with methotrexate and given IV every 2 months
  - **Etanercept:** TNF receptor joined to the Fc portion of human IgG. Binds TNFα and lymphotoxin-α
  - FDA has recently ordered stronger warnings associated with these drugs as increased risk of fatal fungal infections have been reported.
- **Immunosuppressants:** relieve symptoms of RA especially when NSAIDs fail to relieve pain. Rapid onset of action. Used at lower doses than those use to suppress rejection of transplanted tissues.
  - Act during induction and effector phase of the adaptive immune response