Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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• Analgesic
• Antipyretic
• Anti-inflammatory (at higher doses)
# NSAID Classification

## Nonselective COX inhibitors

<table>
<thead>
<tr>
<th>Acetic acid</th>
<th>Propionic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Fenoprofen</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Ketoprofen</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Naproxen</td>
</tr>
<tr>
<td></td>
<td>Oxaprozin</td>
</tr>
</tbody>
</table>

### Fenamate

- Meclofenamate
- Meclofenamic acid

### Naphthylalkanone

- Nabumetone

### Oxicam

- Piroxicam
- Meloxicam

### Salicylate

- Aspirin
- Diflunisal

### Choline magnesium trisalicylate

- Salsalate

## Selective COX-2 inhibitors

- Celecoxib
- Rofecoxib
Common Pharmacological Effects to be covered below

• **Analgesic** (CNS and peripheral effect) may involve non-PG related effects
• **Antipyretic** (CNS effect)
• **Anti-inflammatory** (except acetaminophen) due mainly to PG inhibition.

Some shown to inhibit activation, **aggregation**, adhesion of neutrophils & release of lysosomal enzymes

• Some are **Uricosuric**
Prostaglandin Biosynthesis, Function, and Pharmacologic Inhibition.
Control of vascular tone and platelet activation by thromboxanes and prostacyclins

A

\[
\text{TXA}_2
\]

\[
\text{PGI}_2
\]

B

Blood vessel

Endothelial cell

Platelet

\[
\text{TXA}_2 \quad \rightarrow \quad \text{PGI}_2
\]

C

\[
\text{TXA}_3
\]

\[
\text{PGI}_3
\]

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Pharmacological Effects (cont’d)

- Diverse group of chemicals, but all inhibit cyclooxygenase.
- Resultant inhibition of PG synthesis is largely responsible for their therapeutic effects.
- But, inhibition of PG synthase in gastric mucosa \(\rightarrow\) GIT damage (dyspepsia, gastritis).
Common Adverse Effects

- Platelet Dysfunction
- Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)
- Acute Renal Failure in susceptible
- Sodium+ water retention and edema
- Analgesic nephropathy
- Prolongation of gestation and inhibition of labor.
- Hypersenstivity (not immunologic but due to PG inhibition)
- GIT bleeding and perforation
NSAID

Loss of PGE\(_2\) and PGI\(_2\) mediated inhibition of acid secretion and cytoprotective effect

↑ Leukocyte-Endothelial Interactions

Capillary Obstruction

↓ Ischemic Cell Injury

Proteases + Oxygen Radicals

Endo/Epithelial Cell Injury

Mucosal Ulceration

Loss of PGI\(_2\) induced inhibition of LTB\(_4\) mediated endothelial adhesion and activation of neutrophils
Cyclo-oxygenase (COX)

• Exists in the tissue as constitutive isoform (COX-1).
• At site of inflammation, cytokines stimulate the induction of the 2nd isoform (COX-2).
• Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
• Inhibition of COX-1 is responsible for their GIT toxicity.
• Most currently used NSAIDs are somewhat selective for COX-1, but selective COX-2 inhibitors are available.
COX (cont’d)

• Celecoxib, etoricoxib, valdecoxib – selective COX-2 inhibitors.
• Have similar efficacies to that of the non-selective inhibitors, but the GIT side effects are decr by ~50%.
• But, no cardioprotection and there is actually increased MI.
Peripheral inflammation

- COX-2 upregulation in inflammatory cells

Central cytokine release

- COX-2 upregulation in dorsal horn neurons and supporting cells

- Acetaminophen
- Celecoxib
- NSAIDs

Prostaglandin production

- Constitutive COX-1

Action on peripheral terminal PGE$_2$ receptors

- Peripheral sensitization

Action on PGE$_2$ receptors on dorsal horn neurons

- Enhanced depolarization of secondary sensory neurons
The Salicylates - Aspirin

• **Effect on Respiration: triphasic**

1. Low doses: uncoupling phosphorylation $\rightarrow \uparrow CO_2$ $\rightarrow$ stimulates respiration.
2. Direct stimulation of respiratory center $\rightarrow$ Hyperventilation $\rightarrow$ resp. alkalosis $\rightarrow$ renal compensation
3. Depression of respiratory center and cardiovascular center $\rightarrow \downarrow$ BP, respiratory acidosis, no compensation + metabolic acidosis also
The Salicylates - Aspirin

- Duration of action ~ 4 hr.
- Orally taken.
- Weak acid (pKₐ ~ 3.5); so, non-ionized in stomach → easily absorbed.
- Hydrolyzed by esterases in tissues and blood to salicylate (active) and acetic acid.
- Most salicylate is converted in liver to H₂O-sol conjugates that are rapidly excreted by kids.
Aspirin

- **GI system**
  1. Dose dependent hepatitis
  2. Reye’s syndrome
- **Metabolic**
  1. Uncoupling of Oxidative Phosphorylation
  2. Hyperglycemia and depletion of muscle and hepatic glycogen
- **Endocrine**: corticosteroids, thyroid
Cardiovascular

• Platelets: Inhibition of platelet COX-1-derived $\text{TxA}_2$ with the net effect of increasing bleeding time (inhibition of platelet aggregation)

• Endothelial COX-2 derived PGI$_2$ can inhibit platelet aggregation (inhibition augments aggregation by $\text{TxA}_2$).

Aspirin (acetylsalicylic acid) covalently modifies and, irreversibly inhibits platelet COX. The enzyme is inhibited for the lifetime of the platelet (~8 -11 days). Effect achieved at very low dose.

• *Basis of therapeutic efficacy in stroke and MI (reduces mortality and prevents recurrent events).*
Additional Cardiovascular Considerations

- **Blood vessels/smooth muscle**
  COX-2 derived PGI$_2$ can antagonize catecholamine- and angiotensin II-induced vasoconstriction (NSAIDs can elevate bp).

- **Atherosclerosis**
  Inhibition of COX-2 can destabilize atherosclerotic plaques (due to its anti-inflammatory actions)
Renal

• COX-1 and COX-2 – generated PGs (TxA$_2$, PGF$_2$, PGI$_2$ (glomerulus), PGE$_2$ (medulla), powerful vasodilators) can both incr and decr Na$^+$ retention (natriuresis predominates), usually in response to changes in tubular Cl$^-$, extracellular tonicity or low bp.

• NSAIDs tend to promote Na$^+$ retention and can therefore increase bp. Can counteract effects of many anti-hypertensives (diuretics, ACE inhibitors and -AR antagonists).

• PGs have minimal impact on normal renal blood flow, but become important in the compromised kidney. Patients (particularly elderly and volume depleted) are at risk of renal ischemia with NSAIDs.
Gastrointestinal

- PGs (generated via COX-1)
  1) inhibit stomach acid secretion,
  2) stimulate mucus and $\text{HCO}_3^-$ secretion, vasodilation and therefore,
  3) are cytoprotective for the gastric mucosa.

- Therefore, NSAIDs with COX-1 inhibitory activity will produce opposite effects, leading to:

- Gastric distress, gastric bleeding, sudden acute hemorrhage \textit{(effects are dose-dependent)}
**Gestation**

PGs (generated from COX-2) are involved in the initiation and progression of labor and delivery. Therefore, inhibition of their production by NSAIDs can prolong gestation.

**Respiratory system**

High doses (salicylates) cause partial uncoupling of oxidative phosphorylation with increased CO$_2$ production (COX-independent effects). Increase in plasma CO$_2$ $\rightarrow$ hyperventilation. Even higher doses cause depression of respiration.

Other uses of NSAIDs (mechanisms less understood) -

Decreased risk of fatal colon carcinoma
Aspirin - Therapeutic Uses

• Antipyretic, analgesic
• Anti-inflammatory: rheumatic fever, rheumatoid arthritis (joint dis), other rheumatological diseases. High dose needed (5-8 g/day).
• But many pts cannot tolerate these doses (GIT); so, proprionic acid derivatives, ibuprofen, naproxen tried first.
• Prophylaxis of diseases due to platelet aggregation (CAD, post-op DVT)
• Pre-eclampsia and hypertension of pregnancy (?excess TXA₂)
• **Paracetemol (tylenol)** – no significant anti-inflammatory effect, but used for its mild analgesic effect.

• Well-absorbed and without GIT irritation.

• Serious disadvantage: at high doses, severe hepatotoxicity results.
Mechanisms of Action

• Analgesia – both centrally and peripherally.
  - assoc with anti-inflammatory actions.
  - results from inhibition of PG synthesis in inflamed tissues.
  - [PGs → little pain relief themselves, but potentiate the pain caused by other mediators of inflammation (e.g., histamine, bradykinin).]
Mechanisms of Action

• Anti-inflammatory action – PGs in inflammation ➔ vasodilation and incr vasc permeability.
  - Inhibition of PGs by NSAIDs attenuates, not abolish, inflammation (NSAIDs do not inhibit mediators of inflammation).
  - Very modest relief from pain, stiffness, swelling for RA ➔ often prescribed for their anti-inflammatory actions.
Mechanisms of Action

• Antipyretic actions – Fever, heat stroke, incr $T^\circ$ are hypothalamic problems.
  - So, NSAIDs do not decr body $T^\circ$.
  - Fever $\Rightarrow$ release of endog pyrogens (e.g., interleukin-1) released from leucocytes $\Rightarrow$ acts directly on the thermoregulatory centers in hypothalamus $\Rightarrow$ incr body $T^\circ$.
  - This is assoc with incr in brain PGs (pyrogenic).
  - Aspirin prevents the $T^\circ$-rising effects of interleukin-1 by preventing the incr in brain PGs.
Mechanism of Action on the Active Site of COX

• Possess a long channel (COX-2 channel is wider than in COX-1).
• Non-selective NSAIDs enter channel (but not aspirin).
• Block channels by binding with H-bonds to an arg half of the way in.
• This reversibly inhibits the COX by preventing arachidonic acid from gaining access.
• Aspirin acetylates COX (at ser530) and is, therefore, irreversible.
• Selective COX-2 inhibitors generally more bulky molecules - can enter and block the channel of COX-2, but not that of COX-1.
• Paracetamol – reducing cytoplasmic peroxide:
• Recall: peroxide is necessary to activate heme enzyme to the Fe.
• Acute inflammation: paracetamol is not very effective bec neutrophiles and monocytes produce much $\text{H}_2\text{O}_2$ and lipid peroxide, which overcome the actions of the drug.
Selective COX-2 Inhibitors

• Anti-inflammatory with less adverse effects, especially GI events.
• Potential toxicities: kidney and platelets - increased risk of thrombotic events.
• Assoc with MI and stroke because they do not inhibit platelet aggregation. Thus, should not be given to patients with CV disease
• Role in Cancer prevention
• Role in Alzheimer’s disease
Lipoxins – Anti-inflammatory Mediators

- During inflammation, cells die by apoptosis.
- Lipoxins signal macrophages to clean up.
- During the acute inflammatory process, cytokines (e.g., IFN-γ and IL-1β) can induce the expression of anti-inflammatory mediators (lipoxins and IL-4), which promote the resolution phase of inflammation.
Generation of Lipoxins by Aspirin

Aspirin → COX-2 → 15(R)-HETE

Endothelium

PMN

AA → 5-LO → 15-epi-LXA4

Platelets

AA → 12-LO → LXA4

Ig-like molecule (e.g. ICAM)
Integrin (e.g. CD11/CD18)
P-selectin
Carbohydrate-containing selectin ligand

TRENDS in Pharmacological Sciences
Role of Lipoxins in Anti-inflammatory effects of Aspirin

- Stimulates chemotaxis and adhesion
- Inhibition of P-secin mobilization
- Attenuation of CD11/CD18 expression
- Antagonism at CysLT1 receptor
- Inhibition of proliferation, chemotaxis, contractility and adhesion
- Inhibition of chemotaxis, adhesion and transmigration
- Inhibition of cytokine-stimulated IL-1β and superoxide production
- Inhibition of L-selectin shedding
- Stimulation of IL-4 production

Macrophage
- Stimulates phagocytosis of apoptotic PMN

Monocyte
- Stimulates chemotaxis and adhesion

Endothelium
- Inhibition of P-secin mobilization
- Attenuation of CD11/CD18 expression
- Antagonism at CysLT1 receptor

Mesangial cell
- Inhibition of proliferation, chemotaxis, contractility and adhesion

Fibroblast
- Inhibition of IL-1β-stimulated IL-6 and IL-8 production
- Decreased MMP-3 expression and increased TIMP expression

Eosinophil
- Inhibition of chemotaxis, IL-5 and eotaxin secretion

GI epithelial cell
- Inhibition of cytokine and pathogen-stimulated IL-8 release

PMN
- Inhibition of chemotaxis, adhesion and transmigration
- Inhibition of cytokine-stimulated IL-1β and superoxide production
- Inhibition of L-selectin shedding
- Stimulation of IL-4 production
Effect of NSAID’s on Platelet-Endothelial Interactions
Use of Aspirin in Unstable Angina

Fig. 35-1. Occurrence of cardiac death and nonfatal myocardial infarction in the aspirin (ASA) and no-aspirin groups of the Canadian multicenter trial of unstable angina. The graph is a life table depiction of cumulative risk and time of occurrence of an outcome event according to aspirin allocation. The numbers of patients at risk are noted below the graph. (From Cairns et al., with permission.)
Use of Aspirin in Unstable Angina

Fig. 35-3. Occurrence of death or nonfatal myocardial infarction (MI) among the four regimens in the RISC group trial of unstable angina and non-Q-wave infarction. The graph is a life table depiction of cumulative risk and time of an outcome event, according to treatment allocation. (From the RISC Group.86 with permission.)
Aspirin Toxicity - Salicylism

- Headache - timmitus - dizziness – hearing impairment – dim vision
- Confusion and drowsiness
- Sweating and hyperventilation
- Nausea, vomiting
- Marked acid-base disturbances
- Hyperpyrexia
- Dehydration
- Cardiovascular and respiratory collapse, coma convulsions and death
Aspirin Toxicity - Treatment

- **Decrease absorption** - activated charcoal, emetics, gastric lavage
- **Enhance excretion** – ion trapping (alkalinize urine), forced diuresis, hemodialysis
- **Supportive measures** - fluids, decrease temperature, bicarbonate, electrolytes, glucose, etc...
Other NSAIDs

- **Phenylbutazone**: additional uricosuric effect. Aplastic anemia.
- **Indomethacin**: Common adverse rxns: gastric bleeding, ulceration, CNS most common: hallucinations, depression, seizures, headaches, dizziness.
- **Proprionic acids**: better tolerated. Differ in pharmacokinetics; ibuprofen, fenbufen, naproxen widely used for inflammatory joint disease and few side-effects.
- **Acetaminophen**: differs in effects and adverse rxn from rest. Main toxicity: hepatitis due to toxic intermediate which depletes glutathione. Treat with N-acetylcysteine.
### TABLE II—SUMMARY OF CLINICALLY SIGNIFICANT NSAID DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td>Displacement/additive effect</td>
<td>Increased anticoagulant activity via displacement. Also, some NSAIDS affect platelet function.</td>
</tr>
<tr>
<td>Lithium</td>
<td>NSAIDS inhibit renal elimination of lithium</td>
<td>Elevated serum lithium levels</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>NSAIDS may cause fluid retention and edema</td>
<td>Decreased antihypertensive effects</td>
</tr>
</tbody>
</table>
Attempts to Decrease Toxicity of NSAID’s – Nitroaspirirns
VIGOR - Summary of GI Endpoints

## VIGOR - Confirmed Thrombotic Cardiovascular Events

### Patients with Events (Rates per 100 Patient-Years)

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Rofecoxib N=4047</th>
<th>Naproxen N=4029</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed CV events</td>
<td>45 (1.7)</td>
<td>19 (0.7)</td>
<td>0.42 (0.25, 0.72)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>28 (1.0)</td>
<td>10 (0.4)</td>
<td>0.36 (0.17, 0.74)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>11 (0.4)</td>
<td>8 (0.3)</td>
<td>0.73 (0.29, 1.80)</td>
</tr>
<tr>
<td>Peripheral vascular events</td>
<td>6 (0.2)</td>
<td>1 (0.04)</td>
<td>0.17 (0.00, 1.37)</td>
</tr>
</tbody>
</table>

Source: Data on file, MSD
Effect of Celecoxib & Rofecoxib on PGIM

Urinary 2,3 dinor-6-keto-PGF$_{1\alpha}$ (PGIM)

Single Dose Rx$^\dagger$

<table>
<thead>
<tr>
<th>Drug</th>
<th>dose</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>N=7</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>400 mg</td>
<td>**</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>800 mg</td>
<td>*</td>
</tr>
</tbody>
</table>

Two Weeks Rx$^{\dagger\dagger}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>dose</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>N=12</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>50 mg QD</td>
<td>**</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>50 mg TID</td>
<td>**</td>
</tr>
</tbody>
</table>

*p<0.05 vs. placebo.

**p<0.01 vs. placebo.


Investigator-Reported Thrombotic Cardiovascular Events in the VIGOR Study Compared with Phase IIb/III OA Study

- Rofecoxib (VIGOR)
- Naproxen (VIGOR)
- Ibuprofen, Diclofenac, Nabumetone (OA)
- Rofecoxib (OA)

Cumulative Incidence %

Months of Follow-up

FDA files
Gout

- Characterized by deposition of Na urate crystals in the joint → painful arthritis.
- Acute attacks treated with indomethacin, naproxen, or other NSAIDs, but not with aspirin (incr plasma urate levels at low doses by inhibiting uric acid secretion in the renal tubules).
- Colchicine – bonds tubulin in leukocytes → prevents polymerization in microtubules → inhibits the phagocytic activity and migration of leukocytes to the area of uric acid deposition → decr inflammatory response.
Prophylactic treatment of Gout

- Allopurinol lowers plasma urate by inhibiting xanthine oxidase (xanthine $\rightarrow$ uric acid).
- Uricosuric drugs (sulfinpyrazone, probenicid) inhibit renal tubular reabsorption of uric acid $\rightarrow$ incr excretion.
- Should drink plenty of $H_2O$ to prevent crystallization of urate in the urine.
- These drugs less effective and more toxic than allopurinol.
Treatment of Gout

Purines

Hypoxanthine

Xanthine oxidase

Xanthine

Xanthine oxidase inhibited by Allopurinol

Uric acid

Urate crystals

Release of lysosomal enzymes and other pro-inflammatory enzymes and mediators

Phagocytosis and release inhibited by Colchicine

Reabsorption inhibited by Probenecid and Sulfapyrazone

Excretion in urine