Acetaminophen and NSAIDS

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Lecture Goals

› Understand the indications for acetaminophen and NSAID use in musculoskeletal medicine

› Understand the role of Eicosanoids in the body’s response to injury and how NSAIDS function to reduce inflammation
Acetaminophen

› Analgesic, antipyretic

› Acetaminophen shows affinity for naloxone binding sites, increases brain 5-hydroxytryptamine concentrations, and reduces the number of 5HT₂ receptors in cortical membranes.

› These effects were similar to those of morphine.
Clinical trials have demonstrated that acetaminophen is a safe and effective analgesic for the relief of mild to moderate pain associated with oral surgery, episiotomy, postpartum pain, cancer, osteoarthritis, dysmenorrhea, and headache.

In addition, acetaminophen has a serotonergic analgesic effect by indirectly activating spinal 5HT₃ receptors. This effect of acetaminophen was not blocked by naloxone.

Acetaminophen

Safety profile

- Acetaminophen has a narrow safety profile: liver damage from acetaminophen can occur with only a modest increase over the recommended dosage.
ACETAMINOPHEN TOXICITY

› Hepatotoxic when dose >4 gm/day
› Hepatotoxicity may occur @ doses <4gm/d following binge drinking
› Hepatic centrilobular necrosis
› AST/ALT >1000 units
› Treat with *n*-acetylcysteine orally
ACETAMINOPHEN
ACUTE LIVER FAILURE

› 55% of ALF in US
› Median dose 24 gm
› Unintentional OD 48%
› Intentional(suicide) 44%
› Survival 65%
› Death 27%
› Tx 8%
The studies show that people who took acetaminophen have less pain (when resting, moving, sleeping and overall) and felt better overall than people who took a placebo.

Pain (when measured on a different scale), physical function and stiffness were about the same.

Pain decreased by 4 more points on a scale of 0-100 for people who took acetaminophen instead of a placebo.

There is a ceiling affect for pain relief: increasing the dose past the recommended dosage does not render further pain relief.

Acetaminophen vs Placebo for OA
The evidence to date suggests that NSAIDs are superior to acetaminophen for improving knee and hip pain in people with moderate to severe OA.

The size of the treatment effect was modest, and the median trial duration was only six weeks.

In OA subjects with moderate-to-severe levels of pain, NSAIDs appear to be more effective than acetaminophen.
Acetaminophen use in Hand OA-ACR guidelines

› Note
- Acetaminophen not recommended for hand OA
- Differs from acetaminophen recommendation for use in OA of knee and hip
# List of Available NSAIDs: Prescription & OTC *

* List of trade names is not exhaustive

<table>
<thead>
<tr>
<th>NON-SALICYLATES</th>
<th>SALICYLATES</th>
<th>COX-2 INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac (Voltaren)</td>
<td>Aspirin (^{a,c}) (Zorprin, Easprin)</td>
<td>Celecoxib (Celebrex)</td>
</tr>
<tr>
<td>Diclofenac/Misoprostol (Arthrotec)</td>
<td>Diflunisal (Dolobid)</td>
<td>Rofecoxib (Vioxx)</td>
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<tr>
<td>Etodolac (Lodine)</td>
<td>Salsalate (Disalcid, Salflex)</td>
<td>Valdecoxib (Bextra)</td>
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<tr>
<td>Fenoprofen (Nalfon)</td>
<td>Choline salicylate (Trilisate)</td>
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<tr>
<td>Flurbiprofen (Ansaid)</td>
<td>Magnesium salicylate (Magan)</td>
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<tr>
<td>Ibuprofen (^{a,b,c}) (Motrin, Advil)</td>
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<tr>
<td>Indomethacin (Indocin)</td>
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<tr>
<td>Ketoprofen (^{a,b,c})(Orudis)</td>
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<td></td>
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<tr>
<td>Ketorolac (Toradol)(^c)</td>
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<tr>
<td>Meclofenamate</td>
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<tr>
<td>Mefenamic acid (Ponstel)</td>
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<tr>
<td>Meloxicam (Mobic)</td>
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<tr>
<td>Nabumetone (Relafen)</td>
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<tr>
<td>Naproxen (^{a,b,c})(Naprosyn, Anaprox)</td>
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<td></td>
</tr>
<tr>
<td>Oxaprozin (Daypro)</td>
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<td></td>
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<tr>
<td>Piroxicam (Feldene)</td>
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<td></td>
</tr>
<tr>
<td>Sulindac (Clinoril)</td>
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<tr>
<td>Tolmetin (Tolectin)</td>
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</tbody>
</table>

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**Comments on Over-the-Counter Preparations:**

\(^a\) Also available as OTC preparations in U.S.

\(^b\) OTC dose is usually half of prescribed dose

\(^c\) All OTC NSAIDs are non-selective COX Inhibitors
NSAIDS (including aspirin)

- Analgesic
- Antipyretic
- Anti-inflammatory (at higher doses)
The Inflammatory Cascade

Tissue injury

Adaptive immune system

Leukocyte & endothelial cell activation

Inflammatory mediators

Inflammation (redness, edema, warmth, pain, tissue destruction)

Perceived threat

Infection

Innate immune system
Eicosanoids - prostaglandins, prostacyclins, thrombaxane, leukotrienes

- In biochemistry, **eicosanoids** are **signaling molecules** made by **oxidation** of 20-carbon **fatty acids**.

- They exert complex control over many bodily systems; mainly in **growth** during and after physical activity, **inflammation** or **immunity** after the intake of **toxic** compounds and **pathogens**, and as messengers in the **central nervous system**.

- The networks of controls that depend upon eicosanoids are among the most complex in the human body. *Wikipedia*
# Eicosanoids As Drugs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Analog Of</th>
<th>Clinical Use</th>
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</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>PGI₂</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Dinoprostone</td>
<td>PGE₂</td>
<td>Medical abortion, relax uterine cervix in preparation for induction of labor</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>PGE₁</td>
<td>Peptic ulcer, medical abortion</td>
</tr>
<tr>
<td>Alprostadil</td>
<td>PGE₁</td>
<td>Maintain a patent (open) ductus arteriosus in neonates with certain cardiac malformations until emergency surgery; erectile dysfunction</td>
</tr>
<tr>
<td>Carboprost</td>
<td>PGF₂α</td>
<td>Labor induction</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>PGF₂α</td>
<td>Glaucoma</td>
</tr>
</tbody>
</table>
Diet and Inflammatory activity

Omega 6
Linoleic acid
Arachidonic acid
Cyclo-oxygenase
Lipoxygense
Omega 6 derived eicosanoids
2 series prostanoids
TXA_2, PGE_2, PGJ_2
4 series leukotrienes
LTB_4, LTC_4, LTE_4
Pro-inflammatory

Omega 3
α-linolenic acid
Eicosapentaenoic acid
Cyclo-oxygenase
Lipoxygense
Omega 3 derived eicosanoids
3 series prostanoids
TXA_3, PGE_3, PGI_3
5 series leukotrienes
LTB_5, LTC_5, LTE_5
Anti-inflammatory
Inflammatory Enzymes: PLA₂, Cox, Lipooxygenase

1. Steroids

Phospholipase A₂

Arachidonic acid (AA)

Lipoxygenase products (leukotrienes)

Inflammatory effects (esp. in asthma)

Cyclooxygenase (COX)

Prostaglandins & thromboxanes

Inflammatory effects (inducible)

2. NSAIDS (including aspirin)

3. Zileuton
Montelukast, zafirlukast

Membrane Phospholipids

Homeostatic Functions (stomach mucus)

1. Steroids

2. NSAIDS (including aspirin)

3. Zileuton
Montelukast, zafirlukast
Cox 1 (constitutive) and Cox 2 (inducible)
20:4n-6 AA
- Lipoxygenase
  - Series 4 leucotrienes, lipoxins
    - \( \text{LTB}_4 \): proinflammatory, induce lysosomal enzymes, vascular permeability
    - \( \text{LTE}_4 \): component of slow-reactive substance of anaphylaxis, induces vasodilation and bronchoconstriction
  - Cyclooxygenase
    - Series 2 prostaglandins, thromboxanes
      - \( \text{PGI}_2 \): potent platelet aggregator, blood vessel dilator, and antiarrhythmic
      - \( \text{PGE}_2 \): proinflammatory, pain, inhibits TNF and IL-1, uterine contraction induction
      - \( \text{TXB}_2 \): potent blood vessel constrictor and platelet aggregator
      - \( \text{PGD}_2 \): inhibits platelet and leukocyte aggregation, decreases T-cell proliferation and lymphocyte migration
- Elongase
- 20:5n-3 EPA
- Lipoxygenase
- Cyclooxygenase
- Elongase
  - Series 5 leucotrienes
    - \( \text{LTB}_5 \): anti-asthmatic
    - \( \text{LTE}_5 \): 10-100 times less potent than \( \text{LTE}_4 \)
- DHA
  - Series 3 prostaglandins, thromboxanes
    - \( \text{PGI}_2 \): potent inhibitor of platelet aggregation
    - \( \text{TXB}_2 \): weak platelet aggregator
    - \( \text{PGE}_2 \): weak inducer of COX-2 in fibroblasts, and of IL-6 production by macrophages
NSAIDs: What Are the Risks?
Prescription & OTC

› GI Tract
  – Ulcers, perforations, bleeding, obstruction, strictures, enteropathy

› Kidney
  – Sodium and fluid retention
  – Hyperkalemia
  – Acute renal failure
  – Hypertension

› Platelet
  – Inhibition of aggregation leading to increased potential for bleeding
Renal

› COX-1 and COX-2 – generated PGs (Tx\textsubscript{A} \textsubscript{2}, PGF\textsubscript{2}, PGI\textsubscript{2} (glom), PGE\textsubscript{2} (medulla), powerful vasodilators) can both incr and decr Na\textsuperscript{+} retention (natriuresis predominates), usually in response to changes in tubular Cl\textsuperscript{-}, extracellular tonicity or low bp.

› NSAIDs tend to promote Na\textsuperscript{+} retention and can therefore increase bp. Can counteract effects of many anti-hypertensives.

› 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

- Prostaglandins (generated via COX-1)
  1) inhibit stomach acid secretion,
  2) stimulate mucus and 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 (*effects are dose-dependent*)
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.
NSAIDS in Osteoarthritis of the Hand, Knee and Hip – ACR 2012 Guidelines

› NSAIDS conditionally recommended for moderate to severe OA of the Hand, Hip and Knee

› Specific guidelines given for NSAID use by age, PMH of bleeding, concomitant ASA use, renal insufficiency

› Alternative, non-pharmacological treatments (including acetaminophen) highly recommended prior to NSAID use, and topical NSAIDS recommended before systemic use.
Recommended use of NSAIDS in sports Injury

Table – Highlights of studies on the use of NSAIDs for sports injuries

- Short-term use of NSAIDs may provide relief from pain and swelling after fracture, but long-term use of these medications may result in poor bone healing or nonunion.
- There is little role for NSAIDs in the treatment of patients with tendon injury other than pain relief during the first several days after injury.
- Short courses of NSAIDs of 3 to 7 days may be of benefit in managing ligament injury.
- Pain resulting from muscle injury and the time to return to full activity may be reduced with short-term NSAID use.
- There are a number of alternatives to systemic NSAID administration. These medications should be considered as valid options in the management of musculoskeletal injuries.
Acetaminophen, used in the recommended dose, is a valuable adjunct for mild to moderate pain of OA of the hip and knee

Oral NSAIDS, though widely used in a variety of musculoskeletal conditions, possess side effects that may limit their use long term, especially in the elderly, renal compromised patient. The Cox-2 selective inhibitors are indicated in those patients with a history of GI intolerance.