Cox-1 and Cox-2 inhibitor for treatment acute chronic pain, what’s the difference?

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Introduction

NSAIDs act via inhibition of cyclooxygenase (COX) isoenzyme, discovered >100 years ago.

Key component of the pharmacological management acute and chronic pain.

COX-1 and COX-2 have different biological function.

Analgesic activity primary associated with inhibition COX-2

Different side effect results from inhibition of COX-1 and COX-2.

(Brune and Patrigani, Journal of Pain Research, 2015)
All NSAIDs are associated with potential side effect, particularly gastrointestinal and cardiovascular effect related to their selectivity for COX-1 dan COX-2.

Since all NSAIDs exert their therapeutic activity through inhibition the COX enzyme, strategies needed to reduce the risk associated with NSAIDs.

(Brune and Patrigani, Journal of Pain Research, 2015)
Pain Relief

Non Selective
- Paracetamol
- Ibuprofen
- Piroxicam
- Aspirin
- Indomethacin
- Diclofenac

Selective Cox-2
- Celecoxib
- Etoricoxib
- Rofecoxib


The term NSAIDs is used to refer to both tNSAIDs and coxibs (COX-2 selective inhibitors).

NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states. Many effects of NSAIDs can be explained by inhibition of prostaglandin synthesis in peripheral tissues, nerves and the CNS.
Peripheral & Central Sensitization

Peripheral

- Trauma/inflammation
  - Release of arachidonic acid
    - COX-2
      - ↑ Prostaglandins E2
        - PAIN
          - Peripheral sensitization

Central

- Central sensitization
  - IL-6?
    - IL-1β
      - ↑ Prostaglandins
        - PAIN
          - COX-2
Prostaglandins regulate many physiological functions including:
- gastric mucosal protection,
- bronchodilation,
- renal tubular function and
- intrarenal vasodilation.

Production of endothelial prostacyclin leads to vasodilation and prevents platelet adhesion, whereas thromboxane, produced from platelets by COX, results in platelet aggregation and vasoconstriction.

Prostaglandin and COX

• Protective PGs, which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney, are synthesized by COX-1.
• In addition to the induction of COX-2 in inflammatory lesions, it is present constitutively in the brain and spinal cord, where it may be involved in nerve transmission, particularly that for pain and fever. PGs made by COX-2 are also important in ovulation and in the birth process.
• The discovery of COX-2 has made possible the design of drugs that reduce inflammation without removing the protective PGs in the stomach and kidney made by COX-1.
## Comparison between COX-1 and COX-2

<table>
<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>cDNA</td>
<td>chromosome 9; 22 kB</td>
<td>chromosome 1; 8.3 kB</td>
</tr>
<tr>
<td>mRNA</td>
<td>2.8 kB</td>
<td>4.5 kB</td>
</tr>
<tr>
<td>Protein</td>
<td>72 kDa: 599 amino acids</td>
<td>72 kDa: 604 amino acids</td>
</tr>
<tr>
<td>Difference in active site</td>
<td>COX-1 has a narrow active site</td>
<td>COX-2 has a wider active site</td>
</tr>
<tr>
<td>Regulation</td>
<td>Constitutive, increases 2-4 fold by inflammatory stimuli</td>
<td>Inducible (increases 10-20 fold), constitutive in several organs</td>
</tr>
<tr>
<td>Tissue expression</td>
<td>Several tissues, but mainly platelet, stomach, and kidney.</td>
<td>Inducible by inflammatory stimuli and mitogen on macrophages, monocytes, sinovinocytes, chondrocytes, fibroblasts, and endothelial cells. Inducible by ovarian hormones and fetal membranes. Constitutive on CNS, kidney, testicle, and tracheal epithelial cells.</td>
</tr>
</tbody>
</table>

COX-1 and COX-2

**Physiological Functions**
- TXA2: platelets
- PGI2: Endothelium, Stomach Mucosa
- PGE2: Kidney

**Inflammation**
- COX-2: Induced
- Prostaglandin
- Proteases

**Side effects of NSAIDs**

**Inhibition by NSAIDs**

**Anti-inflammatory Effects of NSAIDs**

Mechanisms of action of NSAIDs: COX-1 and COX-2 inhibition

The antiinflammatory, analgesic, and antipyretic activities are mediated by their inhibition of prostanoid biosynthesis.

Prostanoids are synthesized from arachidonic acid, a fatty acid present in cell membrane as phospholipid ester.

COX isoenzyme convert arachidonic acid first to prostaglandin (PG) G2 and then to PGH2 → PGD2, PGE2, PG2α, PGI2 (prostacyclin) and thromboxane A2 (TXA2).

(Ricciottii and Fitzgerald. Arterioscler Thrombo Vasc Biol. 2011)
NSAIDs: Mechanism Of Action

Arachidonic Acid

- Tromboxane (TxA2)
  - Vasoconstriction
  - ↑ Platelet Aggregation

- Prostaglandins E2 and I2
  - Inhibits gastric acid

Platelets

- Gastric Mucosa

- Joints

- Endothelium

Traditional NSAIDS

Coxibs

Coxibs

Cox-1

Cox-1

Cox-2

NSAIDs: Mechanism Of Action

Atchison, et al., JMCV 2013
- Vasokonstriksi
- Trombosis

![Diagram showing the balance between COX-1 and COX-2, with Tromboksan and Prostasiklin, and the use of NSAIDs selektif to balance vasodilatasi and anti-trombosis.](image-url)
**Side Effect NSAIDS**

### Arachidonic Acid

- **GI mucosa**
  - COX-1
  - \( \text{PGE}_2 \):
    - gastric protection
    - ↑mucus secretion
    - ↑bicarbonate
    - ↑mucosal blood flow
  - **COX-1 inhibition**:
    - Peptic ulcers
    - GI bleeding

- **Kidney**
  - COX-1 & 2
  - \( \text{PGE}_2 \) & \( \text{PGI}_2 \):
    - afferent arteriolar vasodilation (↑GFR)
    - ↑Na & water excretion
  - **COX inhibition**:
    - Na & water retention
    - Hypertension
    - Hemodynamic acute kidney injury

- **Cardiovascular**
  - COX-1 & 2
  - \( \text{PGI}_2 \) & \( \text{TXA}_2 \):
    - Vascular (COX-2: \( \text{PGI}_2 \)):
      - vasodilation
      - inhibit platelet aggregation
    - Platelet (COX-1: \( \text{TXA}_2 \))
      - platelet aggregation
      - vasoconstriction
  - **COX-2 > COX-1 inhibition**:
    - Stroke
    - Myocardial infarction

*Low dose aspirin irreversibly inhibits platelet COX-1*

Wallace, 2008
SIDE EFFECTS OF NSAIDs

- GI (stomach)
  - Cox-1 mediated production of PGE2 and PGI2 → regulating production of bicarbonate and mucous → protective cell lining of the stomach wall from erosive effects.
  - Inhibition of Cox-1 (by aspirin and non-selective COX) → increase incidence of peptic ulceration
PATHOGENESIS OF GASTRIC DAMAGE BY NSAIDS

(Feldman, 2014)
• Kidney
  – Renal prostaglandins function primarily as vasodilator in kidney.
  – In healthy individual: the impact of prostaglandins on renal perfusion is relatively limited.
  – Under condition prolonged renal vasoconstriction (age, heart and kidney failure) → upregulated synthesis prostaglandin → preserve renal blood flow and protect the GFR by decreasing pre-glomerulus arterial resistance.
  – In this setting: episodic use of NSAIDs → decrease blood flow through the glomerulus and increase risk of acute kidney injury.

(Feldman, 2014)
Renal Prostaglandin Expression & Function

Luciano & Perazella, 2015
• Cardiovascular system
  – Previous research: CV great inhibition of cox-2 vs cox-1: normal balance effect produced prostacyclin and thromboxane

(Feldman, 2014)
• Vasokonstriksi
• Trombosis

COX-1
Tromboksan

NSAIDs nonselektif

• Vasodilatasi
• Anti-Trombosis

COX-2
Prostasiklin
• Vasokonstriksi
• Trombosis

COX-1
Tromboksan

NSAIDs selektif

COX-2
Prostasiklin

• Vasodilatasi
• Anti-Trombosis
Selective COX-2 Inhibition & Enhanced CV Risk
(The Thromboxane/Prostacyclin Imbalance Hypothesis)

Anwar, 2015
Risk factor for GI side effects

- Advanced age
- History peptic ulcer and gastric bleeding.
- Serious comorbid medical condition.
- Concomitant Helicobacter pylori infection, use corticosteroid, antiplatelet, anticoagulant.
- High NSAIDs dose.
- Cigarette smoking.

Brune and Patrignani, Journal of Pain Research. 2015:8 105-118
Risk factor for CV side effects

- Unstable angina
- Myocardial infarction.
- Recent bypass surgery, placement of a cardiovascular stent.
- High NSAIDs dose
- Hypertension
- Heart failure.

Brune and Patrignani, Journal of Pain Research. 2015:8 105-118
Comparison side effect COX-2 selective vs NSAIDs diclofenac

MEDAL study: 18 month

- Etoricoxib: 60mg or 90mg → 320 thrombotic cardiovascular event yielding even rates of 1.24 per 100 patient/years. Hazard ratio 0.95 (95% CI 0.81-1.11).

- Diclofenac 150mg → 323 thrombotic cardiovascular event yielding even rates of 1.30 per 100 patient/years.

- Rate of upper GI clinical events: 0.67 vs 0.97.

Canon dkk. 2006 (The lancet. Vol 368.1771-1781)
Study meta-analysis Coxib and Traditional NSAIDs Trialists (CNT):

• Similarly increased cardiovascular events with high dose non-selective NSAIDs (diclofenac 150 mg, ibuprofen 2400 mg/day) compared coxib, but non with naproxen 1000mg

Kearney et al. BMJ. 2006;332:1302-1308
Comparison side effect COX-2 selective vs NSAIDs

- Study meta-analysis by Anwar dkk (2015)
  - Selective cox-2 inhibitor: moderate increase vascular event compared to placebo (1.2% vs 0.9%/years)
  - Moderate increase: similar high dose ibuprofen, diclofenac (not naproxen).
  - Moderate risk for first time myocardial infarct: similar (etodolac, nabumetone, nimesulid, meloxicam vs cox-2 selective (refocoxib, celecoxib, valdecoxib and etoricoxib).
Prevention strategies in patients with cardiovascular/GI tract risk factor treated with NSAIDs

• General rule.
  – Use the lower effective NSAIDs dose for the shorter period of time
  – Immediate-release NSAIDs for formulation are preferred, with repeated administration as necessary
  – Avoid concomitant therapy with corticosteroid, low dose aspirin/other antiplatelet, anticoagulant.
  – Limit use NSAIDs with the highest GI toxicity (ketorolac, piroxicam, ketoprofen).
  – Test for Helicobacter pylori infection in patients with prior peptic ulcer history and eradicate if presented.

(Brune and Patrigani, Journal of Pain Research, 2015)
## Strategies for Choosing NSAID Therapy According to Risk Factors

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low:</td>
<td>• Traditional NSAID</td>
</tr>
<tr>
<td></td>
<td>• Shortest duration and lowest dose possible</td>
</tr>
<tr>
<td></td>
<td>• &lt;65 years old</td>
</tr>
<tr>
<td></td>
<td>• No cardiovascular risk factors</td>
</tr>
<tr>
<td></td>
<td>• No requirement for high-dose or chronic therapy</td>
</tr>
<tr>
<td></td>
<td>• No concomitant aspirin, corticosteroids, or anticoagulants</td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Traditional NSAID + PPI, misoprostol, or high dose H₂RA</td>
</tr>
<tr>
<td></td>
<td>• Once-daily celecoxib + PPI, misoprostol, or high dose H₂Ra if</td>
</tr>
<tr>
<td></td>
<td>taking aspirin</td>
</tr>
<tr>
<td></td>
<td>• If using aspirin, take low dose (75 to 81 mg)</td>
</tr>
<tr>
<td></td>
<td>• IF using aspirin, take traditional NSAID ≥ 2 hours prior to</td>
</tr>
<tr>
<td></td>
<td>aspirin dose</td>
</tr>
<tr>
<td>High</td>
<td>• Use acetaminophen &lt; 3g/day</td>
</tr>
<tr>
<td></td>
<td>• Avoid chronic NSAIDs if at all possible:</td>
</tr>
<tr>
<td></td>
<td>• Use intermittent NSAID dosing</td>
</tr>
<tr>
<td></td>
<td>• Use low-dose, short half-life NSAIDs</td>
</tr>
<tr>
<td></td>
<td>• Do not use extended-release NSAID formulation</td>
</tr>
<tr>
<td></td>
<td>• If chronic NSAID required, consider:</td>
</tr>
<tr>
<td></td>
<td>• Once-daily celecoxib + PPI/misoprostol (GI &gt; CV risk)</td>
</tr>
<tr>
<td></td>
<td>• Naproxen + PPI/misoprostol (CV &gt; GI risk)</td>
</tr>
<tr>
<td></td>
<td>• Avoid PPI if using antiplatelet agent such as clopidogrel</td>
</tr>
<tr>
<td></td>
<td>• Monitor and treat blood pressure</td>
</tr>
<tr>
<td></td>
<td>• Monitor creatinine and electrolytes</td>
</tr>
<tr>
<td></td>
<td>• ≥65 years old</td>
</tr>
<tr>
<td></td>
<td>• No history of previous complicated gastrointestinal ulceration</td>
</tr>
<tr>
<td></td>
<td>• Low cardiovascular risk, may be using aspirin for primary</td>
</tr>
<tr>
<td></td>
<td>prevention</td>
</tr>
<tr>
<td></td>
<td>• Requirement for chronic therapy and/or high-dose therapy</td>
</tr>
<tr>
<td></td>
<td>• Older people, especially if frail or hypotension, renal or</td>
</tr>
<tr>
<td></td>
<td>liver disease present</td>
</tr>
<tr>
<td></td>
<td>• History of previous complicated ulcer or multiple</td>
</tr>
<tr>
<td></td>
<td>gastrointestinal risk factors</td>
</tr>
<tr>
<td></td>
<td>• History of cardiovascular disease and on aspirin or other</td>
</tr>
<tr>
<td></td>
<td>antiplatelet agent for secondary prevention</td>
</tr>
<tr>
<td></td>
<td>• History of heart failure</td>
</tr>
</tbody>
</table>
Prevention strategies for GI risk.

- Low risk: intermediate or highly Cox-2 selective NSAIDs (standard dose) alone or non selective NSAIDs + gastroprotector therapy (PPI, misoprotol).
- One or two risk factor: intermediate or highly Cox-2 selective NSAIDs + gastroprotector therapy
- History of ulcer bleeding:
  - Highly cox-2 selective NSAIDs + gastroprotector therapy
  - Avoid non selective NSAIDs (naproxen).
  - Eradicate H. pylori infection.

(Brune and Patrigani, Journal of Pain Research, 2015)
Previous CV event or risk for CV events (patients under treatment with low dose aspirin)

• Low risk for GI events: non selective NSAIDs (naproxen) + gastroprotector (PPI): aspirin and naproxen must be administered at different time

• High risk for GI events:
  – Avoid use NSAIDs (including non selective and intermediate or high Cox-2 selective)
  – Eradicate H. pylori infection.
  – Avoid use of ibuprofen (interfere with aspirin antipletelet effect).
  – Substitution of aspirin with other antiplatelet (clopidogrel) not recommended.

(Brune and Patrigani, Journal of Pain Research, 2015)
### Strategies for Reducing Cardiovascular Risk

<table>
<thead>
<tr>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>If using aspirin, take aspirin dose ≥ 2 hours prior to NSAID dose</td>
</tr>
<tr>
<td>Do not use NSAIDs within 3 to 6 months of an acute cardiovascular event or procedure</td>
</tr>
<tr>
<td>Carefully monitor and control blood pressure</td>
</tr>
<tr>
<td>Use low-dose, short half-life NSAIDs and avoid extended release formulations</td>
</tr>
</tbody>
</table>

## Prevention of NSAID-related ulcer complications

<table>
<thead>
<tr>
<th></th>
<th>Low GI risk</th>
<th>Moderate GI risk</th>
<th>High GI risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low CV risk</strong></td>
<td>NSAID alone (least ulcerogenic at lowest dose)</td>
<td>NSAID + PPI/misoprostol</td>
<td>Alternative therapy or Coxibs + PPI/misoprostol</td>
</tr>
<tr>
<td><strong>High CV risk</strong></td>
<td>Naproxen + PPI/misoprostol</td>
<td>Naproxen + PPI/misoprostol</td>
<td>Avoid NSAIDs &amp; coxibs</td>
</tr>
</tbody>
</table>

Naproxen may have some cardioprotective properties.

Patients with ulcer history: search for HP & if present eradicated.

ACG guidelines for prevention of NSAID-related ulcer complications.
### Different roles of NSAIDS In Acute and Chronic Pain

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Acute Pain</th>
<th>Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Potent. Strongly suitable for acute pain management, esp. when given at high doses (correlates well with nociceptive pain mitigation)(^1)</td>
<td>Less potent. Confers less pain reduction as chronic pain usually involves a more complex pathway with neuropathic components.(^1)</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>Moderate-to-high dose may be appropriate for acute setting (according to WHO stepladder pain management)(^2)</td>
<td>Ideal to be administered at lowest dose with highest possible pain relief rate(^2)</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Less likely to cause cardiovascular adverse events</td>
<td>More likely to cause cardiovascular adverse events (due to propensity for long-term use)(^3)</td>
</tr>
</tbody>
</table>

Firstly, it is recommended to administer paracetamol or topical NSAIDs (esp. for musculoskeletal pain such as osteoarthritis). When maximum response has not been achieved, additional oral NSAID/COX-2 inhibitor can be considered.

Oral NSAID/COX-2 inhibitor should be given at the lowest effective doses in the shortest period of time, recommended to be co-prescribed with a PPI.

Types of oral NSAID/COX-2 inhibitor prescribed should be tailored to individual risk factors with regard to its potential side effects.

If the patient consumes aspirin, other analgesics should be considered before prescribing oral NSAID/COX-2 inhibitor.

Key Messages

- NSAIDs are commonly used for pain relief.
- Anti-inflammatory, analgesic, and antipyretic actions are acquired by means of COX inhibition which is responsible for catalyzing arachidonic to prostaglandins.
- NSAIDs inhibition of COX-1 and COX-2 have beneficial effects for pain relief, but adverse effects on GIT.
- COX-2 selective have beneficial effects for pain relief without/minimal adverse effects on GIT but increase CV adverse effects.
- A meta-analysis demonstrated similar CV adverse effects between COX-2 and COX-1.
COX-1 Selective  COX-2 Selective

Log [IC₈₀ ratio (COX-2/COX-1)]
NSAIDs inhibit the COX enzyme, which exists in two forms:

- **Arachidonic acid**
- **COX-1** (constitutive)
- **COX-2** (induced by inflammatory stimuli)
- **COX-2 selective NSAIDs**
- **Non-selective NSAIDs**

Prostaglandins:
- **Gastrointestinal cytoprotection**
- **Platelet activity**

Prostaglandins:
- **Inflammation**
- **Pain**
- **Fever**

*Vane & Botting 1995*
MECHANISM OF ACTION
COX ISoenzyme

Arachidonic acid → COX-1 → INSADs → PGH₂ → PGIs
COX-2 → INSADs

Prostanoid syntheses:
- TXS
- H-PGDS
- L-PGDS
- PGFS
- mPGES-1
- mPGES-2
cfPGES

Prostanoids:
- TXA₂
- PGD₂
- PGF₂α
- PGE₂
- PGI₂

Prostanoid receptors:
- TP
- DP
- FP
- CRTH2
- EP₁
- EP₂
- EP₃
- EP₄
- IP

Prostanoid biological activities:
- Platelet aggregation
- Vasoconstriction
- Sleep/Wake
- Reproduction
- GI cytotoxicity
- Temperature
- Renal homoeostasis
- Inflammation
- Pain

Coxibs
Nonsteroidal Anti-Inflammatory

• COX-2 was inducible, and the inducing stimuli included pro-inflammatory cytokines and growth factors, implying a role for COX-2 in both inflammation and control of cell growth.

• The two isoforms of COX are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular locations.

### NSAIDs

**Non-selective**
- Irreversible
- Cardio protective at low dose
- Increased gastrointestinal side effect

**Semi-selective**
- Increased COX-2 affinity but limited in COX-1
- Warning in patient with cardiovascular risk

**Selective**
- Increase cardiovascular risk
- Lower gastrointestinal side effect

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**Aspirin**
- NSAIDs non-selective
- Irreversible
- Cardio protective at low dose
- Increased gastrointestinal side effect

**Ibuprofen, naproxen**
- NSAIDs non-selective
- Lower cardiovascular risk
- Increased gastrointestinal side effect

**Celecoxib**
- NSAIDs selective
- COX 2
- Increase cardiovascular risk
- Lower gastrointestinal side effect
## Differences between Cox-1 & Cox-2

<table>
<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Housekeeping</td>
<td>Inflammation</td>
</tr>
<tr>
<td><strong>Regulation</strong></td>
<td>Constitutive</td>
<td>Inducible</td>
</tr>
<tr>
<td><strong>Range of expression</strong></td>
<td>2 – 4 fold</td>
<td>10 – 80 fold</td>
</tr>
<tr>
<td><strong>Tissue Expression</strong></td>
<td>Most tissues notably</td>
<td>Inflammatory sites</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Synoviocytes</td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
<td>Fibroblasts</td>
</tr>
<tr>
<td></td>
<td>Kidneys</td>
<td>Monocytes</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td></td>
</tr>
</tbody>
</table>
## Non-steroidal anti-inflammatory drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Trade name</th>
<th>Half-Life (h)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arylcarboxylic acids</td>
<td>Diflunisal</td>
<td>Dolobid®</td>
<td>8 – 12</td>
<td>250–500 mg bid</td>
</tr>
<tr>
<td>Arylalkanoic acids</td>
<td>Diclofenac</td>
<td>Voltaren®</td>
<td>2</td>
<td>50–75 mg bid</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Advil®</td>
<td>2 – 2.5</td>
<td>200–800 mg qid</td>
</tr>
<tr>
<td></td>
<td>Fenoprofen</td>
<td>Nalfon®</td>
<td>2–3</td>
<td>300–600 mg qid</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>Naprosyn®</td>
<td>12–17</td>
<td>250–500 bid</td>
</tr>
<tr>
<td>Enolic acids</td>
<td>Indomethacin</td>
<td>Indocin®</td>
<td>4.5</td>
<td>25–50 mg tid</td>
</tr>
<tr>
<td></td>
<td>Sulindac</td>
<td>Clinoril®</td>
<td>16</td>
<td>150–200 mg bid</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
<td>Feldene®</td>
<td>50</td>
<td>10–20 mg qd</td>
</tr>
<tr>
<td></td>
<td>Meloxicam</td>
<td>Mobic®</td>
<td>15–20</td>
<td>7.5–15 mg qd</td>
</tr>
<tr>
<td>Non-acidic</td>
<td>Nabumetone</td>
<td>Relafen®</td>
<td>24</td>
<td>1000 mg qd</td>
</tr>
<tr>
<td>Coxibs</td>
<td>Celecoxib</td>
<td>Celebrex®</td>
<td>11</td>
<td>100–200 mg qd</td>
</tr>
</tbody>
</table>

Prevention strategies of GI risk due to NSAIDs

- Avoid use of NSAID & substitute with acetaminophen
- Use “safer” NSAID: Diclofenac, ibuprofen, coxibs
- Avoid NSAID with higher toxicity: Ketorolac, piroxicam
- Use lowest effective dose for shortest period of time
- Avoid concomitant therapy with:
  Anticoagulants, corticosteroids, low-dose aspirin, APT
- Eradicate HP infection in patients with prior ulcer history

## Patients at increased risk for NSAIDs GI toxicity

| High risk | 1. History of complicated ulcer especially recent  
|           | 2. Multiple (> 2 risk factors) |
| Moderate risk | 1. Age > 65 years  
| (1 – 2 risk factors) | 2. High dose NSAID therapy  
|                   | 3. Previous history of uncomplicated ulcer  
|                   | 4. Concurrent use of aspirin  
|                   | 5. Concurrent use of corticosteroids  
|                   | 6. Concurrent use of anticoagulants |
| Low risk | No risk factors |

HP is independent & additive risk factor & addressed separately

ACG guidelines for prevention of NSAID-related ulcer complications.
### Differences between Cox-1 & Cox-2

<table>
<thead>
<tr>
<th></th>
<th>COX-1</th>
<th></th>
<th>COX-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulation</strong></td>
<td>Constitutive</td>
<td></td>
<td>Inducible</td>
<td></td>
</tr>
<tr>
<td><strong>Range of expression</strong></td>
<td>2 – 4 fold</td>
<td></td>
<td>10 – 80 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Tissue Expression</strong></td>
<td>Most tissues notably Platelets Endothelial cells Kidneys Stomach</td>
<td></td>
<td>Inflammatory sites Synoviocytes Fibroblasts Monocytes</td>
<td></td>
</tr>
</tbody>
</table>
Constitutive: Concentration in the body is stable regardless of stimulus.

Induced: Increased concentration in response to stimulus (up-regulated).

Konsep tentang enzim Cox

Figure 3: The Current COX concept

- Arachidonic Acid
  - COX-1
    - Homeostatic functions
      - Gastrointestinal tract
      - Renal tract
      - Platelet Function
      - Macrophage differentiation
  - COX-2
    - Inflammation
      - Cytokines IL-1, TNF
      - Growth factors
      - Glucocorticoids
      - Cysteines IL-1

Induced expression in the body is involved in chronic inflammation.
COX-I vs COX-II

- **COX-I**
  - Constitutive
  - Produces prostaglandin which is responsible for maintaining GI tract mucosal integrity and thromboxane which mediates platelet aggregation.
  - COX-I inhibition results in GI impairment.

- **COX-II**
  - Induced (upregulated) by arachidonic acid and several cytokines. Inhibited by glucocorticoid.
  - Produces prostaglandin whose responsible during inflammatory event.
  - Inhibiting COX-II prevents pain.
Mechanism: COX-1, COX-2, & COX-3

- **COX-1** (normal constituent)
  - Body homeostasis
    - Stomach
    - Intestine
    - Kidney
    - Platelet

- **COX-2** (inducible)
  - Inflammatory Site
    - Macrophages
    - Synoviocytes
    - Endothelial cells

- **COX-3** (normal constituent)
  - Normal Constituent
    - CNS
    - Kidney
    - Female U/G tract
    - Pain
      - Fever
      - HTN
      - GI

- Arachidonic acid
- Glucocorticoids (block mRNA expression)
- Acetaminophen
- Nonselective NSAID
- Selective COX-2 inhibitor

References:
Chandrasekharan NV et al. Proc Natl Acad Sci USA. 2002;99:13926-31
COX-2/COX-1 Selectivity Ratio

- The degree of selectivity of coxibs is measured by assaying the level of prostaglandin production in blood.
- A measurement of selectivity of individual drugs is the IC50 i.e. the ratio of the concentrations producing 50% inhibition of COX-1 & COX-2.
- The larger the number of the ratio, the greater the selectivity for COX-2 & thus the greater the sparing of COX-1 enzyme systems.

- The following are ratios of some commonly used NSAIDs:
  - Rofecoxib-36, Celecoxib-7, Diclofenac-3, Indometacin-0.4