Pharmacotherapy for Prevention of NSAID-induced Gastropathy

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Learning Objectives

- Describe NSAID-induced gastropathy
- List the risk factors
- Design pharmaceutical regimen
- Compare and contrast the pharmaceutical nuances of protective agents: PPI, H2RA, misoprostol

NSAID Use in the U.S.

- 70% of elderly take NSAIDs at least weekly
- Over 110 million NSAID Rx filled yearly
  - $4.8 billion Rx NSAIDS
  - $3 billion on OTC analgesics (incl. APAP)
- Hospitalization 103,000/yr
- Mortality 5-10%
- $1 dollar spent on NSAIDs $0.35 manage ADEs

### Spectrum of NSAID-related GI injury

<table>
<thead>
<tr>
<th>Upper GI</th>
<th>Small Intestine</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Ulcers</td>
<td>Colitis</td>
</tr>
<tr>
<td>Erosions</td>
<td>Stricture</td>
<td>Ulcers</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Diaphragms</td>
<td>Stricture</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Enteropathy</td>
<td>Diverticular bleed</td>
</tr>
<tr>
<td>Subepithelial</td>
<td></td>
<td>IBD relapse</td>
</tr>
<tr>
<td>petechial hemorrhages</td>
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<td></td>
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<tr>
<td>Perforation/obstruction</td>
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### NSAID Gastropathy: Scope of the Problem
- NSAID-induced gastropathy occurs >90% patients
- Dyspepsia occurs up to 25% of patients
- Discontinuation or change in NSAID 10% users
- Ulcers:
  - Gastric 10-30%
  - Duodenal 4-10%
- Risk of complication is 1-4% annually and increased 4 fold vs control

Wolfe et al. NEJM.1999;340:1888-1899

### Reduce Risk NSAID-related GI Complications
- Identify patient risk factors
- Use gastroprotective agents
- Use safer NSAIDs
Prostaglandins are Key in Defense

**Mechanism of Action**

**COX-1**
- "constitutive"
- Prostaglandins
- Thromboxane
- Gastric mucosa protection
- Hemostasis

**COX-2**
- "inducible"
- Prostaglandins
- Thromboxane
- Pain
- Inflammation
- Fever

**NSAIDs**
- Arachidonic Acid
- Coxibs

**Principles of NSAID Use**
- Avoid NSAID if possible
- Use lowest effective dose
- Switch to safer NSAIDS, selective COX-2 inhibitors, or alternative analgesic
- Eradicate H. pylori infection if present
- Use gastroprotective agent (PPI/misoprostol) if NSAID continued
Pharmacotherapeutic Options:
Misoprostol
- First agent approved for prevention NSAID related ulceration
- Exogenous replacement prostaglandin E1 analog
- Dose dependent efficacy and side effect profile
- Meta-analysis of RCT shown misoprostol superior to H2RA at prevention gastric ulcers

Pharmacotherapeutic Options:
Misoprostol (MUCOSA trial)


Preventing Relapse of NSAID-related ulcers:
Omeprazole vs Misoprostol

OMNIUM study

*** p<0.001 PPI and misoprostol vs placebo
** p<0.005 PPI vs placebo and misoprostol
Preventing Relapse of NSAID-related ulcers: Misoprostol vs Lansoprazole

Preventing Relapse of NSAID-related ulcers: Omeprazole vs Ranitidine

Pharmacotherapeutic Options: Misoprostol or PPI
- Evidence does not support use of H2RA agents
  - Standard doses are inferior to PPI
  - No comparison trials PPI vs high dose H2RA
- Misoprostol as effective to PPI
- Nuance:
  - GI side effects (dose-dependent)
  - Compliance QID dosing
  - Pregnancy category X
- Lower dose (400-600mcg daily) reduced GI side effects while maintaining efficacy


Yeomans et al. NEJM. 1998;338:719-726.
In Vitro Selectivity: COX-2/COX-1 Ratio

Ulcerogenic Potency of NSAIDs

- Less ulcerogenic NSAIDS:
  - Ibuprofen: lower analgesic doses
  - Higher degree of COX-2 selectivity
    - Nabumetone (Relafen®)
    - Meloxicam (Mobic®)
    - Etodolac (Lodine®)

- Greater ulcerogenic NSAIDS:
  - Long half-lives
    - Sulindac (Clinoril®)
    - Piroxicam (Feldene®)
    - Ketorolac (Toradol®)

Gastroprotection: COX-2 Inhibitors

- Cox-2 inhibitors (coxibs) reduce ulcer complications vs traditional NSAIDs
- Associated with increase risk myocardial infarction and other cardiovascular events.
- Co-therapy with low dose aspirin carries similar risk of GI complications as traditional NSAIDs
- Use the lowest dose of coxib to minimize risk of CV events
Managing Patients on Long-term NSAIDs Therapy

- Identify risk factors for gastropathy
  - Non-NSAID options should be considered
- Stratify patients according to gastrointestinal risk
  - Low, moderate or high risk
- Evaluate for H. pylori infection prior to initiation of NSAIDs
- Assess risk factors for CVD and need for prophylactic aspirin

NSAID-induced GI Injury: Risk factors

Stratify Risk for NSAID GI Toxicity

**High Risk**
1. History of complicated ulcer, especially recent
2. Multiple Risk Factors (>2)

**Moderate Risk (1-2 risk factors)**
1. Age > 65 years
2. High Dose NSAID Therapy
3. History of Uncomplicated ulcer
4. Concurrent use of aspirin, corticosteroids, or anticoagulants

**Low Risk (no risk factors)**
1. No risk factors

*H. Pylori is an independent risk factor and should be addressed separately*

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NSAID-related Gastropathy: Strategies for Prevention

<table>
<thead>
<tr>
<th>Gastrointestinal Risk</th>
<th>Low CV risk</th>
<th>High CV Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>NSAID alone</td>
<td>Naproxen + Misoprostol/ PPI</td>
</tr>
<tr>
<td>Moderate</td>
<td>NSAID + Misoprostol/ PPI</td>
<td>Naproxen + Misoprostol/ PPI</td>
</tr>
<tr>
<td>High</td>
<td>COX-2 Inhibitor + Misoprostol/ PPI (alternative therapy preferred)</td>
<td>Use alternative therapy Avoid NSAIDs or COX-2 therapy</td>
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</tbody>
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Key Points
- NSAID-related gastropathy can result in significant morbidity and mortality
- Tailor preventative therapy according to individual gastrointestinal and cardiovascular risk
- Strategies to reduce risk of NSAID-related gastropathy should be directed to patients at greater risk
- Evidence does not support use of H2RA
- Co-therapy with full dose misoprostol and PPI are equally effective in prevention of GU and DU ulcers
- Gastroprotection with COX-2 inhibitors is negated with concomitant aspirin or NSAIDs