Comparative Efficacy and Toxicity of NSAIDs

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17 MILLION Americans use various NSAIDs on a daily basis

Number of prescriptions for older patients is approximately 3.6 fold higher than that for younger patients

5% hospital admission are related to adverse effects of NSAIDs
Questions to be answered...

• Are there clinically importance differences in the efficacy and toxicity between the different NSAIDs?
• If there are differences, which are the ones that are more effective and associated with fewer adverse effects?
• What are the effective therapeutic approaches that could reduce the adverse effects of NSAIDs?
Themes - NSAIDs

- Mechanism of action
- Classification
- Comparative analgesic efficacy
- Comparative gastrointestinal (GI) toxicity
- Comparative cardiovascular (CV) toxicity
- Strategies for prevention of toxicity

NSAID - Mechanism of action

Functions of cyclo-oxygenase (COX)

**COX-1: Constitutive**
- Present in every organ
- Homeostasis
  - Protection of gastric mucosa
  - Platelet activation
  - Renal functions
  - Macrophage differentiation

**COX-2: Inducible**
- Present in inflammatory and neoplastic sites
- Also in small intestine, kidney, brain, uterus, ovary
- Pathologic:
  - Inflammation
  - Pain
  - Fever
  - Tissue Repair
- Physiologic:
  - Reproduction
  - Renal function

**NSAID - Mechanism of action**

- **Arachidonic Acid**
- **COX-1** "Constitutive"
  - GI mucosa
    - Prostaglandins
      - GI mucosal protection
- **COX-2** "Inducible"
  - Platelet
    - Thromboxane A2
      - Hemostasis
  - Prostaglandins
    - Mediate pain, inflammation, fever

NSAID - Mechanism of action

- **Arachidonic Acid**
- **COX-1** (“Constitutive”)
  - GI mucosa
  - Prostaglandins
  - GI mucosal protection
- **COX-2** (“Inducible”)
  - Non-selective NSAIDs
  - Platelet
  - Thromboxane
  - Prostaglandins
  - Hemostasis
  - Mediate pain, inflammation, fever

Classification of NSAIDs by chemical structures

Propionic acid
- Ibuprofen (Advil, Brufen)
- Naproxen (Naprosyn, Synflex)
- Ketoprofen (Ouvail)

Acetic acids
- Diclofenac (Arthrotec, Cataflam, Voltaren)
- Indomethacin (Indocid)
- Sulindac (Clinoril)
- Tolmetin

Oxicams
- Meloxicam (Mobic)
- Piroxicam (Feldene)

Non-acidic
- Nabumetone

Fenamic acid
- Mefenamic

COX-2 inhibitors
- Celecoxib (Celebrex)
- Etoricoxib (Arcoxia)

Classification of NSAIDs by pharmacokinetic properties

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Bio-availability (%)</th>
<th>Half-life (hr)</th>
<th>Volume of distribution</th>
<th>Clearance</th>
<th>Peak (hr)</th>
<th>Renal elimination</th>
<th>Clinical dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>&gt;80</td>
<td>2</td>
<td>0.15 L/kg</td>
<td>3.0-3.5 L/h</td>
<td>1-2</td>
<td>45-79</td>
<td>1200-3200</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50-60</td>
<td>2</td>
<td>0.1-0.2 L/kg</td>
<td>21.0 L/h</td>
<td>2</td>
<td>65</td>
<td>100-150</td>
</tr>
<tr>
<td>Naproxen</td>
<td>95</td>
<td>12-17</td>
<td>0.16 L/kg</td>
<td>0.13 mL/min/kg</td>
<td>2-4</td>
<td>95</td>
<td>500-1000</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>89</td>
<td>15-20</td>
<td>10L</td>
<td>0.4-0.5 L/h</td>
<td>4-5</td>
<td>50</td>
<td>7.5-15.0</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Not specified</td>
<td>11</td>
<td>400L</td>
<td>27.7 L/h</td>
<td>3</td>
<td>27</td>
<td>200</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>90</td>
<td>2.1</td>
<td>0.1 L/kg</td>
<td>6.9 L/h</td>
<td>≤2</td>
<td>80</td>
<td>200-300</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>100</td>
<td>22</td>
<td>120L</td>
<td>50 mL/min</td>
<td>1</td>
<td>75</td>
<td>60</td>
</tr>
</tbody>
</table>

Epidemiology of NSAID prescription

- **Proportion of global sales for NSAIDs**
- IMS Health (2008) IMS MIDAS Quantum based on selected markets

Comparative analgesic efficacy: Placebo vs. NSAIDs

NSAIDs have demonstrated short-term efficacy compared with placebo in the treatment of OA

Comparative analgesic efficacy: non-selective (ns) NSAIDs

Agency for Health-care Research and Quality Effective Healthcare Program (UK):

- No clear differences in efficacy among nsNSAIDs at standard doses in treatment of knee, back, or hip pain


Comparative analgesic efficacy: COX-2 inhibitors vs. nsNSAIDs

- No significant differences in efficacy between COX-2 inhibitors and nsNSAIDs in treatment of knee, back, or hip pain

Comparative analgesic efficacy: COX-2 inhibitors vs. nsNSAIDs

• COX-2 inhibitors had equivalent efficacy to nsNSAIDs for treatment of rheumatoid arthritis (RA) and osteoarthritis (OA)
  – Celecoxib 200-800 mg/day
  – Naproxen 1000 mg/day
  – Diclofenac 100-150 mg/day
  – Ibuprofen 2400 mg/day
  – Etoricoxib 60-120 mg/day


Comparative analgesic efficacy
Celecoxib vs. nsNSAIDs

In Successive Celecoxib Efficacy and Safety Study (SUCCESS):

• Celecoxib 200-400 mg/day have efficacy comparable to naproxen 1000 mg/day and diclofenac 100 mg/day for treatment of more than 13,000 patients with OA over 12 weeks

Comparative analgesic efficacy: Etoricoxib vs. nsNSAIDs

- Etoricoxib 90-120 mg/day have greater efficacy compared with naproxen 1000 mg/day over 12 weeks, but similar efficacy over 121 weeks


Overview of adverse effect of NSAIDs

- Anaphylaxis
- Neutropenia
- Anti-platelet
- Liver injury
- Acute renal failure
- Electrolyte abnormalities
- Aseptic meningitis
- Psychosis
- Cognitive impairment
- Myocardial infarction
- Heart failure
- Hypertension
- Dyspepsia
- Peptic ulcer
- GI bleeding

Liver injury

Acute renal failure

Electrolyte abnormalities

Dyspepsia

Peptic ulcer

GI bleeding
Overview of adverse effect of NSAIDs

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GI toxicity of NSAID

- 60% Dyspepsia
- 10-30% Endoscopic ulcers
- 1-2% Serious ulcer complications

Risk stratification for GI toxicity

**High risk**
1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors

**Moderate risk (1-2 risk factors)**
1. Age >65
2. High dose NSAID therapy
3. A Previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose), corticosteroids, anticoagulants

**Low risk**
1. No risk factors

Helicobacter pylori is an independent and additive risk factor


Comparative GI toxicity

Risk of upper gastrointestinal bleeding/perforation with individual NSAIDs from published studies since 1990

Comparative GI toxicity

<table>
<thead>
<tr>
<th></th>
<th>NS-NSAID</th>
<th>COX-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI bleed or perforation</td>
<td>RR 4.50; 95% CI 3.82, 5.31</td>
<td>RR 1.88; 95% CI 0.96, 3.71</td>
</tr>
</tbody>
</table>


Concomitant use of low-dose aspirin increases the risk of mucosal damage and eliminates the GI benefits of COX-2 inhibitors

<table>
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<tr>
<th></th>
<th>COX-2 inhibitors</th>
<th>Aspirin + COX-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI bleed or perforation</td>
<td>RR 0.6; 95% CI 0.4, 0.9</td>
<td>RR 1.9; 95% CI 10, 3.6</td>
</tr>
</tbody>
</table>


CV toxicity of NSAID

- Myocardial infarction
- Heart failure
- Stroke
- ↑ Blood pressure

Myocardial infarction
Heart failure
↑ Blood pressure
Stroke
CV toxicity with nsNSAID


CV toxicity with nsNSAID

Comparative CV toxicity: nsNSAIDs

• High dose ibuprofen (rate ratio 1.51; 95% CI 0.96, 2.37) and high dose diclofenac (rate ratio 1.63; 95% CI 1.12, 2.37) were associated with a moderately increased risk of any vascular events compared with placebo
• Risks associated with naproxen was substantially lower (rate ratio 0.92; 95% CI 0.67, 1.26)


Comparative CV toxicity: Placebo vs. COX-2 inhibitors

• Significant increased risk of myocardial infarction with COX-2 inhibitors compared with placebo

Comparative CV toxicity: rofecoxib vs. naproxen

• In Vioxx Gastrointestinal Outcomes Research (VIGOR) study, rofecoxib 50 mg/day was associated with a 4 fold increase in incidence of myocardial infarction compared with naproxen 1000 mg/day in patients with RA


Comparative CV toxicity: rofecoxib vs. naproxen

• In Adenomatous Polyp Prevention On Vioxx (APPROVe) study, rofecoxib 25 mg/day was associated with increased RR of thrombotic events compared with placebo in patients with a history of colorectal adenomas after 18 months of treatment and an increased risk of myocardial infarction after 15 months of treatment

Comparative CV toxicity: Celecoxib

- Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT)
- Adenoma Prevention with Celecoxib (APC) study
- Prevention of colorectal Sporadic Adenomatous Polyps (PreSAP) study

- Celecoxib 200-400 mg/day was associated with a significant and dose-related increase in death from CV causes in APC, but not in PreSAP or ADAPT
- All 3 studies were subsequently suspended

Comparative CV toxicity: Etoricoxib

- In a pooled analysis of data from 3 trials in Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, etoricoxib 60 or 90mg/day was compared with diclofenac 150 mg/day
  - No significant risk of thrombotic CV events (hazard ratio 0.95; 95% CI 0.81, 1.11)


Strategies for prevention of NSAID-related GI toxicity

- NSAIDs should be used at the lowest effective dose for the shortest duration of time
- Long-term use should be avoided
- GI risk stratification
- Treat with gastroprotective agent
- PPIs have superior efficacy to H2RA
- Misoprostol has similar efficacy with PPIs in ulcer prevention

Strategies for prevention of NSAID-related GI toxicity

- **Low risk**: nsNSAID alone
- **Moderate risk**: nsNSAID + PPI/misoprostol, COX-2 inhibitor alone
- **High risk**: Alternative therapy if possible, COX-2 inhibitor + PPI/misoprostol


Strategies for prevention of NSAID-related CV toxicity

- NSAIDs should be avoided in patients with risk factors for CV disease
- NSAIDs should be used at their lowest effective dose for the shortest duration of time
- Naproxen is the drug of choice for patients with CV risk factors
Strategies for prevention of NSAID-related GI & CV toxicity

<table>
<thead>
<tr>
<th>Low GI risk</th>
<th>Moderate GI risk</th>
<th>High GI risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV risk</td>
<td>NSAID lone</td>
<td>NSAID + PPI / Misoprostol</td>
</tr>
<tr>
<td>High CV risk (low-dose aspirin required)</td>
<td>Naproxen + PPI / misoprostol</td>
<td>Naproxen + PPI / Misoprostol</td>
</tr>
</tbody>
</table>

- High CV risk is arbitrarily defined as requirement for low-dose aspirin for prevention of serious CV events
- All patients with a history of ulcers who require NSAIDs should be tested for H. pylori, and if the infection is present, eradication therapy should be given


Summary

- No significant difference in efficacy between various NSAIDs in treatment of arthritis pain relief
- NSAIDs are associated with GI and CV adverse effects
- Identify risk factors for GI and CV adverse effects before prescribing NSAID
- Therapy should be tailored according to risk
- Naproxen is the drug of choice for patients with CV risk factors
THANK YOU!
FOR YOUR ATTENTION

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