Clinical Update: Multimodal Perioperative Analgesia
by Kate O’Hanlan, MD

- Review tissue damage cyclooxygenase cascade releasing pain transmitters.
- Discuss COX 1 inhibition and reduction of platelet aggregation, gastric mucosal integrity, and reduction of renal blood flow.
- Discuss COX 2 inhibition and reduction of pain, with coronary vasoconstriction.
- Understand the differences in risk profile between the two parenteral NSAID’s.
- Explain the CNS efficacy of parenteral acetaminophen.
- Integrate the published evidence to write a multimodal analgesic regimen for your surgical patients.

**Diagram:**
- Arachidonic Acid
  - COX-1 (Constitutive)
    - Prostaglandins
      - ↑ GI Cytoprotection
      - ↑ Platelet Function
      - ↑ Renal Function
      - ↓ GI Cytoprotection
      - ↓ Platelet Function
      - ↓ Renal Function
  - NSAID’s
- COX-2 (Inducible)
  - Prostaglandins
    - ↑ Inflammation
    - ↑ Pain
    - ↑ Fever
    - ↑ Prothrombotic Effects
  - NSAID’s
Cyclooxygenase 1 and 2 inhibitors: antipyretic and analgesic

- COX-1: Prostaglandin synthesis in response to stimulation by circulating hormones, as well as maintenance of normal renal function, gastric mucosal integrity, and platelet aggregation.
- Cox-1 Selective inhibition bad for GI, good for heart.

- COX-2: Released by IL-1, TNF, lipopolysaccharide, mitogens, and reactive oxygen intermediates in vasculature.
- COX-2 Selective inhibition is good for GI. Potent anti-inflammatory, no prostacyclin and a lot of thromboxane, so not good for CABG.

Inhibition of COX-2 Relative to COX-1

<table>
<thead>
<tr>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>Meloxicam</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Celecoxib</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Diclofenac</td>
</tr>
</tbody>
</table>

NSAID’s and platelet aggregation

• Aspirin strong inhibitory effect on platelet function, significantly reducing RBC aggregation. \(^1\)
• Platelet effects of ketorolac were moderate, whereas ibuprofen had a minor impact on platelet function.\(^1\)
• Ketorolac has increased COX-1 inhibition compared with naproxen and ibuprofen.\(^2\)


NSAID’s and UGI bleeds

• Systematic review of observational studies on NSAIDs and upper GI bleeding/perforation published between 2000 and 2008.\(^1\)
  – Ibuprofen RRs was 2.69 [95% CI 2.17-3.33]).\(^1\)
  – ketorolac RR was 14.54 [95% CI 5.87-36.04]).\(^1\)
• More COX-1 inhibition associated with more UGI bleeds.\(^1\)
• Ibuprofen OR for UGI bleed was 1.5. \(^2\)
• IV ketorolac OR for UGI bleed was 5.76.\(^2\)
• Parenteral NSAIDs posed a higher risk, but celecoxib and ibuprofen posed a lower risk than other NSAIDs. \(^2\)

Determinants of UGI Bleeding

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 75-89</td>
<td>4.1</td>
<td>(3.5-4.7)</td>
</tr>
<tr>
<td>NSAID use</td>
<td>4.4</td>
<td>(3.7-5.3)</td>
</tr>
<tr>
<td>Multiple NSAIDs</td>
<td>7.8</td>
<td>(5.6-11.0)</td>
</tr>
<tr>
<td>Heavy Smoking</td>
<td>1.6</td>
<td>(1.3-1.9)</td>
</tr>
<tr>
<td>Antiulcer med</td>
<td>3.7</td>
<td>(3.2-4.2)</td>
</tr>
<tr>
<td>Ulcer (no complic)</td>
<td>5.3</td>
<td>(4.2-6.7)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1.6</td>
<td>(1.2-2.2)</td>
</tr>
</tbody>
</table>

81% of pts in ARAMIS study with serious GI complications had no prior GI symptoms.


---

**IV IBU 5-7 Minute Infusion**

![Graph showing the concentration of IBU over time after a 5-7 minute infusion of 800 mg IV ibuprofen and 800 mg PO ibuprofen.](image-url)

Pre-op IV Ibuprofen

- 319 women had elective abdominal hysterectomy received placebo or 800 IV IBU initiated intra-op and q 6h x 8 doses then q 6 h prn for 5 days.
- Also had morphine PCA pump or patient request.

<table>
<thead>
<tr>
<th></th>
<th>Narcotic use after 800 mg IV IBU</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 hours at rest</td>
<td>↓ 21%</td>
</tr>
<tr>
<td>First 24 hours with movement</td>
<td>↓ 14%</td>
</tr>
<tr>
<td>Reduction in median narcotic use</td>
<td>↓ 19%</td>
</tr>
<tr>
<td>Reduction in mean narcotic use</td>
<td>↓ 16% (P &lt; 0.001)</td>
</tr>
</tbody>
</table>


IV IBU pre- and post-operatively

<table>
<thead>
<tr>
<th></th>
<th>Pain reduction</th>
<th>Narcotic reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Joint rplcmt</td>
<td>32%</td>
<td>31%</td>
</tr>
</tbody>
</table>

No significant difference bleeding adverse events, blood transfusions or other serious adverse events.
More patients receiving IV ibuprofen experienced vomiting and more patients receiving placebo experienced dyspepsia.

Reduction in Pain Intensity Scores After Orthopedic Surgery

- 185 patients: knee or hip replacement, reconstruction, or arthroplasty
- Randomized: 800 IBU or placebo at induction, q6h x 5, prn q6h x 5d.
- Rescue with: morphine PCA or patient request.


IV ibuprofen contraindications

- **Respiratory:**
  - Patients experiencing asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs

- **Cardiovascular risk**
  - NSAIDs may increase risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use.
  - IV IBU is contraindicated for the treatment of perioperative pain in the setting of CABG surgery.

- **Gastrointestinal risk**
  - NSAIDs increase risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.
    - Events can occur at any time without warning symptoms.
    - Elderly patients are at greater risk.
Cox-3

- COX-3 and two smaller COX-1 proteins identified (PCOX-1)
- Selectively inhibited by acetaminophen.
- May explain why acetaminophen is antipyretic and analgesic without affecting COX-1 or COX-2.
- Potently inhibited by diclofenac, aspirin, and ibuprofen.
- New drug development that selectively inhibits COX-3.


ASA, Ibuprofen and acetaminophen

- 1/3-1/2 less GI adverse effect than aspirin
- Lowest risk of NSAIDs for UGI bleed or perforation
- Blinded RCT comparing adverse events for 8233.
  - ASA tabs (up to 3 g/day)
  - Acetaminophen (up to 3 g/d) and
  - Ibuprofen (up to 1.2 g/day)
- Adverse events:
  - Ibuprofen 13.7%, acetaminophen 14.5% aspirin 18.7%.
  - No stat difference between ibuprofen and acetaminophen
  - GI events:
    - ibuprofen (4%) acetaminophen (5.3%) aspirin (7.1%)
  - 6 GI bleeds: 4 with acetaminophen and 2 with aspirin.

Peri-operative acetaminophen (ACET)

• “Theory is that of ACET’s positive effects on the serotonergic descending inhibitory pathways. However, interactions with opioidergic systems, eicosanoid systems, and/or nitric oxide containing pathways may be involved as well. Furthermore, endocannabinoid signaling may play a role in ACET’s activation of the serotonergic descending inhibitory pathways.”

• Theorized that ACET has no affinity for the active site of cyclo-oxygenase but instead blocks central activity by reducing the active oxidized form of cyclo-oxygenase to an inactive form.

• Combination ACET/IBU better analgesia than Tylenol No. 3 (p = 0.018). More side effects and higher discontinuation with Tylenol No. 3 (p = 0.045).

• Need CNS levels for effect:
  – Analgesia better when ACET given early at induction compared to end of case.
  – Even IV ACET 30 min preoperatively not better than oral post op IBU.


Gastric absorption of oral ACET is unreliable perioperatively in the starved and stressed patient. Parenteral ACET gave therapeutic concentrations in 96% given parenteral, and 67% given oral ACET. Parenteral ACET gave higher plasma concentrations throughout the study period. Parenteral ACET gave more reliable therapeutic plasma concentrations than oral.

Randomized controlled trial IV acetaminophen 2g

<table>
<thead>
<tr>
<th>Pain reduction</th>
<th>Narcotic reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy¹</td>
<td>30%</td>
</tr>
</tbody>
</table>

- Highly selective COX-2,3 inhibitor blocks uptake of endogenous cannabinoid/vanilloid anandamide by pain neurons. CNS analgesia.
- Lower incidence of postop N&V with IV acetaminophen.
- IV provides better serum levels than PO.²


---

**A Multimodal Approach Addresses**
**the Complex Nature of Pain Transmission**

**Ascending input via Spinothalamic tract**

**Descending modulation**

**Dorsal horn**

**Peripheral nerve**

**Local anesthetics**
- (epidural)
- (peripheral nerve block)¹

**Opioids**, Alpha-2 agonists¹

**Acetaminophen**, some NSAIDs

**NE-reuptake inhibitors**²

**Peripheral nociceptors**

**NE** = norepinephrine

**NSAIDs** = nonsteroidal anti-inflammatory drugs

Multimodal perioperative analgesia

- Must be parenteral for effective pre-incision serum and CSF levels.
- IV Ibuprofen safe and effective, more expensive.
- IV Ketorolac highest risk of GI bleed, cheapest. Must halve dose for age>65.
- IV Acetaminophen: no GI risk. Not for hepatic impairment. Complements either IBU or KET.

Kate’s picks

- Pre-op:
  - IV IBU 800mg + IV acetaminophen 1,000mg for all.
  - IV Protonix 40 for those with GERD, PUD.
- Redose in PACU if transfused >3 uPRBC.
- Post-op:
  - Age>65: IV IBU 800 q6h until PO Naproxen 500 q6h
  - Age<65: IV KET 30 q6h until PO Naproxen 500 q6h
  - IV acetaminophen 1,000mg for all, until PO Acetaminophen 650 q6h.
- Discharge: continue NSAID/acetaminophen 650 q6h x3days