Balanced Analgesia With NSAIDS and Coxibs

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Prostaglandins and Pain

- The primary noxious mediator released from damaged tissue is prostaglandin (PG)
- PG is responsible for nociceptor activation and sensitization
- PG plays a major role in peripheral inflammation

Synthesis of PG can be reduced by selective inhibition of Cox-2
COX = cyclooxygenase; GI = gastrointestinal

Multimodal Analgesia with NSAIDS and Cox-2 Inhibitors

- **Decreased Opioid exposure/ morbidity:** reduction in nausea, sedation, confusion, constipation
- **Functionality:** Decreased pain with effort and ambulation, improved pulmonary function
- **Outcome:** Improved rehabilitation, reduced incidence of pneumonia, DVT and ileus
- **Costs:** Decreased hospital stay, more rapid return to work, reduced risk of chronic pain?
Whenever possible, Anesthesiologists should employ multimodal pain management therapy. Unless contraindicated, all patients should receive around-the-clock regimen of NSAIDs, COXIBs, or acetaminophen.”
Multimodal Analgesia With NSAIDs, Coxibs, and Acetaminophen

- Large meta-analysis of randomized, double-blind studies found that NSAIDs, COX-2 inhibitors, and APAP:
  - Significantly decreased morphine dose requirements by 15%-55%
  - Significantly decreased postoperative nausea by 12%, vomiting 32%, nausea and vomiting by 30%
  - Significantly reduced sedation scores by 29%

24-Hour Morphine Consumption

<table>
<thead>
<tr>
<th>Regimens</th>
<th># patients with active</th>
<th># patients with control</th>
<th>WMD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multiple dose</td>
<td>379</td>
<td>334</td>
<td>-8.31 [-10.9 to -5.72]</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>533</td>
<td>496</td>
<td>-10.3 [-18.3 to -2.34]</td>
</tr>
<tr>
<td>multiple dose</td>
<td>495</td>
<td>398</td>
<td>-19.7 [-26.3 to -13.0]</td>
</tr>
<tr>
<td>continuous</td>
<td>276</td>
<td>253</td>
<td>-18.3 [-26.8 to -9.74]</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>70</td>
<td>69</td>
<td>-7.22 [-10.6 to -3.82]</td>
</tr>
<tr>
<td>multiple low dose</td>
<td>91</td>
<td>91</td>
<td>-27.8 [-44.3 to -11.4]</td>
</tr>
<tr>
<td>multiple high dose</td>
<td>272</td>
<td>273</td>
<td>-9.99 [-13.4 to -6.58]</td>
</tr>
<tr>
<td></td>
<td>535</td>
<td>411</td>
<td>-13.3 [-17.8 to -8.81]</td>
</tr>
</tbody>
</table>
Injectable Ketorolac for Acute Pain Management

- Effective component of Multimodal Analgesia
- Provides useful analgesic and opioid sparing effects
- Ketorolac is associated with an increased incidence of postoperative bleeding and wound hematomas\(^1\)
- Increased risk of perioperative gastric erosion, GI bleeding\(^1\)
- Ketorolac should never be given preemptively (Black Box Warning)

1. Risks are greater when ketorolac is used in higher doses, in older subjects, and for more than 5 days.
Ketorolac as an Adjunct to Fentanyl Patient-Controlled Epidural Analgesia After Radical Prostatectomy

- Ketorolac patients required significantly less PCA fentanyl (50 ± 6 µg/hr vs 33 ± 3 µg/hr)
- Ketorolac patients reported lower pain scores with movement
- Ketorolac patients benefited from a more rapid return of bowel function

Time to Return of GI Function
Control vs Ketorolac

- Bowel Sounds
- Flatus
- Clear Liquids
- Regular Diet

* $P < 0.05$
** $P < 0.01$

Inhibition of COX-2 Relative to COX-1

Ketorolac

Naproxen

Ibuprofen

Diclofenac

Celecoxib

Ibuprofen Injection (Caldolor)

- Indications and usage in adults
  - Management of mild to moderate pain
  - Management of moderate to severe pain as an adjunct to opioid analgesics
  - Reduction of fever

- Clinical data support preoperative dosing

- No limitation on duration of use

Caldolor must be diluted prior to intravenous infusion and should NOT be given as an IV bolus or IM injection.

Caldolor Prescribing Information.
Full prescribing information can be accessed at www.caldolor.com.
Caldolor® Clinical Development

• PK and safety studies
• Fever Indication
  – Single-cause fever study
  – All-cause fever study
• Pain Indication
  – Dose ranging pain study
  – Abdominal hysterectomy pain study
  – Orthopedic pain study
Caldolor® PK 5-7 Minute Infusion

Plasma Ibuprofen Concentration (mg/mL)

- 800 mg Caldolor®
- 800 mg Oral Ibuprofen

Time Post-dose (hours)
Orthopedic Pain Study

- Multicenter, double-blind, placebo-controlled trial
  - 185 patients
  - Elective orthopedic surgery
    - Knee or hip replacement, reconstruction, or arthroplasty

- In addition to morphine by PCA pump or patient request, patients were randomized to receive:
  - 800 mg Caldolor®
    - n = 99
  - Placebo
    - n = 86

- Caldolor and placebo were initiated at induction and administered q 6 hours for 5 doses and then as needed q 6 hours for up to 5 days following surgery
Preemptive/Preventive Analgesia

**Definition:** “Once established pain is more intense and difficult to control”

In clinical Settings models, “preemptive” or pre-operative administration of local anesthetics and NSAIDS/Coxibs reduces postsurgical pain and analgesic requirements.

Benefits are less obvious with opioid analgesics

Woolf et al. 2000,
**Orthopedic Pain Study:**

**VAS Scores at Rest and With Movement**

Reduction in Pain Intensity Scores After Orthopedic Surgery

<table>
<thead>
<tr>
<th>Study Hour</th>
<th>Placebo, n = 86</th>
<th>800 mg CALDOLOR® , n = 99</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>32% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>16</td>
<td>50</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
<tr>
<td>28</td>
<td>20</td>
<td>26% Hours 6-28 (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

* Statistical significance was demonstrated at each assessment point.

Morphine Dose Requirements Following Orthopedic Surgery

<table>
<thead>
<tr>
<th>Placebo Group</th>
<th>Caldolor® (ibuprofen) Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Morphine Dose (59.5mg)</td>
<td>Mean Morphine Dose (41.4mg)</td>
</tr>
</tbody>
</table>

Patients treated with Caldolor used 31% less morphine

Combunox™ A Multimodal Analgesic for Acute Pain

- Oral Preparation containing Oxycodone (5mg) and Ibuprofen (400mg)
- Provides central opioid mediated analgesia as well as peripheral anti-inflammatory effects.
- Pain relief is more rapid and of longer duration than each of its components alone, and is associated with less nausea than oxycodone alone
- Dosing is one tablet every six hours for the short term (no more than 7 days) management of moderate-severe acute pain
Combunox™ Onset and Duration of Analgesia

**Onset**

<table>
<thead>
<tr>
<th>Combunox (n=350)</th>
<th>22.9 minutes¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen (n=357)</td>
<td>29.0 minutes</td>
</tr>
</tbody>
</table>

¹P<0.05 vs Ibuprofen.

Data presented are the median time to onset of pain relief as reported by patients. Median time could not be calculated for the oxycodone and placebo groups because less than 50% of these patients experienced pain relief.

**Duration**

<table>
<thead>
<tr>
<th>Combunox (n=169)</th>
<th>5.23 hours*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen (n=175)</td>
<td>3.95 hours</td>
</tr>
<tr>
<td>Oxycodone (n=52)</td>
<td>2.50 hours</td>
</tr>
<tr>
<td>Placebo (n=60)</td>
<td>2.28 hours</td>
</tr>
</tbody>
</table>

*P<0.05 vs ibuprofen, oxycodone, and placebo.

Duration of action is presented as the median time elapsed from administration of study medication to the time patient received rescue medication.

**Study design:** The trials in this pooled analysis consisted of 2 double-blind, randomized, single-dose, multicenter studies comparing COMBUNOX with oxycodone or ibuprofen alone and placebo in the treatment of acute, moderate to severe postoperative pain (third molar extraction). 952 patients in the 2 primary studies were randomized to COMBUNOX, individual components, or placebo. Average patient age was 21.0 years, 52.9% of patients were female. Patients were treated within 3 hours of third molar extraction and were evaluated for 8 hours posttreatment.

**Study design:** Multicenter, double-blind, randomized, single-dose study to compare the efficacy and safety of COMBUNOX with oxycodone or ibuprofen alone and placebo in an acute, moderate to severe postsurgical abdominal/pelvic pain model. 456 female patients were randomized to medication with a mean age of 41.6 years (range of 20 to 75 years). Study medication was given at least 14 hours postoperatively after discontinuation of all analgesia to patients with moderate to severe pain and a score of 450 mm on the baseline visual analog scale (VAS).
Ketorolac and other NSAIDs are commonly discontinued prior to surgery

• 200% increase in perioperative bleeding
• Increased incidence of wound hematomas
• Risk of perioperative gastric erosion or gastric ulcers, GI bleeding

Ketorolac may be employed in patients recovering from less invasive procedures and who are at minimal risk for occult bleeding. Recommended dose-15mg load, 7.5mg q 6hr

COX-2 Specific Inhibitors: A New Class Of Analgesics for Acute Pain

- High platelet safety profile: allows peri-operative, pre-incisional dosing
- High GI safety: (celecoxib) may reduce the incidence of stress ulcers and GI bleeding
- Extended duration: (celecoxib, 12 hr) offers uniform/prolonged analgesia
- High CNS uptake: CNS-mediated analgesia, use in chronic pain
Celecoxib and Rofecoxib: Selective COX-2 Inhibition for Surgical Pain Management

- High platelet safety profile
- GI safety
- Reduction in pain intensity scores
- Morphine sparing effect
- Reduction in opioid adverse effects (sedation, nausea, slowing of bowel function)
- Rofecoxib withdrawn because of long term CV morbidity
Multiple Dose Rofecoxib: Results

- Patients receiving rofecoxib 50mg, required 32% less opioids over the 5 day trial: 21% less IV-PCA morphine, 42% less oxycodone (p< 0.001)

- They reported lower pain intensity scores with movement from 12-72hrs following surgery (p<0.005) and were less sedated from 12-72hrs (p>0.01)

- They achieved earlier times to: 1. first flatus, (-10.1hrs; p<0.001), 2. first bowel movement (-14.1hrs; p<0.03), and 3. hospital discharge (-11hrs; p< 0.001)
Injectable Acetaminophen (Ofirmev)

An injectable analgesic, widely used in Europe, approved for use in the US in 2009.

- 100ml buffered solution infused over 15min
- Analgesic potency and duration of effect equal to IV-Ketorolac (30mg)
- No effects on platelet function, renal function, respiratory function.
- 25-30% reduction in IV-PCA morphine use and improved pain relief after major orthopedic surgery.
Analgesic Efficacy and Safety of Injectable Acetaminophen, Propacetamol, and Placebo for Pain Control Following Orthopedic Surgery

Anesthesiology, 2004
IV Acetaminophen vs Placebo: Mean Pain Intensity Differences

IV-PCA Morphine Self-Administration At 6 Hr Intervals

- IV Acetaminophen
- IV Placebo
Summary

• IV NSAIDs can be used in the multimodal management of postoperative acute pain.

• Caldolor® (ibuprofen) Injection is the only IV ibuprofen available for treatment of adults in:
  — Mild-to-moderate pain as a single agent
  — Moderate-to-severe pain as adjunct to opioid analgesics

• Study results suggest Caldolor increased pain relief when used preemptively and throughout the postoperative period and decreased narcotic consumption.

• In this clinical trial, there was no significant difference in renal, cardiac, or bleeding adverse events versus placebo.