Evidenced Based Analgesic Efficacy in Post-Surgical Dental Pain

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NEW... TO TAME THE PAIN

NEW vicoprofen®
hydrocodone bitartrate* and ibuprofen tablets 7.5 mg/200 mg *Warning: May be habit forming
A New Breed of Analgesic!
From PAIN to PASTA!!!
Blood, bone and guts!
Remove the bone and split the tooth!
Sew them up!
University of Pennsylvania Surgical Tray
Pioneers in oral surgery!
PROPOSED PERIPHERAL MECHANISM OF NON-NARCOTIC ANALGESICS ACTION

Cell Interior

Cell Membrane

Histamine
Bradykinin

Arachidonic Acid

Phospholipase A₂

Prostaglandin Synthetase

PGE₂

Peripherally Acting Analgesics

Pain Receptor

(Cyclooxygenase)
Peripheral Targets for Analgesia

Courtesy of Sharon Gordon DMD, PhD
<table>
<thead>
<tr>
<th>Pain Syndrome</th>
<th>Total Pain Relief Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual</td>
<td>17.5</td>
</tr>
<tr>
<td>Arthritic</td>
<td>18.8</td>
</tr>
<tr>
<td>Dental (general)</td>
<td>19.5</td>
</tr>
<tr>
<td>Post-Herpetic</td>
<td>22.6</td>
</tr>
<tr>
<td><strong>Dental Impaction (Partial Bony)</strong></td>
<td><strong>23.2</strong></td>
</tr>
<tr>
<td>Phantom Limb</td>
<td>25.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>26.0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>26.3</td>
</tr>
<tr>
<td><strong>Dental Impaction (Full Bony)</strong></td>
<td><strong>32.4</strong></td>
</tr>
</tbody>
</table>

Adapted From Melzack, J: Pain 1976, 1:277-299
In response to placebo more than 60% of dental pain trials had less than 15% of their patients achieving 50% maximum pain relief compared to only 40% of other postsurgical pain models. In fact only 11% of dental pain trials had more than 30% of their patients achieving more than 50% pain relief from placebo compared to more than 30% of other postsurgical pain models.
Basic Principles Of Clinical Studies

Double-blind
Random allocation of treatment to subjects
Inclusion of placebo
Inclusion of standard treatments
Identical appearance of study medication
Cooper, Oral Surgery
Arch Intern Med 1981;141:282-285
Acetaminophen

Glucuronidation (95%)

CYP2E1 (5%)

Glutathione

Conjugated metabolite

N-Acetyl-benzoquinonemine (NAPQI)

Hepatotoxic

From Hersh EV, Moore PA. JADA 2004;135:298-311.
ACETAMINOPHEN 600 mg + CODEINE 60 mg

ACETAMINOPHEN 600 mg

CODEINE 60 mg

PLACEBO

HOURS

PAIN RELIEF SCORES

Beaver, Postsurgical
Arch Intern Med 1981; 141:293-300.

N = 80
(20 per group)
Cooper, Oral Surgery
Hopikinson, Post-Episiotomy
Acetaminophen 1000 + Oxycodone 10 mg (n = 45)
Acetaminophen 1000 + Oxycodone 5 mg (n = 40)
Acetaminophen 500 + Oxycodone 5 mg (n = 45)
Acetaminophen 500 mg (n = 37)
Oxycodone 5 mg (n = 42)
Placebo (n = 38)

Cooper et al, Oral Surgery
## SIDE EFFECT PROFILE

<table>
<thead>
<tr>
<th></th>
<th>PLACEBO (N=38)</th>
<th>ACET 500 mg (N=37)</th>
<th>ACET 500 mg + OXYCOD 5 mg (N=45)</th>
<th>ACET 1000 mg + OXCOD 10 mg (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Drowsy</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Dizzy</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Lightheaded</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Headaches</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td># of Side Effects</td>
<td>7</td>
<td>6</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td># of Subjects with Side Effects</td>
<td>6</td>
<td>3</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>
Narcotic Equivalents

- 5 mg oxycodone
- 10 mg hydrocodone
- 60 mg codeine
- 75 mg tramadol
- 100 mg propoxyphene
BROMFENAC vs. TRAMADOL: ORAL SURGERY

Bromfenac 25 or 50 mg was significantly superior to tramadol at hours 1 - 7.
Cooper et al, Oral Surgery Pharmacotherapy; 1982:2:162-167

- Placebo (n=46)
- Codeine 60 mg (n=41)
- Aspirin 650 mg + Codeine 60 mg (n=45)
- Aspirin 650 mg (n=38)
- Ibuprofen 400 mg (n=38)
Opioids vs Ibuprofen in Postsurgical Dental Pain

Ibuprofen Liquigel (Advil® Liqui-Gels)

- OTC solubilized potassium ibuprofen gel-cap
- Higher Cmax than solid ibuprofen tablet formulations
- Shorter Tmax than solid ibuprofen tablet formulations

IBU 200 > PLA from 0.75–5 hrs,
IBU 400 > PLA from 0.5-6 hrs,
IBU 200 and 400 > APAP from 1½-6hrs
Hersh et al; JDR 2001

Ibuprofen Liquigel 400 mg (n=94)

ASA/APAP/Caffeine (n=98)
500mg 500mg 130mg

Placebo (n=33)

Cum % Remedicated

Ibu Liq < Pla from 1½ hr – 6 hr, p<0.001

Ibu Liq < AAC from 3 hr – 6 hr, p<0.01

AAC < Pla from 1½ hr – 6 hr, p<0.001
## Adverse Events by Number and Percentage

<table>
<thead>
<tr>
<th>AE’s</th>
<th>Placebo (n=33)</th>
<th>Ibuprofen Liquigel 400 mg (n=94)</th>
<th>ASA/APAP/Caffeine 500 mg/500 mg/130mg (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Subjects</td>
<td>6 (18.2%)</td>
<td>9 (9.6%)</td>
<td>12 (12.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (9.1%)</td>
<td>7 (7.4%)</td>
<td>4 (4.1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (6.1%)</td>
<td>2 (2.1%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (6.1%)</td>
<td>2 (2.1%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Numbness</td>
<td>1 (3.0%)</td>
<td>1 (1.1%)</td>
<td>3 (3.1%)</td>
</tr>
</tbody>
</table>
## Pre-emptive Ibuprofen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time to Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>133 minutes</td>
</tr>
<tr>
<td>Placebo</td>
<td>141 minutes</td>
</tr>
<tr>
<td>Ibuprofen 400 mg</td>
<td>236 minutes</td>
</tr>
<tr>
<td>Ibuprofen 400 mg</td>
<td>241 minutes</td>
</tr>
</tbody>
</table>

Pre-emptive and Post-Surgery Flurbiprofen and Acetaminophen + Oxycodone

Dionne RA. Amer J Med 1986; 80(suppl 3A):41-49
Study design: A multicenter, double-blind, randomized, placebo- and active-controlled, parallel-group, single-dose study in the treatment of postoperative dental pain comparing the analgesic effects of COMBUNOX (oxycodone 5 mg/ibuprofen 400 mg) with Percocet (oxycodone 5 mg/acetaminophen 325 mg), Lortab (hydrocodone 7.5 mg/acetaminophen 500 mg), or placebo. Patients rated pain relief using the following scale: 0 (none); 1 (a little); 2 (some); 3 (a lot); 4 (complete).
Mean Pain Relief

Hours After Dose

Naproxen Na 440 mg (n=92)
Acetaminophen 1000 mg (n=89)
Placebo (n=45)

Oral Surgery
Diclofenac 25 mg (n=63)
Diclofenac 50 mg (n=68)
Diclofenac 100 mg (n=66)
Placebo (n=68)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>79%</td>
<td>6%</td>
<td>32%</td>
<td>21%</td>
<td>0%</td>
</tr>
<tr>
<td>Diclofenac 25 mg</td>
<td>32%</td>
<td>6%</td>
<td>6%</td>
<td>68%</td>
<td>0%</td>
</tr>
<tr>
<td>Diclofenac 50 mg</td>
<td>16%</td>
<td>6%</td>
<td>32%</td>
<td>64%</td>
<td>0%</td>
</tr>
<tr>
<td>Diclofenac 100 mg</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
<td>94%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Combining Diclofenac (an NSAID) with Acetaminophen After Oral Surgery

Figure 3. Pain intensity in the immediate postoperative period over the first 4 h after surgery, depicted as the sum of pain intensity (upper panel), and at 48 h after surgery (lower panel), as measured by a 200-mm verbal descriptor scale.

* P < 0.001 Bupivacaine drug effect, 2-ANOVA

* P < 0.05 Bupivacaine drug effect, 2-ANOVA

Single dose oral ibuprofen for acute postoperative pain in adults.
Derry C, Derry S, Moore RA, McQuay HJ.

<table>
<thead>
<tr>
<th>Dose Ibuprofen</th>
<th># Studies</th>
<th># Subjects</th>
<th>% 50% Relief Ibuprofen</th>
<th>% 50% Relief Placebo</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
<td>20</td>
<td>2690</td>
<td>46%</td>
<td>9%</td>
<td>2.7 (2.5-3.0)</td>
</tr>
<tr>
<td>400 mg</td>
<td>61</td>
<td>6475</td>
<td>54%</td>
<td>14%</td>
<td>2.5 (2.4-2.6)</td>
</tr>
<tr>
<td>600 mg</td>
<td>3</td>
<td>203</td>
<td>77%</td>
<td>40%</td>
<td>2.7 (2.0-4.2)</td>
</tr>
<tr>
<td>800 mg</td>
<td>1</td>
<td>76</td>
<td>100%</td>
<td>38%</td>
<td>1.6 (1.3-2.2)</td>
</tr>
</tbody>
</table>
Summary of discussion A: comparison of oxycodone plus paracetamol with codeine plus paracetamol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Studies</th>
<th>Participants</th>
<th>Active (%)</th>
<th>Placebo (%)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone/paracetamol 10/650 mg</td>
<td>10</td>
<td>1043</td>
<td>51</td>
<td>14</td>
<td>2.7 (2.4 to 3.1)</td>
</tr>
<tr>
<td>Codeine/paracetamol 60/600-650 mg</td>
<td>17</td>
<td>1413</td>
<td>43</td>
<td>17</td>
<td>3.9 (3.3 to 4.7)</td>
</tr>
<tr>
<td>Oxycodone/paracetamol 10/1000 mg</td>
<td>2</td>
<td>289</td>
<td>68</td>
<td>13</td>
<td>1.8 (1.6 to 2.2)</td>
</tr>
<tr>
<td>Codeine/paracetamol 60/800-1000 mg</td>
<td>3</td>
<td>192</td>
<td>53</td>
<td>7</td>
<td>2.2 (1.8 to 2.9)</td>
</tr>
</tbody>
</table>

Conclusions

- In postsurgical dental pain studies NSAIDs at optimal doses are superior in efficacy to single entity opioids and are at least as efficacious as optimal doses of peripheral-narcotic combination drugs.
- In postsurgical dental pain studies NSAIDs have a much more favorable side effect profile than agents that contain an opioid.
- The use of pre-emptive NSAIDs and long-acting local anesthetics appear to greatly delay the onset of postsurgical dental pain and may have benefit beyond the immediate postoperative period.
- NSAIDs should be considered the first line drugs in most cases of postsurgical dental pain.