Dentistry and Basic Non-Opioid Prescribing in Pain

Overview – October 2015

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Disclosures

Speaker for Insys, Iroko, Takeda, Teva, Lundbeck, Pamlab

Consultant for Insys, Pamlab, Teva
Goals of Pain Management

- Decrease pain
- Increase function
- Utilize medications that limit unacceptable side effects, including addiction
Goals of this Presentation

• Gain knowledge of appropriate use of NSAIDs and acetaminophen for pain management in dentistry
• Improve insight into benefits and adverse effects of various NSAIDs
• Learn appropriate alternatives to opioid use for pain management
Opioids: Use with Caution

- Use of opioids for the treatment of acute pain may be appropriate in dental practice.
- Chronic use of opioids in dental practice is highly discouraged.
- Patients may abuse and divert pain medications.
- Dentists must do whatever is possible to ensure the best care of patients with pain and minimize abuse and diversion.

Indiana dentists are encouraged to use INSPECT to verify the prescription history of patients before prescribing opioids.

http://www.in.gov/pla/inspect/
NSAIDs associated mortality

- Literature reports 16,500 deaths annually as a result of NSAID-induced GI bleeding
  Data from the Arthritis, Rheumatism, and Aging Medical Information System, 1999

- An alternative estimate reports a smaller number of 3,200 deaths annually

- An overall mortality incidence rate of 48/1,000 person-years was reported for patients taking non-selective NSAIDs compared with 75/1,000 person-years with opioids
Risks of Short vs. Long Course of NSAIDs

- Risk of GI bleeding and cardio-vascular problems starts almost immediately after a patient begins NSAID medication, and the risk is approximately equally high when used for short-term or long-term treatment.

- Risk of kidney failure become higher the longer NSAIDs are used for pain management.
Acetaminophen

• **Use**
  - For mild-to-moderate pain
  - Efficacy comparable to NSAIDs in some musculoskeletal conditions
  - Common combination drug (eg, hydrocodone)

• **Safety**
  - Few adverse effects
  - Hepatic toxicity possible at high doses (> 4 g/d) or with chronic alcohol abuse

• **Dosage**
  - Up to 4 g/d in divided doses in acute use;
  - Up to 3 g/d in divided doses in chronic use;
  - Lower dose in elderly, dehydration or liver disease
Acetaminophen

Mechanism of action

• A centrally acting analgesic, increasing the pain threshold

• Mechanism of action is not known but may involve nitric oxide, NMDA, substance P, and antagonism of COX-2 and COX-3 enzymes

NSAIDs
Beneficial Effects

• Analgesia
• Anti-inflammation
• Antipyresis

• Limited use in chronic pain, standard of care in acute pain
Classes of NSAIDs

- **Propionic**
  - Ibuprofen, naproxen, ketoprofen
- **Acetic**
  - Indomethacin, sulindac, tolmetin
- **Salicylic (carboxylic)**
  - ASA, sodium salicylate, salicylamide, diflunisal
- **Anthranilic (enolic)**
  - Phenylbutazone, piroxicam
- **Pyrrolopyrroles**
  - Ketorolac, etodolac
- **COX-2 inhibitors**
  - Celecoxib
  - (rofecoxib, valdecoxib – off the market)
NSAIDS
The Biological Basis

- The analgesic, anti-inflammatory, and anti-pyretic properties of NSAIDs are mediated through their inhibition of COX enzymes.
- NSAIDs have varying degrees of COX-1 and COX-2 selectivity.
- Inhibition of COX-1 and COX-2 by NSAIDs is dose-related.
NSAID Mechanism of Action

COX-1 Inhibitors

- Cyclooxygenase-1 is a “housekeeping” enzyme responsible for protective cellular functions within platelets, the stomach, and the kidneys.

- COX-1 Inhibitors can produce adverse effects associated with the inhibition of the COX-1 enzyme:
  - These include increased bleeding time, ulcers, and impaired renal function.
COX-2 Inhibitors

- Cyclooxygenase-2 is an enzyme that is responsible for the inflammatory response and mitogen activity (encouragement of cell division)

- **COX-2 Inhibitors** can produce therapeutic effects associated with the inhibition of the COX-2 enzyme
  - These include decreased pain and decreased inflammation
  - These also include prevention of multiple polyps in the large intestine (polyosis)

- **COX-2 Inhibitors** can produce adverse effects associated with the inhibition of the COX-2 enzyme
  - These include heart attacks, strokes, and renal complications, including renal failure
  - COX-2 inhibitors avoid many of the adverse effects associated with COX-1 inhibitors
COX-2 Inhibitors

- Lack of inhibition of platelet aggregation
  - Protection from longer bleeding times

- Lack of effect on gastric mucosa
  - Protection from ulcers and GI bleeds
  - However, combination with even low dose aspirin (ASA) reduces this protection
Levels of COX-1 Inhibition

Levels of COX-2 Inhibition$^{1,2}$

Degree of COX Selectivity Among Common NSAIDs

Y-Axis = Log (IC₈₀ Ratio, Human Modified Whole Bloody Assay COX-2/COX-1)

Beyond Usual NSAIDs Mechanism of Action

Blockade of voltage dependent Na++ channels

Positive allosteric modulation of K- channels (hyperpolarization and keeping them opened)

Note: Both mechanisms are associated with peripheral anesthetic effects, mirroring lidocaine action
Adverse Events with NSAIDS

References:

Basics of Risk

• **Odds ratios** were used in the previous slide to indicate the risks of having various adverse events with NSAIDs, over time

• These **odds ratios** provide **estimates** of **relative risks** of adverse events with NSAIDs

• **Relative risk** is the RATIO obtained by dividing the risk of an adverse event among those taking a medication by the risk of an adverse event among those not taking a medication

• Understanding the concepts of **risk**, **relative risk** (or odds ratio, as an estimate of relative risk), as well as **excess risk**, form the foundation for understanding adverse effects associated with NSAIDs

• **Addendum B** contains more information about these concepts, for those that are interested. From the standpoint of this course, this is optional material

Reference: James R Miller, DDS, MSD, PhD, personal communication, August 2015
**NSAIDs Adverse Effects**

**Time Considerations**

**Not related to time**

**GI events**: Odds ratios for GI events remain about the same over time

**CV events**: Odds ratios for CV events remain about the same over time

**Possibly related to time**

**Renal events**: Odds ratios for renal events appear to increase over time
GI Risk of Individual NSAIDs by Dose

- In a recent systematic review of observational studies, the risk of NSAID-induced GI events (perforations, ulcers, bleeds) was generally shown to be dose related.

Note: The meta-analysis in Appendix B indicates that the RRs for diclofenac are likely less than in this slide, more in line with celecoxib (Dr. James R. Miller).
NSAIDs Adverse Effects
Dose-Related

- **GI** events (Upper GI)
  - Odds ratio (OR), which estimates Relative Risk (RR)
    - x2.4 in low/medium dose
    - x4.5 in high dose

- **MI** events (Myocardial Infarction is one type of CV event)
  - Odds ratio (OR), which estimates Relative Risk (RR)
    - x1.2 in low dose
    - X1.6 in high dose
The Risk of NSAID-Associated Acute Renal Failure (ARF) May be Dose-Related

The Lower the Dose, The Lower the Risk

## NSAIDs and Hypertension

<table>
<thead>
<tr>
<th>Effect Level</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No effect</td>
<td>ASA, sulindac (Clinoril)</td>
</tr>
<tr>
<td>Mild elevation</td>
<td>Celecoxib (Celebrex)</td>
</tr>
<tr>
<td>Intermediate elevation</td>
<td>Ibuprofen (Advil)</td>
</tr>
<tr>
<td>Significant elevation</td>
<td>Indomethacin, piroxicam (Feldene), naproxen (Naprosyn, Aleve)</td>
</tr>
</tbody>
</table>

NSAIDs Adverse Effects

**GI**
- 60-80% of Gastrointestinal bleeds are silent

**CV**
- NSAIDs have a FDA class warning that includes a risk for CV adverse effects
- Among NSAIDs, naproxen is generally considered the safest NSAID for patients at risk for cardiovascular adverse effects
Additional Adverse Effects

• Mental – irritability, anxiety, psychosis

• Menstrual disturbance

• Hemolytic anemia (induces antibodies to Rh antigen)
Common but Frequently Overlooked NSAIDs Adverse Effects

- Fluid retention and edema
- Exfoliative dermatitis, Stevens-Johnson Syndrome, and epidermal necrolysis
- Headache
- Dizziness
- Hot flashes
- Syncope
NSAIDs and Pregnancy

1st and 2nd trimesters
- Category C

3rd trimester
- Category D

Important Notes
Caution should be exercised in prescribing NSAIDs during the 1st and 2nd trimesters

NSAIDs contraindicated in the 3rd trimester
NSAIDs
Drug Interactions

Classes of drugs that can potentially interact with NSAIDS:

• Angiotensin Converting Enzyme inhibitors (ACE inhibitors)
• Anticoagulants
• Angiotensin Receptor Blockers (ARBs)
• Beta-blockers
• Lithium
• Loop diuretics
• SSRIs
Historical Approaches to Mitigate NSAID Risk$^{1-4}$

- **Enteric Coating**
  - Potentially reduce upper GI events but do not protect against lower GI, CV, or renal events

- **Pro-Drug** (ex: nabumetone)

- **NSAIDs + Gastro-protective Agents**

- **COX-2 Inhibitors**
  - May reduce GI events but potential to increase CV & renal risks

- **Topical NSAIDs**
  - Localized delivery but may have limited utility depending on location of pain

Lowering The Dose While Offering Efficacy Offers a Promising Approach

References:
4. RTI Cost Effectiveness Report. Iroko Pharmaceuticals, LLC.
Mitigating Risk
Avoid in High-Risk Patients

- Avoid in **high-risk patients** such as the elderly and those with congestive heart failure, coronary artery disease, hypertension, renal insufficiency, and cirrhosis of the liver
Mitigating Risk
Use minimum dose necessary

- Need IC 50-80 to block pain
- Diclofenac 75mg BID = 99% COX-2 inhibition
Mitigating Risk
NSAIDS with Shorter T-1/2 are Safer

A shorter half-life is *generally* associated with a decreased risk of GI adverse effects

<table>
<thead>
<tr>
<th>Short T-1/2</th>
<th>Long T-1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2h Diclofenac (Voltaren)</td>
<td>• 12-17h Naproxen (Aleve, Naprosyn, etc.)</td>
</tr>
<tr>
<td>• 2-6h Ketorolac (Toradol)</td>
<td>• 15-20h Meloxicam (Mobic)</td>
</tr>
<tr>
<td>• 3-4h Ibuprofen (Advil, Motrin)</td>
<td>• 50h Piroxicam (Feldene)</td>
</tr>
</tbody>
</table>

Note: In addition to half-life, the risk associated with a particular NSAID can be influenced by its dosage, its duration of use, and its relative selectivity for the COX-1 versus COX-2 enzymes.
Mitigating Risk

Be cautious combining medications

• Combo of NSAIDs and ASA significantly increases GI risks (Need 2h break in between doses of NSAID and ASA)

• Avoid drug interactions by knowing potential interactions and taking a good history of medications
July 2015

- FDA strengthens its warning about Motrin, Advil and Aleve

- The over-the-counter drugs can cause serious side effects that can occur as early as the first few weeks of using the temporary pain relievers, the agency said

- “There is no period of use shown to be without risk,” Dr. Judy Racoosin, deputy director of FDA’s Division of Anesthesia, Analgesia and Addiction Products, said in a statement

- People who have cardiovascular disease, particularly those who recently had a heart attack or cardiac bypass surgery, are at the greatest risk

  Note: Among patients with cardiovascular disease, naproxen is considered the safest NSAID

Reference: *Lydia Wheeler “The Hill” 07/10/15 10:37 AM EDT
Cookie Cutter

**High Blood Pressure:**

- *Preferred* use of *sulindac, celecoxib*

- *Avoid* naproxen, ibuprofen, indomethacin, piroxicam
Cookie Cutter

Vascular Risk (MI, strokes):

- Preferred use of naproxen
- Avoid ibuprofen, diclofenac, celecoxib
Cookie Cutter

GI, kidneys, bleeding problems:

• *Preferred* use of *meloxicam, diclofenac, celecoxib*

• *Avoid* ketorolac, indomethacin, ibuprofen, naproxen, ketoprofen, piroxicam
**Cookie Cutter**

**Pregnancy:**
Never use NSAIDs in third trimester

**Patient on aspirin (including 81 mg):**
Two hours interval before or after NSAID