Coxibs, the Cardiologist’s Advice

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University of Manitoba
Disclosure

Have received honoraria for:
- lectures

From: Pfizer, AstraZeneca, Merck/Schering Plough, SanofiAventis, Servier, Boehringer-Ingelheim, Novartis

Have received payment for
- Clinical trial participation

From: Pfizer, AstraZeneca, CSL Ltd, Servier, Schering-Plough, GSK, Roche
Conflict of Interest

• I am paid to give this talk
• Content has been determined by me, not sponsor
• Comments & content reflects my views, not the University of Manitoba Faculty of Medicine

• My intent is to provide a fair & balanced discussion of current science & treatment options

For feedback or questions:
jducas@shaw.ca
At the end of this lecture you should understand:

1. The mechanism of action of NSAIDs
2. The GI affects of NSAIDs
3. The CV effects of NSAIDs
4. The interaction between low dose ASA & NSAIDs
5. Some common misconceptions about NSAIDs
The problem
The problem

1. 1:4 adults have musc-skel pains
   - nsNSAID & sNSAID are commonly Rx’ed
   - nsNSAID are now OTC

2. nsNSAID & sNSAID have serious AE
   - GI
   - CV
     - Renal
     - Hepatic
     - Allergic
The problem

3. Musc-skel pain pts have other problems & risks:

- Chronic inflammatory state
  - Immobility
    - smoking
    - hypertension
    - dyslipidemia
    - alcoholism

- High GI risk
  - previous GI bleed
  - *H pylori* infection
  - anticoagulants
  - oral steroids

- High CV risk
  - elderly
  - CV disease present
  - multiple RF
4. **The Nomenclature**

NSAID, nsNSAID, sNSAID, COX-2 inhibitors, COXIBS, COX-2 selective

**Generic Vs Brand**

- celecoxib (Celebrex®)
- rofecoxib (Vioxx®), valdecoxib (Bextra®), lumiracoxib (Prexige®)
- etoricoxib (Arcoxia®)

**Older Drugs (some OTC)**

- ibuprofen, diclofenac, aspirin, naproxen, indomethacin, sulindac, ketorolac
4. The Nomenclature simplified

All NSAID:

nsNSAID, = Mostly Older Drugs (aspirin, naproxen, etc)
sNSAID = celecoxib (Celebrex®)
Salix sepulcralis - weeping willow

abundant watery sap, bark which is heavily charged with salicylic acid
1700’s bark extract used for effects on fever, pain and inflammation

1829, German chemists isolated salicin from willow bark
Charles Frederic Gerhardt
1853 ASA synthesized in an unstable and impure form

1897, scientists at the drug and dye firm Bayer began investigating acetylsalicylic acid as a less-irritating replacement for standard common salicylate medicine

66 years later…
Indomethacin was discovered in 1963 and it was first approved for use in the U.S. by the Food and Drug Administration in 1965

Efficacy unquestioned
Mechanism of action entirely unknown
Today there is no way this drug would have been approved
Sir John Robert Vane (1927 – November 19, 2004) won a Nobel Prize in Medicine in 1982 for his work in 1971 on aspirin in which he discovered it inhibited prostaglandin biosynthesis.
Prostaglandins

- found in virtually all tissues and organs
- lipid mediators or hormones
  - potent
  - short half-life inactivated rapidly after excretion
  - paracrine (locally active)
  - autocrine (acting on the same cells synthesizing it)
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP&lt;sub&gt;1&lt;/sub&gt;</td>
<td>bronchoconstriction, Gl tract smooth muscle contraction</td>
</tr>
<tr>
<td>EP&lt;sub&gt;2&lt;/sub&gt;</td>
<td>bronchodilatation, Gl tract smooth muscle relaxation, vasodilatation</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;2&lt;/sub&gt;</td>
<td>↓ gastric acid secretion, ↑ gastric mucus secretion, uterus contraction (when pregnant), Gl tract smooth muscle contraction, lipolysis inhibition, ↑ autonomic neurotransmitters&lt;sup&gt;[6]&lt;/sup&gt;</td>
</tr>
<tr>
<td>EP&lt;sub&gt;3&lt;/sub&gt;</td>
<td>hyperalgesia&lt;sup&gt;[6]&lt;/sup&gt;, pyrogenic</td>
</tr>
</tbody>
</table>

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**Prostaglandins**

- **Bronchoconstriction**
- **Bronchoconstriction**
- **Uteroconstriction**
- **Multiple effects**
- **Platelet activation**

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*Circulation* 2005;112;759
Three different types of blockade

1

nsNSAID
Large Dose
Three different types of blockade

- Low dose ASA
  - Platelet irreversible
  - Other sites intermittent
Three different types of blockade

Physiological Stimulus

Inflammatory Stimulus

Macrophages/Other Cells

COX-2 Induced

COX-1 Constitutive

sNSAID (coxib)

TXA2 platelets
PGI2 endothelium
PGE2 stomach mucosa
kidney etc

PGs
Proteases
Other inflammatory mediators

Inflammation
## COX-2 selectivity in human whole blood

<table>
<thead>
<tr>
<th>Drug</th>
<th>COX-2 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabumetone</td>
<td>0.3</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.4</td>
</tr>
<tr>
<td>Ibuprofen / ASA</td>
<td>0.2</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>2</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>7</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>30</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>36</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>106</td>
</tr>
</tbody>
</table>

They have different T1/2
A brief word on the GI effects…

NSAIDs can cause Gastroduodenal Injury

Annals of Internal Medicine 85:299-303, 1976

NSAID damage to the gastric mucosa
Scanning electron micrographs of normal gastric mucosa (left) and mucosal surface (right) 16 minutes after administration of aspirin.
A brief word on the GI effects...

nsNSAIDS cause:

- 100,000 hospital stays USA per year
- 16,500 deaths per year

Incidence in Pts over 2 months:

2:3 .............. dyspepsia
1:5 .............. endoscopically demonstrable ulcer
1:40 .............. symptomatic ulcer
1:145 ............. bleeding ulcer
1:1,220 ........... dies from nsNSAID

J Rheumatol 1999:26(Suppl 56):18
A brief word on the GI effects...

nsNSAIDS cause:

- Perforation
- Ulcer
- Bleeding

Annual ~1%

J Rheumatol 1999:26(Suppl 56):18
Risk factors for developing Gastroduodenal Complications in NSAID users

American College of Gastroenterology, 1998

Relative risk

- Prior peptic ulcer disease: 4-5
- Increasing age: over 60 years: 5-6
- Male gender: men vs women: 2-3
- Alcohol: 1.5-2
- Smoking: 1.3-1.5
- Current use of:
  - NSAIDs (x2): 10
  - Anticoagulants: 10-15
  - Corticosteroids: 4-5
  - Serotonin-RIs: 10-15
VIGOR n=8076 with RA, rofecoxib 50 Vs naprosen 1000

<table>
<thead>
<tr>
<th>TYPE OF UPPER GASTROINTESTINAL EVENT</th>
<th>ALL CONFIRMED UPPER GASTROINTESTINAL EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROFECOXIB GROUP (N = 4047)</td>
</tr>
<tr>
<td></td>
<td>NAPROXEN GROUP (N = 4029)</td>
</tr>
<tr>
<td>Perforations†</td>
<td>3 (0.1)‡</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>28 (0.7)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>27 (0.7)</td>
</tr>
<tr>
<td>Obstruction†</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>14 (0.3)</td>
</tr>
<tr>
<td>Total</td>
<td>56 (1.4)</td>
</tr>
<tr>
<td>MI</td>
<td>12 (0.4)</td>
</tr>
</tbody>
</table>
09/2004, Merck announced a voluntary worldwide withdrawal of Vioxx (rofecoxib) because of increased risk of MI & CVA.
ANGLETON, Tex., Aug. 19, 2005
- the first verdict involving Vioxx
- awarded $253.5 m
-10,000 cases & 180 class action suits pending against Merck

09/2004, Merck announced a voluntary worldwide withdrawal of Vioxx (rofecoxib) because of increased risk of MI & CVA

Carol and Robert Ernst
Robert died 2001
Cardiovascular Effects

- BP
- CHF
  - Kidney
- ASA Blockade by NSAID
- Vessel Wall / Platelet
Cardiovascular Effects

- BP
  - rise averages 3 to 6 mmHg
  - most prominent in Na & high Na diet
  - less effect in pt on CCB
Cardiovascular Effects

- CHF

Cohort study / case–control analysis from UK GP Research Database
1\textsuperscript{st} hospital admission for non-fatal CHF

![Bar chart showing relative risk of CHF for different NSAID categories]

N=5857

- No NSAID
- Current NSAID
- Low Dose
- High Dose
Cardiovascular Effects

- CHF

Cohort study / case–control analysis from UK GP Research Database
new hospital admission for non-fatal CHF

No CHF Prior CHF
No NSAID
Current NSAID

N=6396

Relative Risk CHF

No CHF History Prior CHF

Heart 2006;92:1610
Cardiovascular Effects

- CHF

Databases of hospital discharge summaries & prescription drug claims in Quebec

NSAIDs:
1. Increase BP
2. Cause CHF

N=2256

BMJ 2005;330:1370
Cardiovascular Effects

- Kidney

TABLE 4. Rates of **acute renal failure** by NSAID* category for current new NSAID users older than 66 years of age from the Province of Quebec, Canada, 1999–2002, relative to rates for individuals without an NSAID prescription for 365 days

<table>
<thead>
<tr>
<th>Exposure-time category†</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Unadjusted RR*</th>
<th>95% CI*</th>
<th>Adjusted RR‡</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed (reference category)</td>
<td>1,130</td>
<td>24,566</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Current new use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional NSAIDs</td>
<td>75</td>
<td>1,252</td>
<td>2.54</td>
<td>1.82, 3.55</td>
<td>2.30</td>
<td>1.60, 3.32</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>145</td>
<td>2,217</td>
<td>2.58</td>
<td>1.98, 3.36</td>
<td>2.31</td>
<td>1.73, 3.08</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>112</td>
<td>2,456</td>
<td>1.73</td>
<td>1.30, 2.29</td>
<td>1.54</td>
<td>1.14, 2.09</td>
</tr>
<tr>
<td>Naproxen</td>
<td>35</td>
<td>478</td>
<td>3.12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NSAIDs:**
- 1. increase BP
- 2. cause CHF
- 3. cause ARF
Cardiovascular Effects

- ASA Blockade by NSAID

NSAIDs:
1. increase BP
2. cause CHF
3. cause ARF
4. Block LD ASA

N Engl J Med 2001;345:1809
Cardiovascular Effects

- Vessel Wall / Platelet
Normally, COX-1 (No COX 2 induced) results in a balance between platelet reactivity and vascular reactivity.

Balance
platelet reactivity
vascular reactivity

COX-1

\( \text{TxA}_2 \)

\( \text{PGI}_2 \)
atherosclerosis,

\[ \text{TxA2} \]

\[ \text{PGI2} \]

\[ \uparrow \text{COX-1} \]

\[ \uparrow \text{COX-2 induced} \]
Low dose ASA prevents MI & CVA!

(Low Dose)

\[ \downarrow \text{COX-1} \]

\[ \uparrow \text{COX-1} \]
\[ \uparrow \text{COX 2 induced} \]
sNSAID promotes MI & CVA!

**NSAIDs:**
1. increase BP
2. cause CHF
3. cause ARF
4. cause CV Events
Myths

1. ASA is the only safe NSAID, use in high dose
2. Naproxen is the only safe NSAID
3. All sNSAID are dangerous
4. Just give a PPI with nsNSAID
1. ASA is the only safe NSAID, use in high dose

ACE Trial

n=2849 undergoing CEA, pre op ASA & x 3m

Death, MI, CVA 3m

- ASA 81
- ASA 325
- ASA 650
- ASA 1300

Lancet 1991;353:2179
2. Naproxen is the only safe NSAID

ADAPT

>70 y with family history of AD n=2,528

- celecoxib 200 b.i.d.
- naproxen sodium 220 b.i.d
- placebo

Cardiovascular Death, MI, Stroke, CHF, or TIA

![Graph showing Cardiovascular Death, MI, Stroke, CHF, or TIA](image-url)
3. **All sNSAID are dangerous**

**Point Estimates and Summary Relative Risks for CV With Rofecoxib & Celecoxib**

<table>
<thead>
<tr>
<th>Source</th>
<th>Weight, %</th>
<th>Favors Rofecoxib</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-Control Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGittigan et al.</td>
<td>3.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh et al.</td>
<td>11.86</td>
<td></td>
<td></td>
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<tr>
<td>Sturkenboom et al.</td>
<td>7.86</td>
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<tr>
<td>Hippsley-Cox and Coopland</td>
<td>10.35</td>
<td></td>
<td></td>
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<tr>
<td>Johnsen et al.</td>
<td>10.21</td>
<td></td>
<td></td>
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<tr>
<td>Levesque et al.</td>
<td>10.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kimmel et al.</td>
<td>5.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graham et al.</td>
<td>8.43</td>
<td></td>
<td></td>
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<tr>
<td>Solomon et al.</td>
<td>11.23</td>
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<tr>
<td><strong>Cohort Studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gislason et al.</td>
<td>11.12</td>
<td></td>
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</tr>
<tr>
<td>Marandni et al.</td>
<td>8.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for Heterogeneity: $\chi^2 = 75.94, df = 10$

$(P < .001), I^2 = 86.8$

Test for Overall Effect: $Z = 3.64 (P = .003)$

<table>
<thead>
<tr>
<th>Source</th>
<th>Weight, %</th>
<th>Favors Celecoxib</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-Control Studies</strong></td>
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<tr>
<td>McGittigan et al.</td>
<td>3.89</td>
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<tr>
<td>Singh et al.</td>
<td>12.06</td>
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<tr>
<td>Hippsley-Cox and Coopland</td>
<td>9.48</td>
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<tr>
<td>Johnsen et al.</td>
<td>9.11</td>
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<td>Levesque et al.</td>
<td>10.89</td>
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<td>Kimmel et al.</td>
<td>4.07</td>
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<tr>
<td>Graham et al.</td>
<td>9.78</td>
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<tr>
<td>Solomon et al.</td>
<td>11.71</td>
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<tr>
<td><strong>Cohort Studies</strong></td>
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<tr>
<td>Gislason et al.</td>
<td>10.59</td>
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<td>Marandni et al.</td>
<td>8.87</td>
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<tr>
<td>Ray et al.</td>
<td>9.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for Heterogeneity: $\chi^2 = 81.66, df = 10$

$(P < .001), I^2 = 87.8$

Test for Overall Effect: $Z = 0.71 (P = .48)$

*JAMA. 2006;296:1633-1644*
3. All sNSAID are dangerous

CV Death, MI, CVA, CHF, or Thromboembolism

Hazard Ratio

Circulation. 2008;117:2104
4. Just give a PPI with nsNSAID

- **Video capsule endoscopy**
- **Normal baseline**
- **No ASA**
- N=120 celecoxib 200 BID
- N=118 naproxen 500 BID + Losec 20 OD
- N=118 naproxen 500 BID + placebo

2 weeks

---

**Small bowel mucosal breaks per subject**

- **Celecoxib**
  - (n = 115)
  - 0.32

- **Naproxen + PPI**
  - (n = 111)
  - 2.99
  - p < 0.001

- **Placebo**
  - (n = 113)
  - 0.11
  - p = 0.043

---

4. Just give a PPI with nsNSAID

N = 854, OA + CVD
- baseline endoscopy normal
- all ASA 81 or 325

blind randomization
- celecoxib 200
- naproxen 500² + lansoprazole 30

• Endoscopy 12 w
Take Home

Meta-analysis
99,400 patient years of exposure
Take Home

Assess patient’s CV risk (FRS)

Risk factors present (FRS >10%)

Risk Factor Modification / Low Dose ASA / BP / Statin

assess NSAID GI risk

High
nsNSIAD* +PPI or low dose sNSAID (+PPI)
or
Non-NSAID therapy

Low
nsNSIAD* or
Non-NSAID therapy

Low Risk (FRS <10%)

Assess NSAID GI risk

High
sNSIAD (+PPI)
or
nsNSAID + PPI or
Non-NSAID therapy

Low/none

nsNSAID

* ??Naproxen preferred
Take Home

When starting NSAID Monitor:

- BP
- CHF
- Cr
- GI

• Alter NSAID if necessary
• Use plain ASA not ecASA, 2 hours before nsNSAID
Before NSAIDs or aspirin low dose

H pylori

Asymptomatic – No History
Nothing or Test & treat if high prevalence of H pylori

History of ulcers:
Test & treat
Agenda

At the end of this lecture you should understand:

1. The mechanism of action of NSAIDs
2. The GI affects of NSAIDs
3. The CV effects of NSAIDs
4. The interaction between low dose ASA & NSAIDs
5. Some common misconceptions about NSAIDs
THANK YOU
What do we know about communicating risk? A brief review and suggestion for contextualising serious, but rare, risk, and the example of cox-2 selective and non-selective NSAIDs
R Andrew Moore¹, Sheena Derry¹, Henry J McQuay¹ and John Paling²

Figure 13

Additional risk of dying from GI bleed or heart attack using NSAID or coxib, compared with common risks of death in USA