COX-2 inhibitors: A cautionary tale

October 3, 2005
Molecular interventions in human disease...
An approach as old as human civilization.

With whom the herbs have come together
Like kingly chiefs unto the gathering,
That Brahman is called a “healer” (bhisaj),
A demon-killer, a plague-dispeller.

From the *Rg Veda* (1500-900 BCE)

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**Datura stramonium**
Vol. 2, plate 28 from the *Hortus Indicus Malabaricus*
Published 1679
Source of scopolamine and atropine
Aspirin from willow bark

Written records of willow bark use in ancient Greek and Arabic medical documents
Traditional medication for pain and fever throughout much of the world

“Ethnobotany” - study of the role of plants in human societies
“Zoopharmacognosy” - self-medication in animals (best documented in primates)
Development of aspirin

1830s: Salicin purified from willow bark - too irritating for human use

1850s: Acetylsalicylic acid synthesized - analgesic, antipyretic, anti-inflammatory

1897: Felix Hoffmann synthesizes acetylsalicylic acid for his arthritic father; Bayer gets the patent

1971: John Vane finds that aspirin inhibits prostaglandin synthesis (Nobel Prize 1982)

1970s: Aspirin shown to act by acetylating Serine 530 of cyclooxygenase (prostaglandin synthase)

1988: Physician's Health Study shows daily aspirin reduces incidence of a first heart attack by 40%
Figure 1. An overview of eicosanoid biosynthetic pathways, as understood from the mammalian background. Major families of eicosanoids include prostaglandins, epoxyeicosatrienoic acids and the many lipoxygenase products.

Eicosanoid = 20 carbons (compare icosahedron)
Various prostaglandins, cell types, cell responses...
Regulate smooth muscle contraction
  (lowering blood pressure, stimulating labor)
Mediators of pain and inflammation
Inhibit gastric acid secretion, protect against gastric ulcers

Other GPCRs for prostaglandins signal through calcium

Some prostaglandin receptors are nuclear hormone receptors (e.g. PPAR gamma) that directly activate gene transcription
COX reactions

requires heme, tyrosyl radical formed

second active site on same polypeptide

COX = cyclooxygenase (aka prostaglandin synthase)
Aspirin mechanism

In vitro, aspirin acetylates many targets

Serine 530:
Near active site, NOT involved in catalysis
Contrast penicillin, protease inhibitors (via acyl-enzyme intermediate)

Note COVALENT attachment to enzyme, so irreversible inhibition
Important in platelets: no new gene expression (no nucleus), so one
dose of aspirin is effective for the life of the platelet
Drawback: can contribute to serious bleeding
Low-dose aspirin regimens recommended for decreasing likelihood of stroke and myocardial infarction in at-risk patients
COX structure with indomethacin

Heme

Cyclooxygenase active site

NSAID = non-steroidal anti-inflammatory drug
Ibuprofen, naproxen, sulindac, others.
NONCOVALENT, competitive enzyme inhibition
A role for COX inhibitors in treatment of colorectal cancer

1983: Polyps regress in patients taking NSAIDS

1991-1993: Large scale studies show prophylactic effect of NSAIDS (40-50% risk reduction) and effectiveness in patients with APC deficiency (familial adenomatous polyposis)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Effects of NSAID treatment in animal models of colorectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAID treatment</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>ApcMv mouse</td>
<td>Sulindac*</td>
</tr>
<tr>
<td></td>
<td>Piroxicam*</td>
</tr>
<tr>
<td></td>
<td>Celecoxib‡</td>
</tr>
<tr>
<td>ApcMv mouse</td>
<td>Rofecoxib‡</td>
</tr>
<tr>
<td>Azoxy methane (AOM)-treated rat</td>
<td>Aspirin*</td>
</tr>
<tr>
<td></td>
<td>Celecoxib‡</td>
</tr>
<tr>
<td></td>
<td>NS-398‡</td>
</tr>
<tr>
<td></td>
<td>Nimesulide†</td>
</tr>
<tr>
<td>Nude mouse xenograft</td>
<td>SC-58125‡</td>
</tr>
<tr>
<td></td>
<td>Meloxicam*</td>
</tr>
<tr>
<td></td>
<td>Celecoxib‡</td>
</tr>
</tbody>
</table>

*Non-selective NSAID
‡COX-2-selective NSAID
Why does this work?

Maybe targets other than COX?
But wait, there’s more...

1991: Two different COX enzymes

- COX-1 expressed constitutively in many tissues
  - Generates protective prostaglandins in the GI tract
  - Stimulates platelet activation via thromboxane synthesis
- COX-2 induced at sites of injury and inflammation

2002: COX-3 (splice variant of COX-1)

-expressed in CNS, selectively inhibited by acetaminophen (works for pain and fever, no effect on inflammation)
COX1

NSAID binding space

COX2

'Side pocket'

Intracellular membrane

COX1 inhibitor
Flurbiprofen

COX2 inhibitor
DuP697

Nature Reviews Drug Discovery
COX-2-specific inhibitors identified by drug screening

combined sales worldwide >$4 billion per year (through 2004)

Rofecoxib (Vioxx)

Celecoxib (Celebrex)

Work poorly in standard assay (rat kidney or testis extracts)
Work great in brain extracts
Change in colorectal polyposis for FAP patients on COX-2 inhibitors

- Patients receiving 400 mg of Celecoxib 2x daily show improvement in all areas of colon
- Patients receiving 100 mg of Celecoxib 2x daily show trend towards improvement in rectum, ascending colon, and cecum
- Are these two areas the first targets of cox-2 inhibitor-mediated polyp regression? Is the mechanism different for different dosages?


### Table 3. Change in Colorectal Polyposis Based on Review of Endoscopic Videoframes in Patients with Familial Adenomatous Polyposis Treated with Placebo or Celecoxib for Six Months.*

<table>
<thead>
<tr>
<th>Colorectal Segment</th>
<th>Placebo</th>
<th>400 mg of Celecoxib Twice Daily</th>
<th>400 mg of Celecoxib Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Score</td>
<td>P-value</td>
</tr>
<tr>
<td>Rectum</td>
<td>15</td>
<td>-0.1±0.3</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>0.2±0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Transverse, descending, and sigmoid colon</td>
<td>6</td>
<td>-0.2±0.2</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.1±0.1</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.6±0.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Cecum and ascending colon</td>
<td>5</td>
<td>-0.2±0.4</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.4±0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Total colorectum§</td>
<td>15</td>
<td>-0.07±0.26</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>0.11±0.22</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>0.32±0.22</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The baseline and six-month evaluations were compared by a panel of endoscopists experienced in the management of familial adenomatous polyposis. These endoscopists assigned scores for anatomical segments as follows: -1 = indicated “worse,” 0 = “no change,” and 1 = “better.”

*Plus–minus values are means ±SD of the scores for each group. P-values are based on two-sample Wilcoxon statistic for the comparison of celecoxib with placebo, in the analysis of patients for whom the respective videoframes were available.

†Videoframes were not available for three patients.

‡Videoframes were not available for one patient.

§The score for the total colorectum is the mean of the separate assessments of the transverse, descending, and sigmoid colon, the cecum and ascending colon, and the rectum.
September 30, 2004

Merck Pulls Vioxx Painkiller From Market, and Stock Plunges

By TERENCE NEILAN

Merck & Company announced today that it was immediately pulling its arthritis and acute pain medication Vioxx from the worldwide market after data from a clinical trial showed that the drug produces an increased risk for heart attacks and strokes.

"We are taking this action because we believe it best serves the interests of patients," Merck's chairman, president and chief executive officer, Raymond V. Gilmartin, said.

"Although we believe it would have been possible to continue to market Vioxx with labeling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take," Mr. Gilmartin said in a statement posted on the New Jersey-based company's Web site.

The recall represents a big blow for Merck, with Vioxx accounts shares plunged at the opening bell on the New York Stock Exchange as low as $32.46, and closed only slightly higher, at $33, down result, the company's market capitalization was reduced some $11 billion.

Shares of Pfizer, maker of Celebrex, Vioxx's main competitor, gave up most of that gain to close at $30.60, up 42 cents, or 1.5%.

A Merck company spokesman, Tony Plohoros, said there were no deaths, and that 84 million prescriptions had been written for the drug.
What happened? Why?

- COX-2 inhibitors have a clear clinical advantage for the subset of arthritis patients likely to experience gastric bleeding
- Vioxx and Celebrex were direct-marketed to all arthritis patients without clear explanation of the relevance only to patients at risk for bleeding…millions of otherwise healthy people took an expensive prescription drug instead of an OTC NSAID
- Should the cardiovascular risk have been clear earlier than September 2004?
- Why does COX-2 inhibition carry cardiovascular risk, while inhibition of both COX-1 and COX-2 does not?