Natural Alternatives to Pharmaceutical Cox-2 Inhibitors

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Introduction

• September 30, 2004 – Merck & Co., Inc. voluntarily withdrew the Cox-2 inhibitor VIOXX® (rofecoxib) worldwide
  – Based on new, three-year prospective, randomized, placebo-controlled clinical trial showing increased relative risk for confirmed cardiovascular events (e.g., heart attack and stroke\(^1\))

• December 17, 2004 – FDA warned Celebrex® (celecoxib), may increase risk of heart attacks, strokes, & heart–related deaths
  – Based on a study of 2,000 patients with colorectal cancer. Those patients who took Celebrex® had a much greater chance of developing serious heart problems than did those who took placebos.


How Did They Get Approved?

• Assessing health risks of drugs is challenging
  – Can’t give to people to see what dose causes cancer
  – Instead rely on animal tests (ethical debate)
  – Epidemiologist examine human exposure in field
• Both types of studies have uncertainties
  – Scientists must extrapolate, make causal inferences & recommend protective measures
  – Government officials use best evidence to determine safety of pharmaceuticals
  – Uncertainty is an inherent problem of science
Manufactured Uncertainty

- Pharmaceutical industry groups become involved in investigative process when interests are threatened
  - Its own researchers cast doubt on independent studies (calling it “junk science”)
  - Tout own studies shown no significant health risks, while ignoring others (calling it “sound science”)
- “Doubt is our product since it is the best means of competing with the ‘body of fact’ that exists in the mind of the general public.”
  - Said in 1969 by a cigarette maker executive at Brown & Williamson (now owned by R.J. Reynolds Tobacco Co.)

Vioxx® History

- Before approving Vioxx in 1999, the FDA reviewed data suggesting the drug increased risk of heart disease
  - Independent scientists raised red flags, which were generally ignored.
  - Results of clinical trial in 2000 showed participants taking Vioxx for about 9 months had 5 times the risk of heart disease compared to those taking naproxen (Aleve)
    - Merck interpreted data to mean that naproxen reduced risk by 80%, rather than say Vioxx increased risk by 400%
      - Incredible marketing spin

A Timely Quote

• “The public needs to understand that there is no such thing as an absolutely safe medicine. Any drug powerful enough to do good can also do some harm.”
  – Said by Pfizer CEO Hank McKinnell*

* USA Today, May 20, 2005, pp 6B.
The Ultimate Spin

B.C. by Johnny Hart

HOW DID MY NEW PAINKILLING PILLOW WORK OUT?

NOT GOOD.

AS IT TURNS OUT, IRONICALLY, IT CAN KILL YOU!

EUREKA... THE CURE FOR CHRONIC PAIN!
Vioxx® History¹ – Cont’d

- Merck did take Vioxx off the market in September 2004
  - New trial found participants taking drug for more than 18 months suffered twice as many heart attacks and strokes as those taking placebo.
  - FDA analyst estimated Vioxx caused between 88,000-139,000 heart attacks in 5 years on the market
    - 30-40% of which were probably fatal
  - Wall Street Journal reported Merck Executives were aware of increased risk of heart attacks in the first instance.

What is Cox-2?

- Cox is short for the Cyclo-oxygenase enzymes
- Involved in many different body processes, based on normal prostaglandin synthesis
- In 1991 research discovered two forms
  - Cox-1
  - Cox-2
Cox-1

- Constitutive
- Widespread and serves “housekeeping” functions
  - Cytoprotection of gastric cells
  - Normal vascular endothelial function
  - Platelet aggregation
  - Maintenance of renovascular function
  - Etc.
- Inhibition of Cox-1 results in many problems:
  - Gastric ulceration & gastrointestinal bleeding
  - Cardiovascular problems
  - Etc.
Cox-2

• Inducible
  – Disease
  – Trauma
  – Toxins

• Produces damaging form of prostaglandin (PG E-2)
  – Inflammation
  – Pain
  – Swelling
Cox-2 – Cont’d

- Diseases Associated with Cox-2
  - Allergies
  - Alzheimer’s
  - Arthritis (Osteo, Rheumatoid)
  - Gut
    - Crohn’s Disease
    - Colon Cancer
    - Inflammatory Bowel Disease
  - Diabetes (I and II)
  - Atherosclerosis
  - Systemic Lupus
  - Skin Disease
    - Eczema
    - Psoriasis
  - Cancer
    - Solid Tumors
    - Leukemia
    - Lymphomas
Cox-1 & Cox-2 Inhibiting Drugs

- NSAIDs (e.g., aspirin, ibuprofen) are Cox-1 & Cox-2 inhibitors
- Vioxx & Celebrex were said to be selective Cox-2 inhibitors
  - Meaning significantly less inhibition of Cox-1
  - Supposed to result in less side effects
  - Prescribed for arthritis & other inflammatory disorders
INFLAMMATORY CASCADE

Cell Membrane

↓

Phospholipase A2

↓

Arachidonic Acid

Lipo-oxygenase

Leukotrienes

Cyclo-oxygenase

Prostaglandins
Natural Alternatives

- Herbal Cox-2 inhibitors
  - Also have significantly less inhibition of Cox-1
  - Have greater safety profile
    - Clinical research
    - History of traditional use
- Herbal 5-lipooxygenase inhibitors
- Other natural anti-inflammatory agents
Turmeric

- Traditional remedy used as a medicine, condiment and flavoring in records dating back to 600 BCE.
- Medicinal value due to its curcuminoid content.
  - Inhibit 5-lipoxygenase & Cox-2, resulting in anti-inflammatory action.¹
- Anti-inflammatory research (partial review):
  - As effective as cortisone or NSAID phenylbutazone for acute inflammation; about half as effective for chronic inflammation.²
  - Found to be useful for reducing inflammation, pain and stiffness in rheumatoid arthritis patients.³
  - DB study found it to be superior to placebo or NSAID drug phenylbutazone for alleviating post-surgical inflammation.

Turmeric – *Cont’d*

- Turmeric and its curcuminoids also:
  - Exhibit strong antioxidant activity
  - Enhance cellular resistance to oxidative damage
  - Enhance body's glutathione production
    - Which in turn aids liver in detoxification.
    - Found to have hepatoprotective (i.e., liver-protective) properties against a variety of liver-toxic chemicals and drugs.
Turmeric – *Cont’d*

• Have anticancer effect against
  – Angiogenesis (new blood vessel growth)
  – Tumor growth
  – Suppressing activity of common mutagens and carcinogens.
Turmeric – Cont’d

- Inhibit growth of various bacteria, parasites, and pathogenic fungi
- Protective effect on cardiovascular system
  - Lower cholesterol & triglyceride levels
  - Decrease LDL oxidation
  - Inhibit platelet aggregation.

- Digestive effects of Turmeric
  - Helpful for people with indigestion in double-blind trial
  - Effective in animal research at inhibiting ulcer formation caused by stress, alcohol, and drugs.
Turmeric – Cont’d

• Dosage: 1200 -3000 mg extract standardized for 95% curcuminoids daily
• Clinically Significant Cautions
  – Not to be used during pregnancy. Therapeutic quantities of Curcuma longa should not be taken by people with bile duct obstruction or gall stones; nor should it be administered to patients who suffer from stomach ulcers or hyperacidity
  • Although research does indicate value in treating indigestion; & ulcer prevention in animal research
Bromelain

- A proteolytic (i.e., protein-digesting) enzyme found in pineapples
- Does not appear to be Cox-2 inhibitor; mechanisms of action not completely resolved
  - Included since a good anti-inflammatory agent
- Four studies demonstrated its effectiveness in treating minor injuries (bruises, sprains, strains, hematomas, lacerations, abrasions) & severe injuries (low back pain, fractures, minor surgery)\(^1\)
- Effective at decreasing inflammation & edema from surgery and injury\(^2\)

Bromelain – Cont’d

- Clinical reports of decreasing thrombophlebitis (inflammation of veins) & pain from angina and thrombophlebitis\(^1\)
- Helped patients with rheumatoid arthritis; 73% of whom had good to excellent results\(^2\)
- Helped relieve symptoms of acute sinusitis in DB study\(^3\)
- Dosage: 1000-1500 mg daily of 2400 GDU/g material

Ginger

- Mainly known for anti-nausea properties (i.e., treatment of motion sickness and morning sickness)
- Also effective anti-inflammatory herb that has historically been used for arthritis and rheumatism
- Inhibits Cox-2 and lipoxygenase\(^1\)
- Patients with rheumatoid & osteo-arthritis and muscular discomfort experienced varying degrees of pain relief & swelling for up to 2.5 years of study\(^2\)
  - No adverse effects reported.

Ginger – Cont’d

- In DB trial, ginger extract more effective than placebo at relieving pain OA of the hip or knee\(^1\)
- In DB trial ginger extract more effective than a placebo in pain relief and overall improvement of OA\(^2\)
- Dosage: 200-510 mg daily, standardized to 6% gingerols

Boswellia

- The resin used traditionally for inflammatory diseases, such as rheumatoid arthritis, osteoarthritis, and cervical spondylitis (inflammation of the vertebrae)
  - Main constituents of resin are boswellic acids, which inhibit 5-lipoxygenase & leukotriene formation\(^1\)
  - Unlike corticosteroids which also inhibit leukotriene synthesis, boswellic acids exhibit no significant side effects or toxicity\(^2\)

Boswellia – Cont’d

• Investigation showed rheumatoid arthritis patients given boswellic acids:\(^1\)
  – Had reduction of swelling and pain as compared to placebo
  – Morning stiffness was reduced
  – Reduced intake of NSAIDs during the treatment period
  – General health and well-being showed improvement
  – Boswellic acids found effective in reducing symptoms in 50-60% of the patients involved in the investigation

• Dosage: 150 mg boswellic acids up to 3X daily

Salicin

• 300 species of Salix (willow) native to England, Europe, Asia, and North America
• Historical use:
  – In *De Materia Medica* (1st century CE), willow used therapeutically for gout & rheumatic joint diseases.
  – Ancient Egyptians the bark for pain and inflammation
  – Native Americans relied on Willow for its analgesic properties
Salicin – Cont’d

• In 1829 willow’s active chemical, salicin was discovered.
• In 1838, pure salicylic acid was synthesized (not from Willow but Wintergreen and other plants).
• Salicin and salicylic acid were widely used through the 19th century for fever, gout, pain, and inflammation.
  – High doses of salicylic acid used routinely led to gastric irritation and vomiting.
• In 1893, Felix Hoffman at the Bayer Company synthesized acetylsalicylic acid (aspirin).
  – Had less gastric side effects than salicylic acid.
Salicin – Cont’d

• Salicin from willow, meadowsweet, etc. can be converted by body to create salicylic acid\(^1\)
  – Providing anti-inflammatory and pain-relieving actions
  – Same COX-2 inhibition properties as aspirin
    • Salicin will not function as an anticoagulant (blood thinner)

• Studies
  – 240 mg of salicin (from wwb) showed modest effectiveness in treating pain associated with knee and/or hip osteoarthritis\(^2\)
  – 120-240 mg of salicin (from violet willow) was successful at reducing low back pain in some patients\(^3\)
    • Higher concentration was more effective, although it took up to 1 week for significant relief

• Dosage: 120-240 mg

Hops

• Best known as a flavoring agent in beer
• Also used to reduce anxiety$^1$ & insomnia$^2$
• Recent research on hops extract high in alpha acids
  – Exhibited COX-2 inhibition over 9 hours, equivalent to ibuprofen 400 mg
    • Extract had very mild COX-1 inhibition

Hops – Cont’d

• Open-label, 8 week trial\(^1\): combination of alpha acids from hops, rosemary extract, and oleanolic acid tested in subjects with osteoarthritis, rheumatoid arthritis, and fibromyalgia.
  – Osteoarthritis subjects showed a 50% decrease in pain
  – No statistically significant differences in the rheumatoid arthritis and fibromyalgia subjects.

• Dosage: 500 mg standardized for 40% alpha acids

Conclusion

• Natural alternative to pharmaceutical Cox-2 inhibitors
  – Have evidence of clinical effectiveness
  – Work by different mechanisms
  – Also have significantly less inhibition of Cox-1
  – Have greater safety profile
    • Clinical research
    • History of traditional use

• Structure/function claims for consumers
  – Turmeric, Ginger, Boswellia, Hops and Salicin are all Cox 2 inhibitions that may help provide you with relief for common everyday aches and pains
    • Don’t use the terms “joint” or “chronic”.
  – Bromelain is a proteolytic enzyme from pineapple that may help provide you with relief for common everyday aches and pains
Thank You – Questions?

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