Natural Alternatives to Pharmaceutical Cox-2 Inhibitors

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Gene Bruno, MHS

Dean of Academics, Huntington College of Health Sciences

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.

1. Merck Announces Voluntary Worldwide withdrawal of VIOXX® (press release); September 30, 2004. Accessed October 25, 2004 from http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp.

2. NIH Halts Use of COX-2 Inhibitor in Large Cancer Prevention Trial (press release; December 17, 2004. Accessed May 23, 2004 from http://www.nci.nih.gov/newscenter/pressreleases/APCtrialCOX2

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.”[1]
  - Said in 1969 by a cigarette maker executive at Brown & Williamson (now owned by R.J. Reynolds Tobacco Co.)

1. Michaels D. Doubt is their product. *Scientific American*. June 2005, pp. 96-101.

Vioxx® History[1]

- 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

1. Michaels D. Doubt is their product. *Scientific American*. June 2005, pp. 96-101.

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

Vioxx® History[1] – *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.

1. Michaels D. Doubt is their product. *Scientific American*. June 2005, pp. 96-101.

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

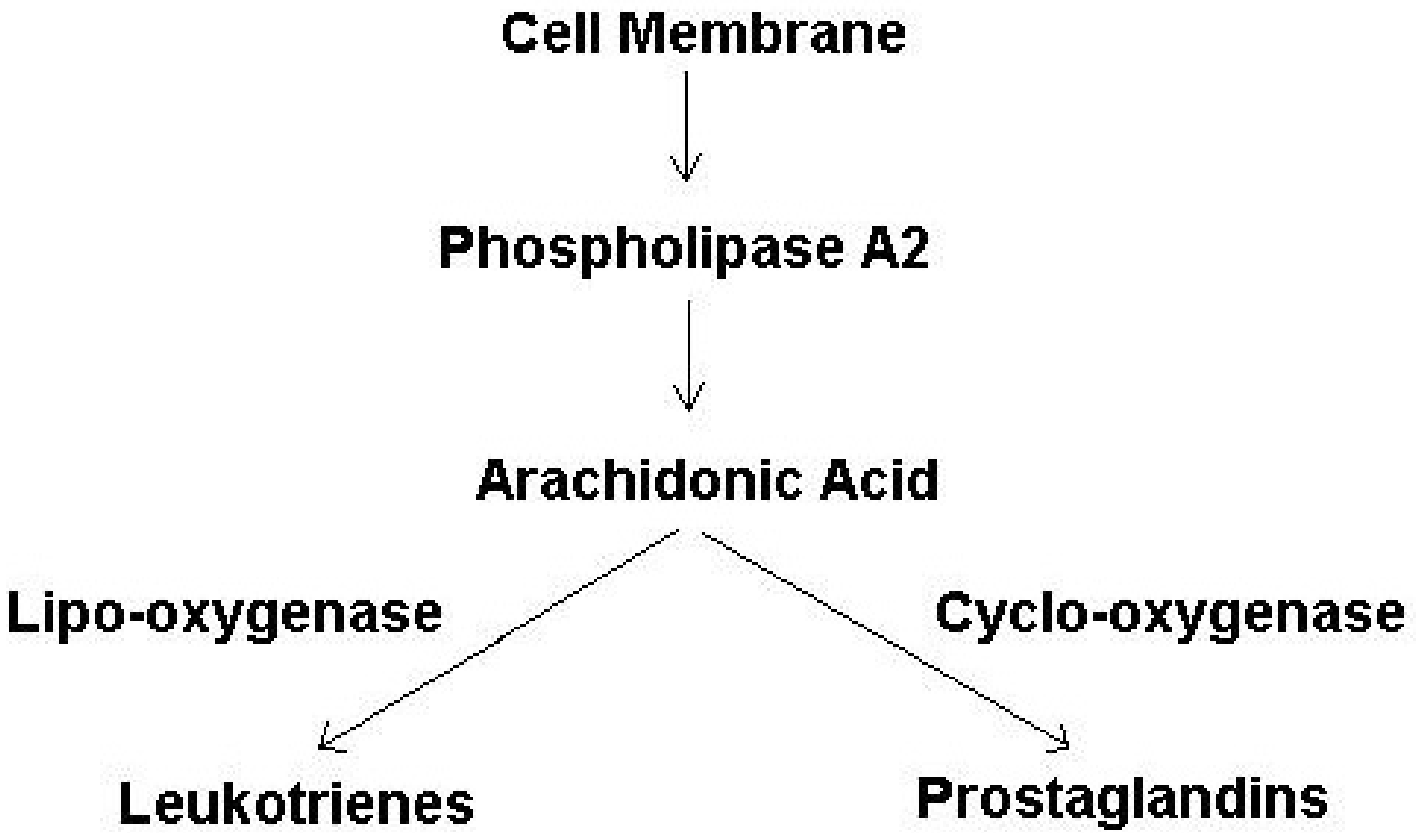
Cox-2 – *Cont'd*

- 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



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

1. Arora R, Basu N, Kapoor V, et al. Ind J Med Res 1971;59:1289-1295
2. Mukhopadhyay A, Basu N, Ghatak N, et al. Agents Actions 1982; 12:508-515.
3. Deodhar SD, Sethi R, Srimal RC. Ind J Med Res 1980; 71:632-4.
4. Satoskar RR, Shah SJ, Shenoy SG. Int J Clin Pharmacol Ther Toxicol 1986; 24:651-4.

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]

1. Bucci LR, Stiles J. Today's Chiropractic 1977; 16(1): 31-34.

2. Osol A, Hoover JE, ed. Remington's Pharmaceutical Sciences (1975), Mack Publishing Company, Easton, PA, pp. 974.

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

1. Nieper HA, Acta Med Empirica (1978) 5:274-78.

2. Cohen A, Goldman J. Pennsylvania Med J 1964; 67:27-30.

3. Ryan R, Headache 1967; 7:13-17.

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.

1. Srivastava KC, Mustafa T. Medical Hypotheses 1989; 29:25-8.

2. Srivastava KC, Mustafa T. Med Hypotheses 1992; 39:342-8.

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

1. Bliddal H, Rosetzsky A, Schlichting P, et al. Osteoarthritis Cartilage 2000;8:9-12.
2. Altman RD, Marcussen KC. Arthritis Rheum 2001; 44:2531-8.

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]

1. Safayhi H, Sailer ER, RF Howenlein, HPT Ammon, H Fafayhi. Phytomedicine 1996; 3(1):71-72.

2. Singh, G.B., S. Bani, and S. Singh. Phytomedicine 1996; 3(1): 87-90

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

Etzel, R.. Phytomedicine 1996; 3(1):91-94.

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

1. Bradley PR (ed). British Herbal Compendium, vol 1. Bournemouth, Dorset, UK: British Herbal Medicine Association; 1992:224-6.
2. Schmid B, Tschirdewahn B, Kàtter I, et al. Fact 1998; 3:186.
3. Chrubasik S, Eisenberg E, Balan E, et al. Am J Med 2000; 109:9-14.

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

1. Bradley PR (ed). British Herbal Compendium. Bournemouth: British Herbal Medicine Association; 1992:128-30.
2. Weiss RF. Herbal Medicine. Gothenburg, Sweden: Ab Arcanum; 1988:285-6.
3. Lemay M, Murray MA, Davies A, Roh-Schmidt H, Randolph RK. Asia Pacific journal of clinical nutrition 2004; 13(Suppl):S110.

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

1. Lukaczer DO, Lerman RH, Darland GK, Liska DJ, Schiltz BC, Tripp ML, Bland JS. FASEB Journal 2004; 18 (4-5): pAbst. 354.10.

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 pineappe that may help provide you with relief for common everyday aches and pains

Thank You – Questions?

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www.hchs.edu • 800-290-4226
1204-D Kenesaw • Knoxville, TN 37919
E-mail: studentservices@hchs.edu