Anti-inflammatory Options: VIOXX and other Selective COX-2 Inhibitors v Natural Agents

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Question: How does the controversy about Vioxx, and other selective COX-2 inhibiting anti-inflammatory medications, change the recommendations on the use of anti-inflammatory agents?

Answer: It does not change the recommendations on the use of natural anti-inflammatory agents, such as high-bioflavonoid botanicals (i.e., Zingiberer officinale, Curcuma longa, Salix nigra/alba, Boswellia serrata, etc.), bioflavonoids (i.e., quercetin, rutin, hesperidin, etc.), proteolytic enzymes (i.e., trypsin, chymotrypsin, etc.) and essential fatty acids (i.e., EPA, DHA, GLA, etc.), other than reinforcing and supporting their efficacy as better alternatives in the management of many chronic inflammatory conditions. The recent news on pharmaceutical selective COX-2 inhibitors confirms previous research, which pointed to problems such as hyper-coagulation and hypertension arising from inhibiting COX-2 **selectively** (without inhibiting COX-1). See abstracts below.

Some important facts about natural anti-inflammatory compounds:

1. Natural anti-inflammatory compounds do not act as **selective** COX-2 inhibitors. They constitute an array of compounds that have a combination effect of inhibiting both COX-2 and COX-1, in addition to the LOX and phosholipase A2 enzymes. It is important that they also inhibit COX1 to some degree because this provides a mild blood thinning effect, counteracting the blood clotting effect of COX-2 inhibition. In this sense, they act similar to non-selective NSAID's (such as Naproxen, Motrin), but they have many additional benefits and do not promote G.I. bleeding.
2. Natural anti-inflammatory agents may be a better choice for blood thinning than aspirin, which acts predominantly as a selective COX1 inhibitor. Aspirin binds to the platelets in an irreversible manner, with serious risk of bleeding in case of overdose, and strong GI side-effects. This is not the case with the natural anti-inflammatory agents.
3. Natural anti-inflammatory compounds prevent the expression of "inducible" COX-2 caused by oxidative stress, due to the potent antioxidant effect of many of these compounds.
4. Proteolytic enzymes help reduce acute and chronic inflammation in ways unrelated to COX inhibition, such as the molecular debribement of the chemotaxis-promoting protein fragments and inflammatory mediators liberated from injured cells. These enzymes also have additional anti-thrombotic and anti-inflammatory effects.

Please see the table below for a more complete understanding the differences between the compounds mentioned above.

Anti-inflammatory compounds	COX1 inhibition	COX2 inhibition	Reduce inducible COX2 expression	LOX inhibition	Anti-oxidant effect	Other anti-inflammatory effects	GI side effects	Increases clotting and blood pressure
Natural anti-inflammatory compounds	mild	yes	yes	yes	yes	proteolytic enzyme actions	unlikely	No
NSAID's (Naproxen, Motrin)	yes	yes	no	no	no	no	yes	No
Selective COX-2 inhibitors (Vioxx, Celebrex, Bextra)	no	yes	no	no	no	no	mild	Yes
Aspirin	yes	very mild	no	no	no	no	strong	No

In addition to using natural anti-inflammatory compounds, it is important to emphasize correcting other

aspects of the inflammatory process with nutritional and preventive methods, including:

1. The various causes of inflammation (infections, leaky gut, toxic metals, diabetes, oxidative stress, etc.)
2. Imbalances in the body stores of EPA/DHA/GLA versus AA, which are the substrates of the COX1 & 2 enzymes
3. Suboptimal adrenal production of cortisol due to chronic stress.

CONCLUSION:

It should be stressed that natural anti-inflammatory compounds do not have the pro-clotting effects of **selective** COX-2 inhibitors and have a milder blood thinning effect than aspirin. They reduce inflammation effectively, and are unlikely to cause GI side-effects.

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SUPPORTING ABSTRACTS:

Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. Mukherjee D. Biochem Pharmacol. 2002 Mar 1;63(5):817-21. Division of Cardiology, University Hospital, University of Michigan Health System, B1-F245, 1500 East Medical Center Drive, Ann Arbor, MI 48103-0022, USA

"Selective cyclooxygenase-2 (COX-2) inhibitors were developed as a response to the gastrointestinal toxicity of conventional nonsteroidal anti-inflammatory agents (NSAIDs). However, COX-2 inhibitors decrease vascular prostacyclin (PGI(2)) production and may disrupt the homeostatic mechanisms that limit the effects of platelet activation. Basic and clinical data raise concerns about a potential prothrombotic effect of this class of drugs. The widespread popularity of these agents mandates their prospective evaluation in patients with cardiovascular diseases or who are at risk for cardiovascular events".

Effect of CSIs (cyclooxygenase-2 selective inhibitors) on blood pressure. Johnson DL, Hisel TM, Phillips BB. University of Iowa Hospitals and Clinics, Iowa City, IA, USA.

OBJECTIVE: To evaluate the effect of cyclooxygenase-2 selective inhibitors (CSIs) on blood pressure. DATA SOURCES: Clinical literature accessed through MEDLINE (1966-May 2002). Key search terms included COX-2 selective inhibitors; anti-inflammatory agents, nonsteroidal; celecoxib; rofecoxib; and hypertension. DATA SYNTHESIS: Data from prospective studies on the effects of CSIs on blood pressure are conflicting. Several studies have reported increased blood pressure as an adverse effect of CSIs. CONCLUSIONS: Additional studies are needed to evaluate the effects of CSIs on blood pressure. CSIs should be used with caution in hypertensive patients and blood pressure monitored closely if a CSI is indicated.

Spontaneous reports of hypertension leading to hospitalisation in association with rofecoxib, celecoxib, nabumetone and oxaprozin. Brinker A, Goldkind L, Bonnel R, Beitz J. Division of Drug Risk Evaluation, Office of Drug Safety, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland 20875, USA. brinkera@cder.fda.gov.

BACKGROUND AND OBJECTIVE: Data on file with the US FDA, and other published studies, suggest that the selective cyclo-oxygenase (COX)-2 inhibitor NSAID rofecoxib has a greater hypertensive adverse effect than other NSAIDs, including celecoxib. In this study we describe a pharmacoepidemiologic analysis of spontaneous adverse event reports of acute, clinically serious hypertension (as defined by hospitalisation) reported in association with rofecoxib, celecoxib, nabumetone and oxaprozin. The objective of this analysis is to assess whether postmarketing data are consistent with results of clinical trials. We also collapse cases into series for the identification of possible risk factors for clinically severe, NSAID-associated hyper-

tension. METHODS: Domestic (US) cases of apparently unconfounded, acute hypertension leading to hospitalisation were collected and reviewed from the spontaneous adverse events database of the FDA for rofecoxib, celecoxib, nabumetone and oxaprozin for the initial 3 years of marketing. Drug use data for the same intervals enabled calculation of reporting rates. RESULTS: In an analysis of reporting rates, hospitalisation for acute blood pressure (BP) elevation was reported more frequently (3.8-fold) for rofecoxib compared with celecoxib. A total of 34 cases are collapsed into case series. No cases were identified for either nabumetone or oxaprozin. Inspection of reviewed cases for celecoxib and rofecoxib suggest that these patients (average age 72 years) were potentially high-risk candidates for NSAID therapy. DISCUSSION AND CONCLUSION: During early marketing, hospitalisation for acute BP elevation appears to have been reported more frequently for rofecoxib compared with celecoxib. This is consistent with clinical trial data on file with the FDA, and other published studies that found rofecoxib to have a greater effect on BP than other NSAIDs, including celecoxib. This finding may be particularly relevant in older patients given the prevalence of hypertension and cardiovascular disease in this age group.

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