Anti-Inflammatories:
Making an Informed Decision

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Chronic inflammatory disease affects a significant part of the North American population and is the number one cause of disabilities.[1]

Cyclo-oxygenase type 1 (COX-1) mediates the production of prostaglandins responsible for the maintenance of the GI mucosa integrity, whereas COX-2 is related to prostaglandins that mediate pain and inflammation. COX-2 is also expressed in normal endothelium leading to vasodilatation and other effects thought to be antiatherogenic. Chronic anti-inflammatory therapy is limited by their known side-effects in the GI system caused by COX-1 inhibition. Specific COX-2 inhibitors (COXIBs) were developed to provide significant anti-inflammatory activity without deleterious GI side effects.

Epidemiological and randomized clinical trials (RCTs) suggested an increase in the incidence of MI with the use of COXIBs. The following is a summary of the available evidence.

Observational studies

Solomon, *et al*[2] published a case-control study with > 54,000 individuals divided into three categories:

1. No exposure to COXIBs
2. Exposure to celecoxib
3. Exposure to rofecoxib

Exposure to celecoxib compared to no exposure did not show any increase in MI. Exposure to rofecoxib was associated with a marginal increase in MI. Graham, *et al*[3] evaluated the risk of MI and sudden cardiac death in individuals exposed to COXIBs and NSAIDS through a case-control study in approximately six million individuals. Compared to a remote exposure to anti-inflammatories, current users of naproxen and rofecoxib ≥ 25 mg q.d. had a marginal, odds ratio (OR) of 1.14 (95% CI 1.00 to 1.34, p = 0.05) and a significant three-fold (95% CI 1.09 to 8.31, p = 0.03) increase in MI, respectively.

RCTs

Published RCTs can be classified into two major topics:

1. Trials evaluating GI endpoints
2. Prevention of colorectal adenoma

The former evaluated significant number of patients ranging from approximately 8,000 to 34,000. Only the Vioxx Gastrointestinal Outcomes Research (VIGOR)[4] trial (using rofecoxib) showed an increase in the incidence of MI. Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[5] (lumiracoxib), Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL)[6] (etoricoxib) and Celecoxib Long-Term Arthritis Safety Study (CLASS)[7] (celecoxib) did not

show differences in MI. This raised the question that naproxen (the control arm used in VIGOR) was of some protection against MI. The latter gathered approximately 2,500 to 3,500 patients. The Adenomatous Polyp Prevention on Vioxx (APPROVe)[8] and Adenoma Prevention with Celebrex (APC)[9] trials revealed a significant increase in the incidence of MI with rofecoxib and celecoxib, respectively. The Prevention of Colorectal Sporadic Adenomatous Polyps (preSAP)[9] trial did not show any difference in CV endpoints between celecoxib and placebo. However, the placebo event rate in preSAP was higher than in APC and might explain its negative result.

Meta analyses

Juni, *et al*[10] evaluated the risks of CV events in patients exposed to celecoxib vs. placebo or NSAIDs. Eighteen trials were identified revealing a relative risk (RR) for MI of 2.30 (95% CI 1.22 to 4.33). Matchaba, *et al*[11] plotted 21 studies with lumiracoxib, most of them with a short duration. It revealed no significant difference in the incidence of CV endpoints vs. placebo, naproxen and non-naproxen NSAIDs. Kearney, *et al*[12] evaluated COXIBs and NSAIDs on the risk of vascular events. After plotting results from 121 trials, there was an increase in the incidence of MI in patients allocated to COXIBs with a RR of 1.86 (95% CI 1.33 to 2.59, p=0.0003). Interestingly, this meta-analysis also showed similar risks of MI in patients taking high-dose diclofenac and ibuprofen but not naproxen. White et al[13] evaluated 39 studies of celecoxib with NSAIDs or placebo. The incidence of CV events was not significantly different; however, the majority of the trials were short-term (ranging from six to 12 weeks of follow-up) not allowing a proper exposure to celecoxib in order to evaluate its association with CV events.

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Guidelines

COXIBs being associated with CV events prompted publication of guidelines from a Consensus Panel in Canada[14] and professional societies of Cardiology.[15] They all recommend caution in the use of COXIBs and urge physicians to balance the risks/benefits when prescribing pain-killer medications. The following is a summary of their recommendations:

1. Initial approach:
   a. Physical therapy
   b. Heat/cold
   c. Orthotics
2. Acetaminophen/ASA at lowest efficacious dose
3. Consider short-term narcotics in spite of the risk of addiction
4. Long-term:
   a. NSAIDs. Naproxen appears to be the first choice
   b. Consider that the treatment of pain may be at cost of increased CV events
   c. If symptoms are not properly controlled consider subsequent steps involving drugs with increasing degrees of COX-2 inhibition

d. Consider acetaminophen for patients with previous GI bleed on ASA/NSAIDS
e. PPIs should be considered for patients taking low-dose ASA
f. Renal function and BP should be monitored Dx

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