Editorial

Hyperbole, Innuendo, and Fact: The Strange Case of COX-2 Selective Inhibitors

It is about time. In this issue of *The Journal*, Tannenbaum, *et al* have "taken the bull by the horns" and have produced a thoughtful and up to date (at least as of this past summer) analysis[1] of the conundrum that has been foisted upon the chronic pain community of practitioners, academics, and their patients by a consortium of possibly irresponsible clinical investigators from other disciplines, particularly cardiologists, pontificating pundits who have taken advantage of poorly understood science to castigate both the pharmaceutical industry and hard-working and well-meaning regulators of the drug industry around the world, while scaring patients and their doctors. All of which has been aggravated by the decision of one company to voluntarily remove rofecoxib from the commercial markets, ostensibly to protect themselves from devastating court cases. In the end, much of this noise was precipitated by the initial way in which the cyclooxygenase-2 (COX-2) selective inhibitors were marketed. The general broad attempt to sell these drugs diminished the message regarding their important benefit for certain patients. It is important to remember: When these drugs were first launched, patients previously unable to tolerate the nonselective nonsteroidal antiinflammatories (NSAID), due to their inherent mechanistically-based risk for potential gastrointestinal (GI) adverse events, could now use analgesic and antiinflammatory drugs chronically. As Tannenbaum and colleagues rightly point out, it was clear that patients who were at particular increased risk for potential GI adverse events would derive a benefit of decreased pain with the COX-2 selective inhibitors that was equal to a nonselective NSAID in the context of increased GI safety[1]. Unfortunately, the companies that manufactured these products developed a much broader marketing message, leading many to perceive that profits were being pursued without real concern for the appropriate use of these drugs.

The COX-2 selective drugs have been controversial from their initial development[2-9]. Although the science is reasonable, the utility of the therapy was lost in the ubiquitous marketing message assailing the general public. Evidence reveals that there are 2 COX enzymes that produce different effects, mostly through activation of the different enzymes by different stimuli[2-4]. With time, it has become clear that COX-1 is primarily constitutive in activity, while COX-2 is upregulated in inflammation and pain. However, there is also important evidence demonstrating that COX-2 activity is also constitutive in the brain and kidneys, as well as temporally involved in ovulation[3,4]. Much evidence has shown that inhibition of COX-2 activity is important to decrease pain and inflammation at both the peripheral tissue level and in the central nervous system[10]. There is also good evidence that upregulation of COX-2 activity is associated with production of tissue factors, perhaps related to angiogenesis, suggesting that inhibition of COX-2 may have some benefit in altering the biology of certain cancers[3,4]. This evidence has been supported by clinical studies as well. Further, there is some suggestion that COX-2 activity and inflammation also may play a role in progressive Alzheimer's disease.

Such potential benefits, as with all therapies, are tempered by potential side effects. The well known increased hazard rate related to nonselective NSAID of inducing GI damage was lessened in patients treated with the selective COX-2 inhibitors[11,12]. This GI benefit was observed in studies in which the COX-2 selective inhibitors were dosed at twice the maximally approved doses for chronic use in arthritis as compared with the standard doses of the active comparator drugs including naproxen, diclofenac, and ibuprofen. Unfortunately, this benefit with the COX-2 selective drugs was not also realized in the context of renal effects, hypertension, edema, and now cardiovascular (CV) events. The mechanisms behind the renal effects of both the nonselective and selective NSAID are now better understood[13-15]. Unfortunately, there remains significant contro-

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versy surrounding the causes of the now observed potential for any COX-2 inhibitor, be it nonselective or a selective NSAID, to induce CV events. Given the observed effects on the kidney and salt and water handling, as well as risk for hypertension with these drugs, the issues of increased risk for congestive heart failure with therapy is not as difficult to explain.

However, it is unclear whether the primary cause of the observed increased risk with such drugs is the fact that COX-2 selective drugs are COX-1-sparing (leading possibly to a coagulation imbalance in the right patient, which might lead to the increase in CV risk), or whether there is other confounding evidence pointing to other effects. Such evidence includes the similarity in the slopes of the curves of the post-hoc adjudicated outcomes defined in the CLASS trial depicting similar event rates for CV events of celecoxib 400 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID[10], and the lack of statistical significance in results of the TARGET trial between the event rates of high-dose lumiracoxib compared with ibuprofen 800 mg TID and naproxen 500 mg BID[14,15]. Thus, these data suggest that drugs that are COX-1-sparing, as well as nonselective NSAID, have event rates for CV signals similar to secondary outcomes in prolonged randomized clinical trials. Unfortunately, none of these trials included a placebo arm, and appropriately so, since they were studying patients with symptoms of pain.

In studies of valdecoxib and its intravenous form, parecoxib, in patients undergoing coronary artery bypass graft procedures, there was a clear increased risk of CV thromboembolic events with the COX-2 selective inhibitor as compared with standard care, yet all patients received both low-dose aspirin and clopidogrel[15]. Thus correcting the lack of effect on COX-1 activity with the low-dose aspirin did not appear to protect against a CV event, suggesting that the effect on inhibition of COX-2-generated prostacyclin cannot be the full explanation of the observed adverse outcome.

More recently, the prospective studies of the COX-2 selective inhibitors, which were designed to analyze their potential to prevent progression of recurrent spontaneous colonic polyps, would have demonstrated definitive evidence of the potential effect of these drugs in modulating cancer risk, allowed for longterm prospective prevention trials comparing these selective NSAID with true placebo[16,17].

As summarized in Tannenbaum, *et al* in this issue[1], these results were certainly not definitive proof that this class of drugs induced thromboembolic events. Of 3 trials in studies designed to ascertain the effect of these drugs on recurrent colonic polyposis, the trial of rofecoxib versus placebo demonstrated a clear 2-fold increased CV risk as determined by risk of myocardial infarction, sudden cardiac death, and stroke, but the trials including celecoxib were less clear and required congestive heart failure to be included in the composite outcomes to achieve statistical significance. This represents, again, a moving away from the original proposed causal imbalance hypothesis and points toward an understanding that these events are likely driven by a complex series of effects induced by all NSAID, including the facts that these drugs inhibit COX-2 activity, that they alter salt and water balance, that they can induce small but chronic increases in systolic blood pressure, and that they may have different effects on nitric oxide, tissue proliferation factors and endothelial function, as well as on blood flow to certain tissues[18-22]. Without trials designed to study these questions, we may never know the mechanisms behind these clinical observations.

Unfortunately, the ability to do such clinical studies has been limited by the inappropriate furor that ensued once Merck removed rofecoxib from the market. Further, a meeting in February 2005 called by the US Food and Drug Administration (FDA) was hijacked by groups of nonclinicians who maintained that only randomized control trial evidence should be considered. However, they did not admit that such evidence was flawed, i.e., it represented secondary outcomes, was adjudicated evidence, the trials were not powered to look at these issues, and thus there were not enough patients in the trials to provide definitive evidence, and overall in each trial there were very few events concerning a medical event that is very common in these patients within the US.

The overall epidemiological evidence, which was tacitly ignored by the FDA Advisory Committee in February, provides a different view of this problem. In trials with large patient exposures it appears that all of the NSAID may have a risk of thromboembolic events[23-25]. The FDA is charged to consider all available evidence; this was confirmed when they announced that they now require that all drugs, selective and nonselective NSAID, be further labeled with a box warning for CV risk, admitting clearly that they do not distinguish, based on the data at hand, that there is increased risk of the COX-2 selective inhibitors above that observed with the nonselective NSAID. It is a shame that the convened committee was as biased as it was. The database observed in both the CLASS and TARGET trials is the largest and longest concerning the nonselective drugs ibuprofen, diclofenac, and naproxen, all of which demonstrated similar hazard rates for all of the study drugs, which are no different than observed with either celecoxib or lumiracoxib. Thus it is possible that there is a different effect of rofecoxib than that observed with the other COX-2 selective drugs, which might be related to its propensity for a dose response for hypertension and edema absent from the other drugs[26-29]. This is not to say that the COX-2 selective inhibitors, as well as the nonselective NSAID, do not induce hypertension and/or edema in some patients. The rate of these events for all these drugs is about 1%–3%; however, there is little evidence to demonstrate a dose response. The situation was very different with rofecoxib, which demon-

strated an increasing rate as the dose approached 50 mg/day.

Thus, given all the hype and innuendo that has occupied the popular press, it is nice to see a considered effort by experts in musculoskeletal medicine to grapple with the practical issues that are confronting the community about the use of these drugs[1]. The recommendations made by the group are reasonable and they consider the facts; and to their credit, the committee does not waste time considering the hyperbole and innuendo. It is about time that professionalism, science, and the needs of our patients are brought forth into this discussion. I wonder if anyone will listen.

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