Cardiovascular Events: A Class Effect by COX-2 Inhibitors

Leila Fernandes Araujo, Alexandre de Matos Soeiro,
Juliano de Lara Fernandes, Carlos Vicente Serrano Júnior
Instituto do Coração do Hospital das Clínicas – FMUSP - São Paulo, SP - Brazil

Non-steroidal anti-inflamatories (NSAIDs) are widely used in the treatment of post-surgery pain[1], osteoarthritis[2], rheumatoid arthritis[3] and muscle-skeletal pain[4,5], in different conditions. Major effects are: anti-inflammatory, analgesic, and antipyretic[6]. Generally speaking, such effects are associated to the inhibition of the enzyme cyclooxygenase (COX). COX catalyzes the transformation of arachidonic acid into different lipid mediators called prostaglandins and thromboxanes[2]. Those substances play a relevant hemostatic role in protecting gastric mucosa, renal physiology, and platelet aggregation, in addition to having their production induced under conditions such as inflammation and cancer[7]. Two isozymes – or forms of the COX enzyme – have been characterized: cyclooxygenase-1 (COX-1) and cycloxygenase-2(COX-2)[2]. COX-1 has shown to be constitutive in all body tissues[8]. It is the only isozyme found in platelets, leading to the formation of TXA2. It is found in gastric mucosa, among other tissues, where it catalyzes the biosynthesis of cytoprotective prostaglandins in vascular endotelium and in renal tissue.

Finally, it is believed that COX-1 also plays a role in pathologic conditions such as inflammation[7]. On the other hand, COX-2 is shown to be increased in inflammatory and cell transformation processes particularly[9-12], although its constitutive expression has been demonstrated in some CNS and kidney tissues[7].

The first NSAIDs to be developed were the classic, non-specific NSAIDs, acting as inhibitors for both COX isozymes.[7] Despite the proven anti-inflammatory efficacy they are meant to deliver, continued use is limited due to gastro-intestinal adverse effects[8], such as dyspepsia and abdominal pain, in addition to gastro-duodenal perforation or bleeding at a lower scale[2]. Those first NSAIDs include: indometacin, naproxen, ibuprofen, and nabumetone, among others[6]. Against such scenario, a sub-class of NSAIDs was developed – the specific COX-2 inhibitors, for the purpose of reducing inflammation as efficaciously while free from COX-1 inhibitors gastro-intestinal effects[2,5,7,8,13,14]. Among those: rofecoxib, celecoxib, etoricoxib, valdecoxib and lumiracoxib[6].

That creation of a subclass was based on the assumption that COX-1 was a constitutive enzyme, while COX-2, an enzyme induced at pathologic situations[2,7]. Such classification woud, however, stand for a dangerous simplification of the real scenario[2]. A number of studies were developed – as of the introduction of specific COX-2 inhibitors in the market – associating their anti-inflammatory potential to gastrointestinal safety. From then on, data have been made available to suggest class potential to increase cardiovascular adverse events[7].

The first study to point out such risks was published in 2000, by comparing rofecoxib to naproxen[8]. A number of other publications followed, all reporting controversial results on the potential cardiovascular risk posed by rofecoxib and the specific COX-2 inhibitors, until the medication was withdrawn from the market in September, 2004, immediately after the early termination of a study on colonic adenomas[15]. The study - *Vioxx Gastrintestinal Outcomes Research* (VIGOR)[8] – reported a 3.9 significant increase in thromboembolic adverse effects in the groups being administered rofecoxib as compared to the placebo group. Right afterwards, significantly increased risk of cardiovascular adverse events was also detected with the administration of celecoxib as compared to placebo, in addition to data on valdecoxib when compared to placebo.

Despite the high inconsistency in the results published to date, most recent studies on the cardiovascular safety of COX-2 specific inhibitors provide evidence of their potential cardiovascular adverse effects[1,13,14]. Questioning on such potential was raised after the publication of a study comparing rofecoxib and naproxen, as mentioned earlier. Delayed elucidation was due to the non-existence of multicenter, randomized, extensive, controlled, long-term studies to directly evaluate the cardiovascular effects of those agents[16-18].

Mailing address: Carlos Vicente Serrano Jr • Av. Dr Enéas de Carvalho Aguiar, 44 – 05403-000 – São Paulo, SP - Brazil
E-mail: carlos.serrano@incor.usp.br

The present paper has the purpose of illustrating the role played by COX-2 enzyme and its inhibitors on the vascular system. In addition, the paper will present literature review on such role, with a descripton of major studies involved in demonstrating the cardiovascuolar effect of those medications. Finally, recommendations by the *American College of Cardiology* on the use of specific COX-2 inhibitors will be pointed out.

Non-Steroidal Anti-inflammatories: Action Mechanisms

There are three classes of cyclooxygenase inhibitors. The differences between them are based on the selectivity regarding the different isozymes. Those classes are: 1) aspirin, 2) indometacin, and other traditional NSAIDs, and 3) COX-2 specific inhibitors. For the purpose of assessing cyclooxygenase selectivity the assays are based on the production of thromboxane B_2 during clotting - to assess COX-1 platelet activity - and on the production of prostaglandin E_2 in bacteria lipopolysacharides; COX-2 activity in monocytes is assessed based on total blood assays[2]. However, the prostanoids responsible for vascular homeostasis maintenance are thromboxane A_2 (TXA_2) and prostaglandin I_2 (PGI_2).

Platelet synthetized TXA_2 has its production triggered by platelet activation, leading to platelet aggregation, vasoconstriction, and smooth muscle proliferation[7]. Therefore, it is an important mediator of acute vaso-occlusive events associated to COX-1 enzyme. Increased production of TXA_2 metabolites was reported in patients with unstable angina, during episodes of chest pain, and was also associated to increasing risk of adverse cardiovascular events in patients with peripheral artery diseases[7].

PGI_2, or prostacyclin, in its turn, is the main product from vascular endothelium cells, whose production is activated by COX-2. PGI_2 effects consist in powerful vasodilation and inhibition of platelet aggregation, as well as proliferation of vascular smooth muscle. Having that in mind, some authors suggest that prostacyclin is an anti-proliferative eicosanoid, and the relative deficiency of COX-2-derived prostacyclin may predispose atherogenesis.[19] However, prostacyclin combined with prostaglandin E_2 (PGE_2) has been referred to as a pro-inflammatory mediator activated by the expression of COX-2 during inflammatory stimulus. Thus, the impact of COX-2 inhibition on the progression of atherosclerosis has been kept a controversy.[7]
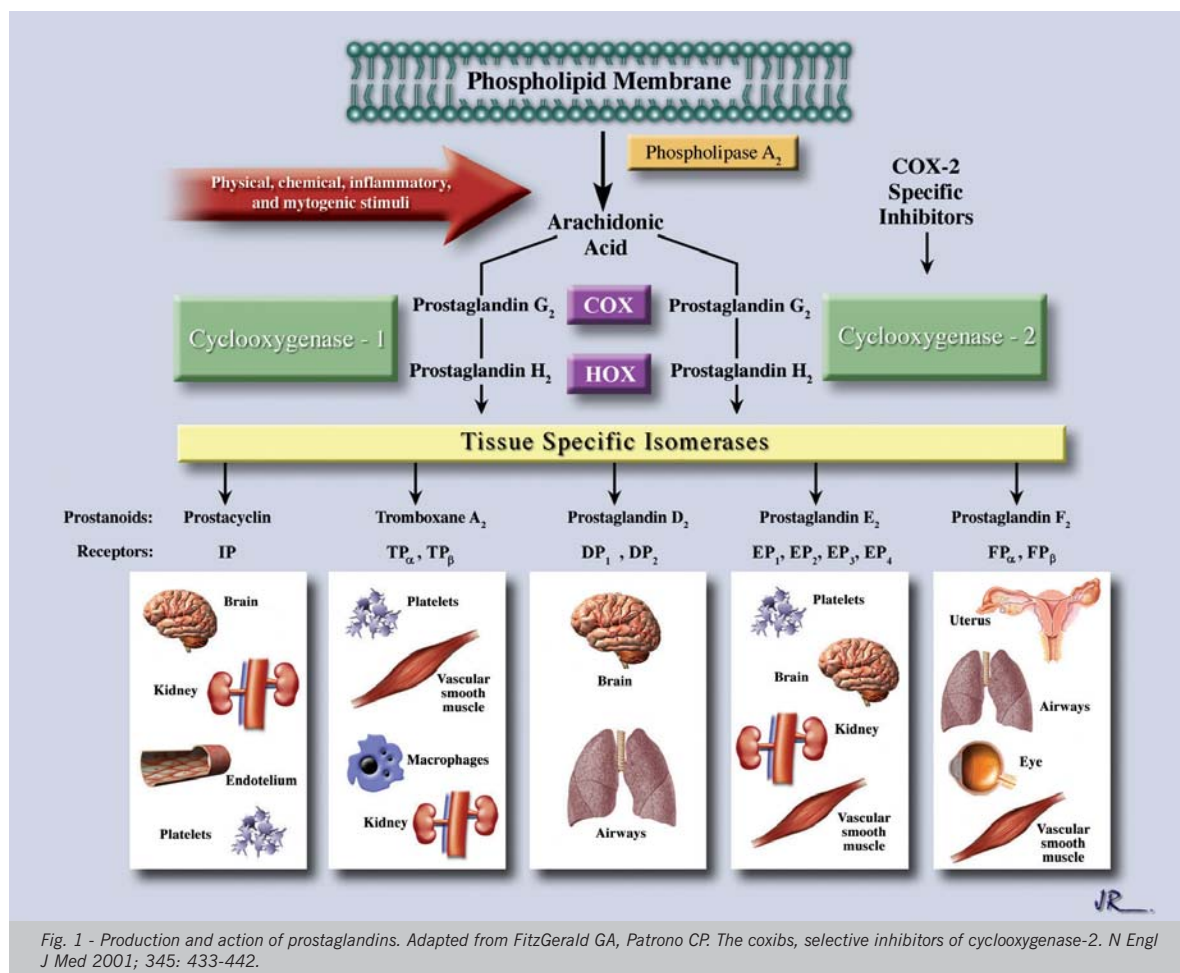

Fig. 1 - Production and action of prostaglandins. Adapted from FitzGerald GA, Patrono CP. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345: 433-442.

When analyzing classes of cyclooxygenase inhibitors, aspirin is shown to trigger a covalent change in the enzyme, irreversibly blocking its activity. Since human platelets express COX-1 only, aspirin blocks that enzyme in an irreversible way. Consequently, TXA_2 production is blocked. Functional inhibition of TXA_2-dependent platelet activation requires the supression of above 95% capacity in generating that prostanoid; only aspirin has proven to be able to sustain such effect during administration intervals. {0>Apesar de também provocar supressão de prostaciclina, a supressão concomitante de tromboxano predomina e o efeito final é cardioprotetor[7].<}0{>Although prostacyclin suppression is also provoked, concurrent thromboxane suppression predominates and the final outcome is cardioprotective[7].

A classe de AINEs tradicionais inibe a produção de TXA_2 e de prostaciclina a um grau semelhante - apesar de haver pequenas variações na seletividade bioquímica por cada isoforma entre os diversos medicamentos - e este efeito é reversível durante o intervalo de administração.<}0{>Traditional NSAIDs inhibit TXA_2 and prostacyclin production at similar level, although there are slight variations in biochemical selectivity by each isozyme in the different drugs – a reversible effect during administration interval.<0} Therefore, intermitent inhibition of platelet function would not result in final cardioprotective effect.

Doubt still remains, though, on the cardiovascular effect of protacyclin suppresion with no concurrent suppression of thromboxane, as determined by COX-2 specific inhibitors. Studies on the deletion of genes that codify prostacyclin receptors (IP) and PGE_2 (EP_2) in rats did not show the occurrence of spontaneous thrombosis, although the animals whose genes for IP had been deleted
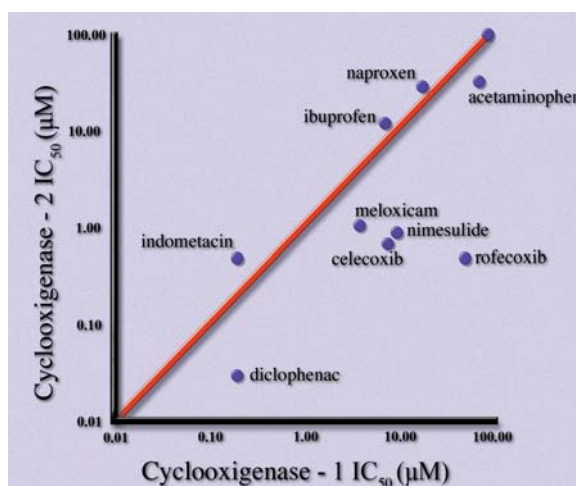

Fig. 2 - Concentrations of different medications required for 50% inhibition of cyclooxigenase-1 and cyclooxigenase-2 em 50%, in total blood assays. Medications under the equivalence indicating line are more powerful COX-2 inhibitors as compared to those above the line. Adapted from FitzGerald GA, Patrono CP. The coxibs, selective inhibitors of cycloxygenase-2. N Engl J Med 2001; 345: 433-442.

presented increased responsiveness to thrombotic stimuli[20,21]. So, some increase in cardiovascular adverse effects would be expected from predisposed individuals.

A number of clinical assays were carried out as of the availability of COX-2 specific inhibitors, with the purpose of investigating their analgesic and anti-inflammatory efficacy, in addition to adverse effects. The concern in regard to the cardiovascular effects from that class was raised in 2000, after the VIGOR[8] study was published with its results seen as unexpected until that point in time. It has been proposed that such effects may be due to: 1) prostacyclin inhibition, with consequent inactivation of a primordial endothelium defense mechanism against platelet aggregation, hypertension, and atherosclerosis, and 2) the promotion of some imbalance that may favor vasoconstriction[17]. However, clinical trials take turns in either evidencing cardiovascular risk or denying it.

Clinical Experiences with COX-2 Inhibitors

First Suspicions of Cardiovascular Adverse Effects

After COX-2 specific inhibitors were made available a number of studies have been carried out with the purpose to prove their high gastrointestinal safety level. However, the same studies have raised doubts concerning their cardiovascular safety level. The first to raise those doubts was the VIGOR[8] study, published in 2000, with the purpose to compare the gastrointestinal toxicity level of 2 NSAIDs: rofecoxib and naproxen. Researchers recruited 8,076 patients with rheumatoid arthritis for a prospective, double-blind, randomized study. Patients' average age was 58 years old, 80% females, all submitted to 9 months of treatment in average. Patients submitted to treatment with aspirin were excluded from the study.

A 50 mg daily dose Rofecoxib – a COX-2 specific inhibitor – was compared to a 500 mg dose of naproxen administered twice a day to compare anti-inflammatory efficacy and the occurrence of gastro-duodenal obstruction or perforation, upper gastrointestinal bleeding, and symptomatic gastro-duodenal ulcer. Both medications reported equivalent efficacy level. The incidence of gastrointestinal events, though, was: 2.1 events for every 100 patients/year for rofecoxib against 4.5 events per 100 patients/year for naproxen. Such result supported the assumption of the higher gastrointestinal safety level by rofecoxib, but did bring to light another alarming piece of information. The incidence of acute myocardial infarction (AMI) was significantly lower in the group being administered naproxen: 0.1% for naproxen versus 0.4% for rofecoxib, with relative risk at 0.2.

The study points out that such difference in AMI incidence was due to the high rate of AMI reported by the 4% higher risk population for coronary diseases. That group would have had the indication for treatment with aspirin as secondary prophylaxis. The difference between

AMI incidence levels for each of the drugs in the population not in need of that prophylaxis would not have been significant. In addition, the study also states that naproxen causes an 88% inhibition of platelet aggregation, similar to aspirin, a protective effect also suggested by Solomon and collaborators[22] and Capone and collaborators[23]. Therefore, effects from regular use of that drug would have cardioprotective effect, as opposed to rofecoxib, which could explain the difference between the two AMI rates as mentioned earlier.

Another study, in the same year, had the purpose of similar comparison. A prospective, double-blind, randomized, controlled study entitled *Celecoxib Long-term Arthritis Safety Study* (CLASS)[5] monitored 8,059 patients with osteoarthritis or rheumatoid arthritis for six months in their treatment. The intervention consisted in the administration of 400 mg of celecoxib twice a day, 800 mg of ibuprofen three times a day, or 75 mg of diclofenac twice a day. The occurrence of upper, symptomatic gastrointestinal ulcers and their complications, in addition to other adverse effects would be investigated. The use of aspirin for cardiovascular prophylaxis was allowed, contrarily to the other study. Patients' average age was approximately 60; nearly 70% were females.

Researchers concluded that when compared to ibuprofen or diclofenac, celecoxib showed to be associated to lower incidence of symptomatic ulcers and consequent complications, in addition to other clinically important toxic effects. In the two comparisons, the analysis of cardiovascular adverse effects pointed out similar incidence levels, both in regard to cardiovascular effects in general, as to specifically AMI. For those patients who were not on aspirin AMI was reported to be 0.3% in both comparisons, against 0.1% also in the two comparisons for those on aspirin.

In the following year[2], an article published by FitzGerald pointed out relevant differences between the two studies that could account for the inconsistent results. The differences included concurrent use of aspirin, patients's substratum and the non-specific NSAID used[2]. Rofecoxib and celecoxib supress prostacyclin equivalently; however, concurrent use of aspirin may have excluded evidence of such phenomenon, particularly in patients with higher risk of thrombotic events. It still remains unclear whether the concurrent use of aspirin anihilates the gastrointestinal safety of COX-2 specific inhibitors; however, such combination is preferred to that of aspirin and ibuprofen, since ibuprofen blocks aspirin access to its site in COX-1, with consequent reduction of anti-aggregating activity[2].

Additionally, only 27% of patients in the CLASS study had been diagnosed for rheumatoid arthritis versus all those diagnosed in VIGOR. Epidemiologic analyses demonstrate that the incidence of acute thrombotic events reports a 33% increase in such patients when compared to patients with osteoarthritis or to the general population[7]. Based on such findings, it is possible to believe that the

population under study being administered rofecoxib would be more exposed to a prostacyclin-dependend mechanism, which would support the louder alarm by the VIGOR study.

Ultimately, naproxen differences that safeguard cardiovascular safety when compared to other non-specific NSAIDs provide limited evidence. Some studies suggest that naproxen has cardioprotective effects.[8,22] There is evidence of 8-hour maximum sustained inhibition of thromboxane platelet production in volunteers being administered naproxen[24]. On the other hand, other studies deny any cardioprotective effect.[25,26] Epidemiologic data are restricted, and the issue is still pending, with no satisfactory conclusion.

Topol and collaborators[4] have compared results from four studies on COX-2 specific inhibitors - celecoxib and rofecoxib – to those of a placebo group in a meta-analysis on primary prevention with aspirin. Yearly rate for AMI in the meta-analysis placebo group was 0.52% versus 0.74%, in the rofecoxib group (P=0.04, when compared to placebo) and 0.80%, in the celecoxib group (P=0.02, when compared to placebo). Although aware of the limitations for the comparison of populations in different studies, researchers obtained data to point out the pro-thrombotic effect of COX-2 inhibitors as responsible for the increased rates of adverse cardiovascular events in those groups.

Lumiracoxib was not associated to the increase of cardiovascular events

Farkouh and collaborators published a cardiovascular and gastrointestinal safety analysis of COX-2 inhibitor lumiracoxib as compared to naproxen and ibuprofen in *Therapeutic Arthritis Research and Gastrintestinal Event Trial* (TARGET)[27]. The randomized, controlled assay included 18,325 patients with osteoarthritis. All patients were over 50 years old, were being administered 400 mg of lumiracoxib twice a day, 500 mg of naproxen twice a day, or 800 mg of ibuprofen three times a day. After a one-year follow-up, the cardiovascular outcome - which included AMI – did not change significantly when comparing lumiracoxib and the other agents, irrespective of the use of aspirin. However, a non-significant increase was found for AMI risk with lumiracoxib when compared to naproxen in patients who were not being administered aspirin. The difference was seen as fortuitous, or to the anti-thrombotic effect of naproxen, as discussed earlier. So, lumiracoxib was found to be the ideal treatment for patients with osteoarthritis by TARGET researchers.

Studies on rofecoxib reported controversial results

A studied that followed had the purpose to determine whether patients on rofecoxib reported more thrombotic

cardiovascular events as compared to patients on placebo, naproxen or other traditional, non-specific NSAIDs (diclofenac, ibuprofen and nabumetone) through a combined data analysis of over 28,000 patients[28]. Twenty-three Phase IIb-V, randomized, double-blind, controlled clinical trials were carried out. Study outcome consisted in the grouping of events as defined by the *Anti-Platelet Trialists' Collaboration* (APTC): cardiovascular, hemorrhagic, and unknown cause deaths, non-fatal myocardial infaction, and non-fatal cerebrovascular accidents (CVA).

While comparing rofecoxib to placebo, relative risk to one of the outcomes was 0.84 (CI 95%: = 0.51 – 1.38). While comparing rofecoxib to NSAIDs - except for naproxen – relative risk was 0.79 (CI 95% = 0.40 – 1.55). While comparring rofecoxib to naproxen, however, relative risk was 1.69 (CI 95% = 1.07 – 2.69). The analysis did not come across any excessive number of adverse cardiovascular events for rofecoxib as compared to placebo or to NSAIDs, naproxen excluded. Based on that, researchers concluded that although results were inconclusive on the specific effect, the difference between rofecoxib and naproxen might be due to naproxen's anti-platelet effect.

To be added to that analysis is a data base analysis where 8 Phase IIb-III double-blind, controlled clinical trials which included 5,435 patients with osteoarthritis, with similar results[29]. With the purpose of investigating the risk of cardiovascular thrombotic events among patients on rofecoxib, traditional NSAIDS and placebo, the intervention lasted an average of 3 and a half months, and the APTC events were considered for the outcome. The study reported equivalent rates of cardiovascular adverse events for users of rofecoxib, placebo and non-specific NSAIDS (ibuprofen, diclofenac and nabumetone).

Retrospective cohorts were also carried out. Ray and collaborators put together over 400,000 individuals in a cohort to investigate serious coronary disease in NSAIDs users and controls for a period of 5 ½ years, anc controls, for a period of 2 ½ years[26]. Users of rofecoxib at high doses had 1.70 times higher risk (95%, CI 0.98-2.95, p=0.058) of coronary diseases than non-users. Additionally, the risk increased to 1.93 among new users (95%, CI 1.09-2.95, p=0.024). However, there was no evidence of high risk among users of rofecoxib at or under 25 mg/day dose. A Canadian cohort that followed and was published in 2003[30] failed to demonstrate increases risk for AMI in recent users of rofecoxib when compared to the control group.

After all the studies had rejected the possible association between rofecoxib and cardiovascular adverse events, other studies came to light to support the assumption initially suggested by the VIGOR[8] study. A recent meta-analysis[31] suggested increased relative risk of those events among patients on many doses of rofecoxib when compared to those on naproxen, but not placebo. Results were very similar to the VIGOR study. Juni and collaborators[32] developed, right afterwards, a new meta-analysis involving 18 randomized, controlled clinical trials, which compared rofecoxib with other NSAIDs or with placebo, and 11 observational studies on cardiovascular risk and naproxen. Significant relative risks were found – higher than 2 – with little evidence of dependent risk variation in control group (placebo, non-naproxen NSAID, and naproxen) or intervention duration time.

Observational studies also questioned the cardiovascular safety of rofecoxib. In 2004, Solomon and collaborators[33] conducted a case-control study where 54,475 patients over 65 years of age were observed in regard to hospital admission resulting from AMI. The use of rofecoxib, celecoxib, non-specific NSAIDs and no NSAIDs was the reference for comparison. Rofecoxib was found to be associated to high risk of AMI when compared to celecoxib or no NSAID at all. In addition, higher than 25 mg doses were associated to higher risk as compared to those under 25 mg. Finally, risk was shown to be high only in the first 90 days of use, but not in the period following it.

Rofecoxib Cardiotoxicity Results in Drug Withdrawal from the Market

The results reported by the study entitled *Adenomatous Polyp Prevention on Vioxx* (APPROVe)[13] were the ones to cause highest commotion among health authorities, scientific community, pharmaceutical companies and public opinion. Results released in September, 2004 led to the immediate withdrawal of rofecoxib from the market by the company marketing it.

As COX-2 is expressed inflammation sites – as is the case for neoplasias – an assumption was raised that its inhibition could be useful for the treatment or the prevention of different neoplasia diseases. A total of 1,586 patients with a history of colonic adenomas was included in a double-blind, randomized, controlled clinical trial, where one group would be administe red 25 mg of rofecoxib per day, and the other group, placebo. The purpose was to investigate if the use of the agent for a 3-year period would change the risk of neoplastic polyp in the large intestine. After 18 months of treatment, the intervention was terminated after the agent was associated to significant increase of cardiovascular risk. Relative risk reported was 1.92 (95%, CI =1.19-3.11, p=0.008), and was shown only after 18 months of treatment. Even though, researchers found it to be uncertain whether re-sults obtained were due to rofecoxib alone or to COX-2 specific inhibitors class. They also questioned the cardiovascular safety of traditional NSAIDs as well, though.

Class Effect Proven

Concurrent to the publication of APPROVe, two other studies offered additional support to the hypothesis of class effect. The first – *Adenoma Prevention with Celecoxib* (APC)[14] – included 2,035 patients with a history of colorectal neoplasia to compare two doses of celecoxib (200mg or 400mg twice a day) to placebo for colorectal adenoma prevention. Once again intervention had early termination, when data from 2.8 to 3.1 years of follow-up were already available. An increase for events defined as death from cardiovascular event, AMI, CVA or heart failure was observed. When compared to placebo, the group being administered lower dose of the medication reported hazard ratio at 2.3 (95%, CI = 0.9-5.5), whereas the group under higher dose reported hazard ratio at 3.4 (95%, CI = 1.4-7.8). Celecoxib dose-dependent cardiovascular risk was determined at that point in time.

APC study researchers discussed the results of other studies involving celecoxib. In their opinion, preliminary analyses of PreSAP trial did not report increase of cardiovascular risk. They believe the fact that PreSAP uses a 400 mg daily dose of celecoxib with no risk increase supports the assumption that sustained inhibition of prostacyclin to be accounted for such increase. In addition, researchers point out that such increase was also demonstrated in a celecoxib randomized, controlled clinical trial, with patients with Alzheimer disease, as reported to FDA (*Food and Drug Administration*). While considering other publications on the cardiovascular adverse effects of other class agents, the APC study emphasizes the evidence of increased risks of those events with prolonged use of COX-2 inhibitors.

Another publication to support those evidences evaluated cardiovascular safety of another COX-2 inhibitor while administrating valdecoxib and its IV pro-drug parecoxib to 1,671 patients submitted to coronary artery bypass surgery[1]. The agents were to be administered for 10 days to treat post-surgery pain as follows: IV parecoxib for at least 3 days, followed by valdecoxib orally up to day 10; IV placebo, followed by valdecoxib orally; or placebo for 10 days. Patients also had access to opioids. Observational follow-up for adverse effects lasted 30 days. Higher rate of cardiovascular events was found among patients being administered parecoxib and valdecoxib as compared to those being administered placebo, with risk ratio at 3.7 (95%, CI = 1.0-13.5, p=0.03). The significant risk finding for thromboembolic events in patients at high risk for such events increased concerns related to the safety of medications in that class. That concern had been raised in 2003 after the publication by Ott and collaborators[34] on similar results from a smaller study involving 311 patients.

Discussion

Recent results from the last three studies involving rofecoxib, celecoxib and valdecoxib have provided further previous evidence[17] and convinced specialists of the higher risk of cardiovascular adverse events by the class, such as AMI, CVA, hypertension and heart failure[13,17]. There are indications about cardiotoxicity being dose-dependent and proportional do COX-2 selectivity[35]. Such selectivity is ranked from highest to lowest: lumiracoxib; etoricoxib, rofecoxib and valdecoxib; celecoxib and diclofenac. As discussed previously, the TARGET[27] study failed to detect cardiovascular risk for lumiracoxib. However, such result may have been due to study small range and short term[35]. It is also reasonable to add the role played by lumiracoxib half life in such difference in results[35]. It is also to be pointed out that although it is marketed as a non-specific NSAID, COX-2 selectivity reported by diclofenac is very similar to that by celecoxib[35], which may have had some influence in CLASS study results and in others.

However, the delay in defining COX-2 inhibitors cardiotoxicity raised great concern in scientific community[15-18,35]. Papers published on the subject have presented considerable failure in regard to that definition. The VIGOR[8] study, for instance, excluded individuals with recent cardiovascular events and aspirin users. By doing that, it eliminated a considerable risk group for those events. High risk patients for cardiovascular disease are known to be responsible for a major share of COX-2[7] users; their exclusion stands for a serious bias in study screening. Another factor to hinder elucidation was the choice for primary outcome. The study focused gastrointestinal effects by agent, which poses difficulty in measuring cardiovascular effects[18]. Those effects may have been mistakengly classified, or even gone unnoticed, which would have posed difficulty in formulating consistent associations.

The CLASS[5] study also had a number of constraints. In the first place, it was a short-term study, and APPROVe[13] demonstrated that a longer-term follow-up would be necessary to detect outcomes. Additionally, CLASS was similar to VIGOR, since it was not designed for formal and systematic detection of cardiovascular events, and included patients at relatively low risk for such events[14]. Finally, some suggest that CLASS does not deny evidence on cardiovascular risk increase when comparing the use of celecoxib with ibuprofen among non-users of aspirin[36].

Therefore, it is suggested that following the release of COX-2 inhibitors in the market – and particularly after the first doubt was raised regarding cardiovascular safety – multicenter, randomized, controlled, long-term clinical trials should have been carried out, not excluding high risk patients and addressing primarily cardiovascular events[16,17,18,35]. The control group would count on users of naproxen associated to a proton-pump inhibitor, following FDA recomendation[35]. Such studies would follow to establish risk levels for each medication, treatment time associated to that risk, and possible populations to be benefitted from the use of the agents.[18] Some believe that should those studies have been carried out

immediately, morbimortality rate from such wide use of COX-2 inhibitors could have been reduced[17].

However, there is controversy on how practical those large scope studies could be, since patients at high risk for cardiovascular diseases would be reluctant to participate[35]. Even though, detecting increased incidence of a common clinical event – as is the case for cardiovascular diseases – is not an easy task at all[17], in addition to having high impacting on public health – which characterizes one more need to implement those studies.

Recommendations

Conventional NSAIDs – aspirin and paracetamol (acetaminofen) – are agents reporting effectiveness similar to that by COX-2 specific inhibitors in regard to analgesia[18,37-40]. There is no scientific evidence of higher effectiveness by COX-2 specific inhibitors[35]. Therefore, their use should be restricted to patients for whom other treatment strategies had failed. The clinical recommendations developed at scientific sessions of the *American College of Cardiology* (ACC)[35] for the use of anti-inflammatory are the following:

• Continuous use of low dose aspirin whenever there is indication;

• Alternatives to NSAIDs should be considered, such as paracetamol and topic therapies;

• If the use of an NSAID is made necessary, first choice is naproxen associated to a proton pump inhibitor;

• COX-2 specific inhibitors must not be used unless all strategies above have failed.

Should the use of COX-2 inhibitors be indispensable, therapy risks and benefits must be carefully analyzed[14]. Additionally, pacients must be aware of the risks involved; dose must be the lowest possible; and treatment time frame the shortest possible. It is important to point out, once again, that risk assessment still poses diffi-culties, since no proper evaluation has been made available by long-term studies involving high and low risk populations[16,17].

Finally, regulatory agencies, such as the FDA in the United States, have received severe criticism regarding the control and the surveillance of such processes[5,16]. Those agencies should require compatible knowledge update on the part of manufacturers, that including changes in package inserts and drug indications; education of patients and health professionals; advertising limitations; use restrictions for certain groups of patients; implementation of studies and assays related to the safety of agents; sales interruption and agent withdrawal from the market[18]. When drugs are so widely used[3,15,16,41-44] public health issues are involved; therefore, they should not have been marketed for such a long time without accurate definition on theis cardiovascular safety. Every time a new agent is launched the market is expanded; annual sales volume is estimated to be over US$ 2 billion worlwide[3] for the industry. The concern in regard to public health must come before the commercial interests by the pharmaceutical companies.

FDA positioning

Based on article by Okie[45], the FDA decided COX-2 selective inhibitors could be kept being marketed provided the following recommendations were complied with: packaging must contain warnings about recently proven effects, in addition to other measures to restrict use. After FDA's positioning rofecoxib manufacturers declared the product will be reintroduced in the market in the near future[45].

The American agency also pointed out the need for a wide-range multicenter study to investigate the safety of the NSAIDs class as a whole - long and short-term. The study would take years, and would include, according to the FDA, patients with osteoarthritis, rheumatoid arthritis, or chronic pain, stratified by cardiovascular disease risk at baseline. A proposal was made to compare groups with over 1,000 individuals being administered ibuprofen, naproxen, diclofenac and celecoxib, with a control group being administered therapeutic doses of aspirin and proton pump inhibitor or paracetamol with codeine. The outcome should consider death from cardiovascular disease, CVA, AMI and bleeding. Blood pressure should be monitored and patients at increased risk for conorany diseases should be administered aspirin at low doses. However, funds are not yet available for such study; and as discussed earlier, there is still controversy regarding its practicality.

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