Anti-inflammatory therapy and cardiovascular risk: new insights



Silvano Adami University of Verona, Reumatologia, Ospedale 37067 Valeggio, Verona, Italy Tel.:+39 045 633 8607; Fax:+39 045 795 2000; silvano.adami@univr.it

'...increased cardiovascular risk is not a problem specific to rofecoxib, but is common to all analogous molecules.'

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the predominant treatment for inflammatory conditions and chronic pain for nearly 40 years. However, when taken on a regular basis, anti-inflammatory agents are associated with a high risk of adverse events involving the upper gastrointestinal tract. It is estimated that approximately 1.1% of those taking NSAIDs develop significant gastrointestinal lesions (bleeding and gastric perforation), for which hospital recovery is necessary [1].

The inhibition of cyclooxygenase (COX) by NSAIDs produces both their therapeutic and their adverse events. The distinction between the enzymatic properties of COX-1 and COX-2 has led to the inception of selective COX-2 antiinflammatory agents (coxibs). The development and commercialization of these agents have led researchers to believe that problems with safety have been resolved, and that prolonged use of these new anti-inflammatory agents would allow easier control of many chronic pathologies, especially rheumatological disorders and arthritis. However, during their clinical development, an unexpectedly high incidence of cardiovascular events was observed.

Clinical trial data first demonstrating increased cardiovascular risk with the use of these drugs came from the VIoxx Gastrointestinal Outcomes Research (VIGOR) trial that compared the gastrointestinal tolerability of rofecoxib (50 mg/day)with naproxen (1000 mg/day) in patients with rheumatoid arthritis [2]. The study demonstrated that rofecoxib was associated with a four-times greater risk of myocardial infarction than naproxen. This was attributed initially to a protective effect of naproxen [2], rather than to a specific effect of rofecoxib [3-6]. The problem became more evident in the Adenomatous Polyp PRevention On Vioxx (APPROVe) study carried out in patients with a history of colon adenomas [7]; this trial was interrupted when it was found that rofecoxib was associated with a two-fold higher risk of cardiovascular events than placebo (relative risk [RR] 1.92, confidence interval [CI] 1.19–3.11). In September 2004, Merck Sharpe & Dohme announced the voluntary worldwide withdrawal of Vioxx.

Following publication of the APPROVe trial, other data from randomized, controlled clinical trials, as well as epidemiological data, became available. These studies suggested that increased cardiovascular risk is not a problem specific to rofecoxib, but is common to all analogous molecules. In the Adenoma Prevention with Celecoxib (APC) study, conducted in patients with adenomatous colorectal polyps, celecoxib (200 or 400 mg twice daily) was associated with a cardiovascular risk almost three-times higher than that of placebo (RR 2.8, CI 1.3-6.3) [8]. An increased cardiovascular risk, with respect to placebo, was also seen with valdecoxib (and its precursor parecoxib) in patients undergoing a coronary bypass [9,10]. It is likely that, in similar studies, without evidence of increased cardiovascular risk. this was actually due to insufficient statistical power (inadequate number, inclusion of a lowrisk population and low number of adverse events overall) more than intrinsic properties of that particular coxib!

Biological plausibility

Various mechanisms may contribute to the observed increase in cardiovascular risk during therapy with coxibs. The hypertensive effect is a problem with both coxibs and NSAIDs [11,12], and this may increase the risk of cardiovascular events. Several experimental studies have demonstrated a pro-oxidative effect of coxibs but this occurs at doses much higher than those used in therapy [13].

A disequilibrium between pro- and antithrombotic factors is the most favored hypothesis. The prostacyclins produced by COX-2 at the endothelial level have an important vasodilating effect that balances the pro-aggregating/prothrombotic effects of thromboxane (produced by COX-1). Molecules that interact selectively with COX-2 would thus minimize



7

any potential protective effects of prostacyclins without having any influence on the production of thromboxane (prothrombotic), mediated by COX-1. However, along these lines, one should also keep in mind that several experimental studies have indicated that COX-1 also has a role in the synthesis of prostacyclin [14-16]. Thus, by acting on both COX-1 and COX-2, nonselective anti-inflammatory agents (such as NSAIDs) can block the production of vasodilating prostacyclins even more than coxibs. In addition, the anti-aggregating effects of NSAIDs (mediated by COX-1), even if pharmacologically demonstrable, do not appear to be clinically relevant. In a study of 165,000 women in menopause, prolonged use of NSAIDs did not provide any protection against cardiac infarction [17]. The coadministration of NSAIDs and small doses of apirin remains a relevant clinical problem [18]. NSAIDs may have a negative effect on the action of aspirin because they occupy the same binding sites on platelets. In these situations, it is recommended that anti-inflammatory agents with a short half-life should be used, and the two drugs should be taken some time apart to maximize the anti-aggregating effects of aspirin. This precaution does not need to be applied to coxibs.

Cardiovascular events & traditional anti-inflammatory inhibitors

The biological mechanisms behind the increased cardiovascular risk associated with coxibs may be related to the inhibition of COX and, therefore, may be shared potentially with more traditional anti-inflammatory agents. It should also be highlighted that, along these lines, much data regarding NSAIDs have been collected during clinical trials that last only a few weeks and thus eventual increases in cardiovascular risk would not be seen. Moreover, their elevated gastrointestinal toxicity prohibits their continuous and prolonged use. More recently, long-term studies have been planned, or have been completed, comparing traditional antiinflammatory agents with coxibs [19,20] The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) study involved more than 18,000 patients with osteoarthritis that were treated for at least 1 year with lumiracoxib (400 mg/day, or twice the dose indicated for arthrosis), naproxen (500 mg twice daily) or ibuprofen (800 mg three-times daily) [19]. There was no difference in cardiovascular risk between the three groups in terms of either absolute risk or risk of cardiac or myocardial infarction [21]

(14 events or 1.23% given lumiracoxib vs 13 events or 1.22% of those given anti-inflammatory agents). The incidence of myocardial infarction was also similar: seven events or 0.61% given lumiracoxib versus six events or 0.56% of those given anti-inflammatory agents.

> '...all coxibs appear to be associated with some increased cardiovascular risk...'

The Etoricoxib Diclofenac Gastrointestinal Events (EDGE) study, presented at the American College of Rheumatology meeting in 2004, included 7111 patients affected by osteoarthritis (involving the knee, hip, hands or vertebral column) [21]. The patient cohort included individuals over 50 years of age who were treated with etoricoxib (90 mg/day) or diclofenac (50 mg three-times daily) for 1 year. The percentage of suspensions due to all adverse events was significantly less in the etoricoxib group (13.4 vs 26.3%), while the risk of cardiovascular events was similar in the two treatment groups. Thus, neither the TARGET nor EDGE studies demonstrated a higher risk for cardiovascular events for coxibs than traditional anti-inflammatory agents. Thus, two hypotheses are possible: either the two coxibs studied (lumiracoxib and etoricoxib) are not associated with increased cardiovascular risk; or the safety profile of these coxibs is similar to that of the NSAIDs used in the studies (ibuprofen and diclofenac).

The second hypothesis is supported by the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), in which patients were administered naproxen (220 mg twice daily), celecoxib (200 mg twice daily) or placebo. This trial was stopped early owing to an apparent increase in cardiovascular events in the naproxen arm [101,102].

Similarly, the results of a recent, retrospective case–control study are of relevance [22]. The study was based on the QRESEARCH database in the UK and compared 9218 cases of myo-cardial infarction (between 2000 and 2004) with a group of 86,349 subjects. A significant increase in risk of myocardial infarction was observed following the use of both rofecoxib and traditional anti-inflammatory agents:

- Rofecoxib (RR 1.69, CI 1.09–1.61)
- Diclofenac (RR 1.55, CI 1.39–1.72)
- Ibuprofen (RR 1.24, CI 1.11-1.39)
- Naproxen (RR 1.27, CI 1.01–1.60)

In another retrospective, case–control study aimed at assessing the role of traditional antiinflammatory agents in protecting against oral cancers, therapy with NSAIDs (but not acetaminophen) was associated with a two-fold increased risk of cardiovascular events (RR 2.06, CI 1.34–3.18) [23].

Conclusions

The data available to date permit a number of observations to be made. First, all coxibs appear to be associated with some increased cardiovascular risk, however, how the risk manifests is unclear. It is also still unclear if the increased cardiovascular risk is related to the duration of administration. In the APPROVe study, the cumulative incidence of cardiovascular event curves showed an initial divergence between rofecoxib and placebo after 18 months, with a noticeable difference after 36 months of follow-up. However, in the VIGOR study, the two curves diverge after 6 months of follow-up. Early divergence of the risk curves was also seen in the APC study with celecoxib [8].

The absolute risk of cardiovascular events during coxib administration is found generally to be higher in high-risk patients, however, it is still not clear if the relative risk is different according to the pretherapy risk. This information is of critical clinical importance in order to identify patients that may be able to benefit from coxibs without increased cardiovascular risk.

It is likely that the use of traditional NSAIDs is also associated with increased cardiovascular risk, and this justifies the black box warning on the product information sheet imposed by the FDA, not only to coxibs, but also to traditional anti-inflammatory agents.

Since randomized, placebo-controlled clinical trials designed to investigate the cardiovascular risk of anti-inflammatory agents are unlikely to be planned, an extensive, active pharmacovigilance is needed urgently in order to answer the following critical questions: what compound (if any) should be preferred in patients with a very high risk of cardiovascular events? How long can each anti-inflammatory agent be used safely? What dosage of each anti-inflammatory agent can be considered relatively safe? Who might be treated without any relevant concern regarding cardiovascular risk?

Bibliography

- Wolfe MM, Lichtenstein DR, Singh G: Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N. Engl. J. Med.* 340, 1888–1899 (1999).
- Bombardier C, Laine L, Reicin A *et al.*: Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N. Engl. J. Med.* 343, 1520–1528 (2000).
- Rahme E, Pilote L, LeLorier J: Association between naproxen use and protection against acute myocardial infarction. *Arch. Intern. Med.* 162, 1111–1115 (2002).
- Watson DJ, Rhodes T, Cai B, Guess HA: Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch. Intern. Med.* 162, 1105–1110 (2002).
- Catella-Lawson F, Reilly MP, Kapoor SC et al.: Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N. Engl. J. Med.* 345, 1809–1817 (2001).
- Capone ML, Tacconelli S, Sciulli MG *et al*.: Clinical pharmacology of platelet, monocyte, and vascular cyclooxygenase inhibition by naproxen and low-dose aspirin in healthy subjects. *Circulation* 109, 1468–1471 (2004).

- Bresalier RS, Sandler RS, Quan H et al.: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N. Engl. J. Med.* 352, 1092–1102 (2005).
- Solomon SD, McMurray JJ, Pfeffer MA et al.: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N. Engl. J. Med.* 352, 1071–1080 (2005).
- Nussmeier NA, Whelton AA, Brown MT et al.: Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N. Engl. J. Med. 352, 1081–1091 (2005).
- Ott E, Nussmeier NA, Duke PC *et al.*: Efficacy and safety of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J. Thorac. Cardiovasc. Surg.* 125, 1481–1492 (2003).
- Gurwitz JH, Avorn J, Bohn RL *et al.*: Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 272, 781–786 (1994).
- Pope JE, Anderson JJ, Felson DT: A metaanalysis of the effects of nonsteroidal antiinflammatory drugs on blood pressure. *Arch. Intern. Med.* 153, 477–484 (1993).

- Walter MF, Jacob RF, Day CA *et al.*: Sulfone COX-2 inhibitors increase susceptibility of human LDL and plasma to oxidative modification: comparison to sulfonamide COX-2 inhibitors and NSAIDs. *Atherosclerosis* 177, 235–243 (2004).
- FitzGerald GA: COX-2 and beyond: approaches to prostaglandin inhibition in human disease. *Nature Rev. Drug Discov.* 2, 879–890 (2003).
- Tuleja E, Mejza F, Cmiel A, Szczeklik A: Effects of cyclooxygenases inhibitors on vasoactive prostanoids and thrombin generation at the site of microvascular injury in healthy men. *Arterioscler*. *Thromb. Vasc. Biol.* 23, 1111–1115 (2003).
- Wong E, Huang JQ, Tagari P, Riendeau D: Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. *Atherosclerosis* 157(2), 393–402 (2001).
- Garcia Rodriguez LA, Varas C, Patrono C: Differential effects of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. *Epidemiology* 11(4), 382–387 (2000).

- Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C: Low-dose aspirin for prevention of atherothrombosis. *N. Engl. J. Med.* 353, 2373–2383 (2005).
- Schnitzer TJ, Burmester GR, Mysler E et al.: Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 364(9435), 665–674 (2004).
- Farkouh ME, Kirshner H, Harrington RA et al.: Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. TARGET Study Group. *Lancet* 364(9435), 675–684 (2004).
- 21. Baraf HSB, Fuentealba C, Greenwald M *et al.*: Tolerability and effectiveness of

etoricoxib compared to diclofenac sodium in patients with osteoarthritis: a randomized controlled study (EDGE trial). *Arthritis Rheum.* 50(Suppl.), 346–347 (2004).

- Hippisley-Cox J, Coupland C: Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal antiinflammatory drugs: population based nested case-control analysis. *Br. Med. J.* 330, 1366 (2005).
- Sudbo J, Lee JJ, Lippman SM *et al.*: Nonsteroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study. *Lancet* 366, 1359–1366 (2005).

Websites

 US Department of Health and Human Services.
 Use of non-steroidal anti-inflammatory drugs suspended in large Alzheimer's disease prevention trial. NIH News 2004. www.nih.gov/news/pr/dec2004/od-20.htm (Accessed 21 November 2005).

102. Pfizer, Inc. News Release.
Pfizer says new NIH study results are consistent with large body of evidence supporting cardiovascular safety of Celebrex.
December 21, (2004).
www.pfizer.com/pfizer/are/news_releases/20 04pr/mn_2004_1221.jsp (Accessed 21 November 2005).

Affiliation

 Silvano Adami University of Verona, Reumatologia, Ospedale 37067 Valeggio, Verona, Italy Tel.:+39 045 633 8607; Fax:+39 045 795 2000; silvano.adami@univr.it