Coxibs: a significant therapeutic opportunity

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Abstract. Pain is the main reason why people decide to see a doctor; hence, the widespread use of anti-inflammatory drugs which were specifically developed to control pain and inflammation. One of the main causes of pain is represented by osteoarticular conditions, the most common one being arthrosis. Paracetamol is universally indicated as the therapy of first choice in degenerative pathologies of the joints, although it is often insufficient to control adequately the clinical picture and less efficacious than anti-inflammatory drugs. These latter, however, especially when taken chronically, exhibit an unfavourable safety profile. The most common side effect of anti-inflammatory drugs is gastric discomfort; coxibs – COX-2 selective inhibitors – were developed to solve this problem. The use of these drugs, relative to conventional NSAIDs, is associated to a significantly lesser gastroduodenal ulcer rate and to fewer clinically relevant complications, as well as to a smaller rate of treatment discontinuation due to gastrointestinal (GI) symptoms. From a clinical and practical standpoint, the use of coxibs is associated to a remarkably reduced risk of gastroduodenal lesions, similar as the one resulting from the combination of a conventional NSAID and a proton-pump inhibitor. By adding a proton-pump inhibitor to a coxib, such risk seems to become virtually non-existent, even in a high risk population and regardless of ASA administration. It is important to stress that the better tolerability of coxibs does not imply an inferior anti-inflammatory and pain-relieving efficacy, especially with regard to etoricoxib, whose efficacy is at least equivalent as other competing NSAIDs, even in quite severe and complex musculoskeletal pain models. This clear-cut advantage of coxibs at gastric level clashed against a documented increased cardiovascular (CV) risk, which led to the much-talked-about withdrawal of rofecoxib from the market. The most credited pathogenetic hypothesis to explain the association between chronic use of coxibs and CV risk seems to be related to a trombophilic effect due to an imbalance of prothrombotic and antithrombotic factors. Several observational and case-control studies, however, led to suspect that conventional NSAIDs share with coxibs an increased cardiovascular risk; such suspicion was experimentally confirmed by the MEDAL trial. In this trial, the cardiovascular risk of thrombosis among patients who were treated on a long-term basis with a coxib (etoricoxib) was shown to be similar as the risk observed in patients receiving a conventional NSAID (diclofenac). In conclusion, coxibs represent a valid therapeutic option in the treatment of patients with osteoarticular conditions. In terms of cardiovascular risk their efficacy is associated to a similar safety profile as conventional NSAIDs, whereas the gastrointestinal risk related to coxibs seems to be significantly lesser. (www.actabiomedica.it)

Key words: Pain, NSAIDs, coxibs, ASA, CV risk

Anti-inflammatory therapy

Non steroidal anti-inflammatory drugs (NSAIDs), although their discovery dates back to about 40 years ago, are still now one of the most prescribed classes of drugs, thanks to the fact that they fulfill a paramount therapeutic need: to control both acute and chronic pain as well as flogosis. One of the most common causes of pain, especially among adults and the elderly, is musculoskeletal pain. A large Cana-

dian survey showed that one-fourth of the population is seen by their primary care physician (PCP) because of this type of pain and over 70% of patients are treated by their PCP without being referred to a specialist (1) This Canadian epidemiology finding was confirmed in Italy by a study conducted in the Marche Region among 3,664 subjects randomly selected among the patients of 16 PCPs (2), with an observed prevalence of musculoskeletal conditions of 27.6% in the surveyed population. Such prevalence is even higher among subjects older than 65, who suffer from these conditions in over 50% of cases (3).

The natural indication of an anti-inflammatory therapy includes both acute and chronic inflammatory disease and the management of degenerative conditions (arthrosis). In some forms of arthritis (like, for example, gouty arthritis and ankylosing spondylitis), anti-inflammatory drugs are the therapy of first choice (4, 5), whereas in other conditions they represent a valid contribution in managing painful symptoms (rheumatoid arthritis). A recent study showed that factors associated to a higher risk of chronic use of these drugs in the working population include age (RR 1.8, 95% CI ranging between 1.6 and 1.9 every 10 more years of age), osteoarthrosis (RR 1.8, 95% CI ranging between 1.5 and 2.1 versus patients with a diagnosis of low back pain), obesity (BMI >30 is associated to a RR 1.8 with 95% CI ranging between 1.5 and 2.2) and the type of occupation (blue versus white collars, RR 1.4 with 95% CI ranging between 1.2 and 1.6) (6).

Undoubtedly, arthrosis is the most common osteoarticular pathology. Anti-inflammatory drugs control pain and flogosis caused by the disease. Paracetamol, a first-choice agent according to the guidelines for the treatment of arthrosis developed by the main international scientific societies (7-10), has only a pain-relieving action that, in the long run, is significantly lesser than the one achieved by anti-inflammatory drugs. This explains why, in two double-blind, randomized, head-to-head trials, patients with arthrosis expressed their preference for anti-inflammatory therapy instead of paracetamol (11). The greater efficacy of anti-inflammatory drugs versus acetaminophen or paracetamol is highlighted also in the guidelines on the management of low back pain (12), another common cause of musculoskeletal pain. In about 85% of cases, this clinical manifestation does not depend on any specific pathology or spinal abnormality ("non-specific low back pain") (13); in these patients, paracetamol seem to be preferred because of its reduced toxicity, although anti-inflammatory drugs are clearly more efficacious (12). Hence, the real problem of anti-inflammatory drugs, especially when administered chronically as it typically happens in rheumatology, is their low safety profile. Moreover, several NSAIDs are sold as over-the-counter products and are therefore self-prescribed by patients with no medical control whatsoever.

Anti-inflammatory drugs and the gastrointestinal system

As to the side effects of anti-inflammatory drugs, gastric discomfort is certainly the most common; in the United States, it accounts for a significant number of hospitalizations and deaths (14). In the geriatric population, certainly the one most at risk, this issue was recently explored by a Canadian study on hospitalizations due to gastrointestinal pathologies (15). The study demonstrated not only gastric injury caused by NSAIDs, but also the important role played by the concomitant use of paracetamol in enhancing such toxicity, strongly questioning the rationale underlying the combination of these two classes of drugs.

Anti-inflammatory drugs inhibit cyclooxygenase (COX), with subsequent reduction of prostaglandins. Conventional NSAIDs are considered non-selective inhibitors, because they act on both enzymatic isoforms, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). Gastrointestinal toxicity is mostly due to COX-1 inhibition, since it is the constituent isoform involved in the biosynthesis of prostanoids with cytoprotective properties on the gastric mucosa and of thromboxane A_2 (TXA_2), a platelet pro-aggregant. In order to minimize this NSAIDs-related problem, cyclooxygenase selective inhibitors (COX-2), called coxibs, were developed; they act only on the inducible isoform which is typically found in inflammation. The reduced gastroduodenal toxicity of coxibs was explored in a Cochrane Collaboration systematic review

(16); these drugs were found to be related to a significantly smaller number of gastroduodenal ulcers and clinically important complications, as well to as a smaller number of treatment discontinuations due to GI symptoms, versus conventional NSAIDs. These conclusions were later confirmed in a review of literature data (17) aimed at evaluating the clinical efficacy and cost-effectiveness of coxibs in patients with arthrosis and arthritis.

The use of coxibs is associated to a significant reduction of gastroduodenal injury risk, similar as the one resulting from the combination of a conventional NSAID and a proton-pump inhibitor (18, 19); this aspect should be considered when evaluating the cost of therapy. The equation coxib = NSAIDs + proton-pump inhibitor is confirmed also in patients who take low doses of ASA as an anti-aggregant (20), a factor known to enhance the risk of bleeding.

Also, the coxib + proton-pump inhibitor combination, even in a high-risk population and irrespective of ASA use, seems to reduce the risk of gastric disease down to zero (21)

Coxibs: safety and anti-inflammatory efficacy

The true innovation introduced by coxibs is their improved gastrointestinal safety profile, without an impaired or decreased anti-inflammatory efficacy. This feature is fundamental, since this type of drugs is first and foremost employed to control pain and inflammation.

With regard to various rheumatological diseases, especially etoricoxib proved to be at least as effective as other competing NSAIDs, not only in arthrosis but also in more severe, complex musculoskeletal pain models. An eight-day etoricoxib course (120 mg in single administration) was shown to be as efficacious as an indomethacin course of equal length (50 mg 3 times a day) to resolve the clinical picture resulting from an acute attack of gouty arthritis (22, 23) (Fig. 1).

In patients with rheumatoid arthritis, etoricoxib (90 mg/day) was superior to placebo and at least as effective as naproxen (500 mg x 2/day) in reducing the number of tender, swollen joints, according to both the doctors' and patients' opinion (24, 25).

Studies on ankylosing spondylitis patients are particularly interesting; etoricoxib (90-120 mg) produced a significantly greater clinical improvement both versus placebo after 6 weeks and, most of all, versus naproxen 500 mg x 2/day after 52 weeks (26, 27) (Fig. 2). Such superior efficacy enabled a longer treatment persistence and a significantly lower drop-out rate for lack of efficacy.

In the light of the above clinical experience, several remarks can be made:

- these results were obtained with etoricoxib in single administration versus 2-3 administrations required with other NSAIDs
- in the study on ankylosing spondylitis, it is quite evident that the higher clinical efficacy may be due to a long-term better tolerability of coxibs as a class and specifically of etoricoxib; with this agent, it is possible to achieve therapeutic doses (90-120 mg/day) that cannot be achieved with other NSAIDs (e.g. naproxen).

At any rate, no currently available anti-inflammatory drug can resolve pain completely. Broadly speaking, 50-60% of arthrosis patients receiving anti-inflammatory drugs report a good response (pain reduction by at least 50%) while 20-30% report a very good response (over 70% pain reduction); on the other hand, 20-25% of patients report a positive response to placebo, too.[28] In a recent meta-analysis it was shown that the use of anti-inflammatory drugs in patients with arthrosis has a significantly superior effect versus placebo; moreover, even at the lowest etoricoxib doses (30 and 60 mg), a good response can be obtained (pain reduction greater than 50%) in a proportion of patients higher or equal to other anti-inflammatory drugs at full doses (naproxen 1000 mg/day; ibuprofen 2400 mg/day, celecoxib 200 mg/day) (28) (Fig. 3).

Anti-inflammatory drugs and CV risk

Despite their efficacy and gastroduodenal tolerability, coxibs are notorious because of the cardiovascular problems which led to rofecoxib withdrawal from the market in September 2004. In fact, during the clinical development of COX-2 selective inhibitors, a

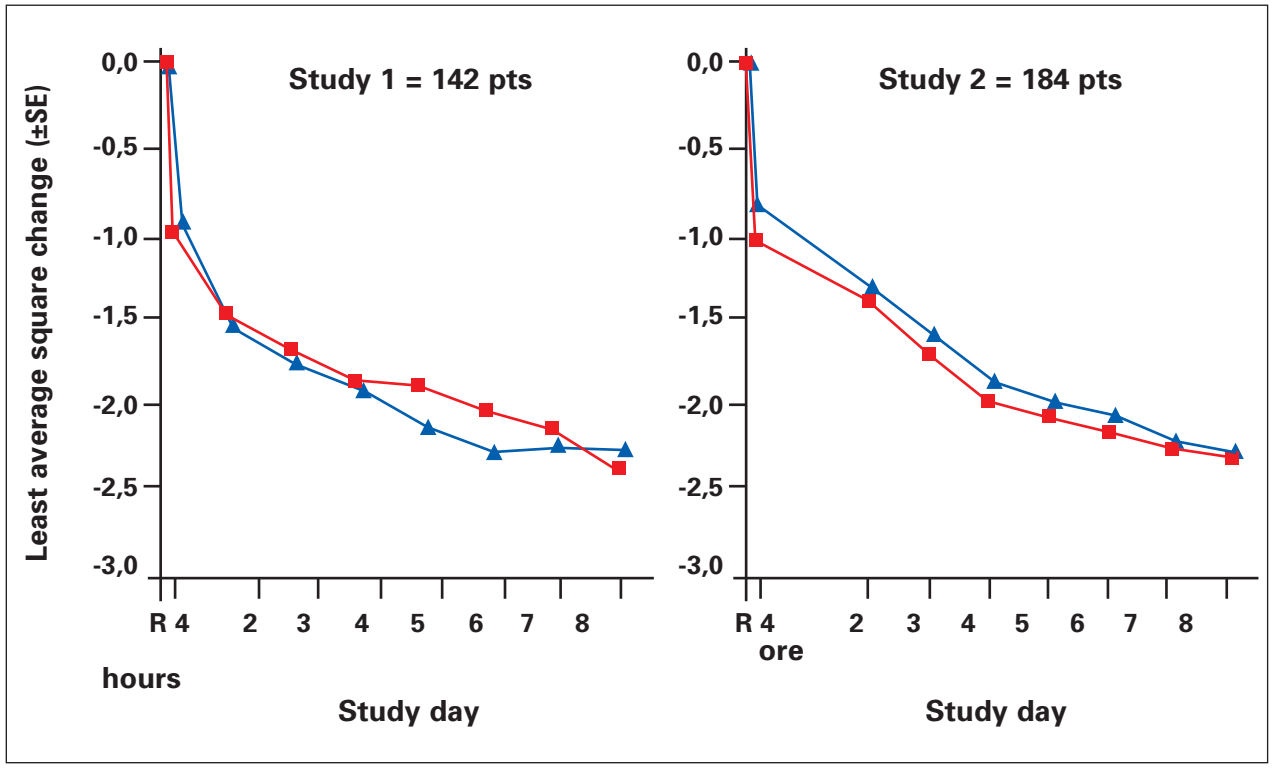

Figure 1. Figure 1. Etoricoxib efficacy in acute gout: etoricoxib 120 mg in single administration provides a similar effect as indomethacin 50 mg x 3/day [Mod. from (22, 23)]

Study 1 = 142 pts Study 2= 184 pts
Least average square change (±SE)
Study day
4 hours

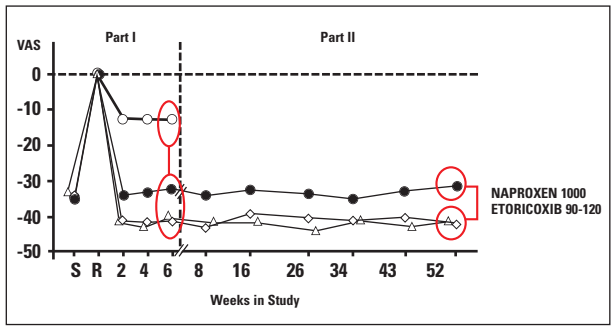

Figure 2. Efficacy of anti-inflammatory drugs in ankylosing spondylitis (effect on pain). This paper confirms that both naproxen and etoricoxib are efficacious, although etoricoxib achieves a significantly greater VAS score reduction. The superior efficacy of etoricoxib is related to the fact that doses providing a more pronounced anti-inflammatory action than full-dose naproxen can be administered (whereas naproxen dosing cannot be increased because of the well-known tolerability problems) [Mod. from (26)]

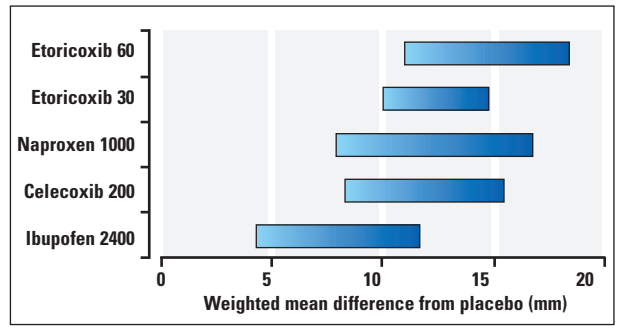

Figure 3. Pain-relieving efficacy of various therapeutic strategies versus placebo on the WOMAC pain scale in patients with arthrosis. Etoricoxib 60 mg produced the greatest improvement versus placebo, consistent with a clinically significant effect in approximately 60% of treated patients [Mod. from (28)]

significantly elevated cardiovascular (CV) risk versus placebo unexpectedly emerged (29-31).

The most credited pathogenetic hypothesis to explain the association between the chronic use of coxibs and CV risk seems to be related with a trombophilic effect due to an imbalance of prothrombotic and antithrombotic factors. Prostacyclin, produced by the vascular endothelium mainly through COX-2 activity, has a significant vasodilation and anti-aggregant effect. While COX-2 selective inhibitors inhibit the COX-2-dependent vascular synthesis of prostacyclin, they cannot affect the platelet synthesis of thromboxane-TXA_2, the main product of platelet COX-1 activity. Thromboxane-TXA_2 has an opposite action to prostacyclin and is an important pro-aggregant and vasoconstrictor. It appears, then, that coxibs promote a pro-thrombotic state that, in turn, seems to induce an accelerated atherosclerosis. On the opposite, with conventional NSAIDs the negative effect due to the blockage of COX-2-dependent endothelial prostacyclin production would be somehow counterbalanced by the platelet anti-aggregant effect mediated by the platelet COX-1 inhibition. However, it should be noted that the anti-aggregant effect of NSAIDs (mediated by COX-1), although pretty clear in *in vitro* studies, does not seem to be clinically relevant. The action of ASA leads to an irreversible inhibition of platelet COX-1 (new platelets need to be produced); this effect is persistent and complete even at low doses, as low as 75-100 mg/day (32-34). The inhibition of platelet COX-1, and therefore of TXA_2 production, caused by NSAIDs is instead partial and transient (35, 36) and is therefore likely to have no clinical value whatsoever (36).

Some interesting observations are related to the cardio-protective effect of ASA. In a study of patients with arterial disease (undergoing carotid endo-arteriectomy) (37), the use of ASA at doses greater or equal to 650 mg/day provided a significantly lower CV protection than doses lower or equal to 325 mg/day, with a statistically significant difference as early as after 3 months. It should be observed that the different ASA dosing expresses a different clinical pharmacological effect: low doses (lower or equal to 325 mg/day) act only on platelet COX-1 and have therefore a platelet anti-aggregant effect only; high doses (greater or equal to 650 mg/day) exert an anti-inflammatory effect mediated by COX-2 inhibition as well (36).

It is natural, therefore, to hypothesize that endothelial COX-2 inhibition, whatever way it is produced (coxibs, NSAIDs, ASA) is associated to an absolute or relative increase of CV risk (36). This phenomenon did not emerge earlier because conventional NSAIDs were registered on the basis of clinical trials with very small series, having a duration of just a few weeks, and thus totally inadequate to highlight a possible elevation of CV risk. Several observational or case-control studies led to suppose that also conventional NSAIDs, when compared to placebo, could share with coxibs an increased cardiovascular risk (36, 38-45); still, an experimental confirmation was needed and this was obtained through the MEDAL study (46). This trial showed that the thrombotic cardiovascular risk in patients on a long term coxib treatment (etoricoxib) is the same as the risk observed among patients taking conventional NSAIDs (diclofenac). The trial included over 34,700 patients aged 50 or older, with arthrosis and rheumatoid arthritis. In patients with vascular disease or diabetes, low-dose ASA was recommended; this treatment was administered to over 34% of the study population. As to the study endpoint, no significant difference was observed in the incidence of thrombotic cardiovascular effects between the two therapeutic strategies.

The study findings provide an undisputable solution to the CV risk comparison between NSAIDs and coxibs; as now, this is the only clinical trial specifically designed for such purpose.

The only NSAID which may have a different cardiac toxicity profile is naproxen; at high doses it does not seem to be associated with an increased CV risk (36) although some uncertainty has emerged from the ADAPT study findings. This latter trial included 2,400 healthy subjects older than 70, at risk for Alzheimer's disease, treated with placebo, celecoxib (200 mg x 2/day) or naproxen (220 mg x 2/day), and was prematurely discontinued since the naproxen group showed an overall increase of vascular events (47).

Most plausibly, naproxen, in terms of cardiovascular toxicity, may have a different effect according to the dosing employed. A chronic high-dose treatment

(500 mg x 2/day) does provide a potentially relevant platelet anti-aggregant effect (48-50). At lower doses, naproxen tends to have a similar action as other NSAIDs, also with respect to CV risk (36). The "pharmacological" benefit of high-dose naproxen hardly allows to administer it in the clinical practice, though, since missing just one dose is sufficient to cancel its protective anti-aggregant effect as well as the possibly concomitant effect of low-dose ASA (51).

Anti-inflammatory drugs and ASA interaction

The interaction between ASA and NSAIDs is another hot, often overlooked topic. The negative effect of some NSAIDs, like, for instance, ibuprofen, is so evident that it can be quantified in terms of a difference in mortality rate in the ASA-only group versus the group receiving both ASA and ibuprofen (52). In fact, in patients treated with ASA, ibuprofen suppresses the platelet anti-aggregant effect because of the competition at COX-1 level (53); possibly, this applies to all NSAIDs, with the only exception of diclofenac (54). For this reason, the most rational choice for such patients cannot be but coxibs: by selectively acting on COX-2, these drugs do not interfere with the anti-aggregant effect of ASA and its protective action (51), while providing a better gastroduodenal tolerability profile (20).

Conclusions

Coxib represent a valid therapeutic option in the treatment of patients with osteoarticular pathologies. Their efficacy is associated to a similar safety profile as conventional NSAIDs in terms of cardiovascular risk and to a significantly superior profile with respect to gastrointestinal risk; in addition, they do not interfere with the anti-aggregant action of ASA.

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