Novel nonsteroidal anti-inflammatory drugs

Y. Boutsen, W. Esselinckx

Service de Rhumatologie, Cliniques de l'Université Catholique de Louvain (UCL) à Mont-Godinne, B-5530 Yvoir.

Abstract

The authors first briefly review how the concept of COX-2 selectivity was brought to light, then tested against the known gastrotoxicity ranking of currently used NSAIDs, from the old classics to the most recent.

One truly selective COX-2 agent — celecoxib — is now being marketed in an ever increasing number of countries. So far it seems to keep its main promises, i.e. high — albeit not total — safety regarding gastrointestinal adverse effects, and undisturbed platelet function. Association with warfarin drugs seems to raise no problems, but one should still be wary of possible renal side-effects. Efficacy, at least as assessed in osteoarthritis and rheumatoid patients, appears satisfactory. However, treatment of intense inflammatory crises, such as gout or ankylosing spondylitis, has not been assessed, as yet.

Another COX-2 agent — rofecoxib — is on the brink of being released. Its even more potent COX-2 selectivity raises new issues. What about some COX-1 activity that several authors detected in rheumatic synovitis ? On the other hand, in particular circumstances, organs such as the stomach, the kidney and small blood vessels, seem to have their homeostasis partly controlled by COX-2 mechanisms also. These questions should be answered soon, whilst clinical experience with the COX-2 agent builds up. (Acta gastroenterol. belg., **1999**, 62, **421-424**).

Key words : cyclooxygenase isoforms, COX-2 inhibitors, gastroprotection, nonsteroidal antiinflammatory drugs.

I. Introduction

Nonsteroidal anti-inflammatory drugs (NAIDs) inhibit the activity of cyclooxygenase (COX), which mediates the conversion of arachidonic acid to the prostaglandins (PG) that serve as key components of the inflammatory process. However, PG are also known to have a role in maintaining normal gastrointestinal (GI) and platelet function, as well as renal function under physiological stressed conditions.

Recently, 2 distinct isoforms of COX have been identified, and designated COX-1 and COX-2. COX-1 is a constitutive form that is expressed in many tissues, including the GI tract, kidney, and platelets. COX-2, a cytokine-inducible form, is found in very low levels in healthy tissue, but is expressed prominently in inflamed tissue.

These observations gave rise to the hypothesis that NSAID-induced GI damage as well as platelet and renal dysfunction result from inhibition of COX-1, whereas the therapeutic effect results from COX-2 inhibition at inflammation sites.

Indeed, further studies (1,2) have shown that : (a) up-regulation of COX-2 expression is blocked by anti-inflammatory glucocorticoids, which do not alter COX-1 expression ; (b) in animals, selective inhibition of COX-2 expression has an anti-inflammatory effect, but does not cause GI toxicity. In contrast, currently available NSAIDs, which non-selectively inhibit both COX-1 and COX-2, cause pronounced GI damage when administered in therapeutic doses.

II. Screening for COX selectivity

The results of the initial *in vitro* screening of COX inhibitors are typically reported as the concentration that causes 50% reduction in enzyme activity, i.e. 'IC_{50}'. The ratio of the IC_{50} for COX-1 versus COX-2 has become commonly used, so that the more COX-2 selective an agent is, the smaller the quoted ratio. Some authors promote the use of the inverse of this ratio.

Important differences in the numerous experimental conditions between the test models have resulted in considerable variations in IC_{50}, and given rise to confusing comparisons.

Currently, the whole human blood assay has many advantages : (a) intact human cells are used which are target cells for the anti-inflammatory effects (synthesis of PGE_2 from stimulated monocytes : COX-2 activity) and the side-efffects (synthesis of thromboxane from platelets during clotting : COX-1 activity) of NSAIDs ; (b) whole blood used for both assays is taken from the same volunteer (or patient) at the same time to allow a direct comparison ; (c) the assay can be performed using blood from volunteers (or patients) who have previously been treated with NSAID (*ex vivo* assay) thus allowing a comparison of the *in vivo* relevance of *in vitro* findings (3).

Still more appropriate markers of COX-1 and COX-2 activity *in vivo* would be PGI_2 production by the gastric mucosa and PGE_2 production by inflamed synovial tissue, respectively. However, in practice the target tissues are not easily obtainable, since prostaglandin production occurs during tissue removal, and prostaglandin concentration in gastric juice or synovial fluid may not reflect accuretely the synthetic activity (4).

Correspondance and request of reprints : Dr Yves Boutsen, Service de Rhumatologie, Cliniques de l'Université Catholique de Louvain (UCL) à Mont-Godinne, B-5530 Yvoir.

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III. Preliminary clinical validation

Extensive epidemiological data of the gastrointestinal side-effects of existing NSAIDs were compiled (5,6,7).

When these results are compared with the spectrum of COX-2/COX-1 ratios, a satisfactory parallel relationship appears (8), confirming the value of COX selectivity for further research and clinical benefits.

IV. Tentative classifications

Many COX-2/COX-1 cut-off ratios have been suggested to rank COX inhibitors, whether already in use or still experimental, leading to both a variety of classifications and several well-meant but confusing pictures (9). The following categories seem sensible to help clinicians and researchers in their efforts to improve NSAID treatment (3).

(a) A *COX-1 specific* inhibitor has no measurable effect on COX-2 activity. Low (non anti-inflammatory) dose aspirin is the only drug in this category (10) ;
(b) A *COX non-specific* inhibitor exhibits no meaningful biologic or clinical difference between COX-1 and COX-2 inhibition, especially when pharmacodynamic and pharmacokinetic properties are also taken into account ;
(c) A *preferential COX-2* inhibitor manifests some anti-inflammatory activity within a given dose range and in a predictable number of patients, whereas at higher doses inhibition of COX-1 is likely to occur ;
(d) A *specific COX-2* inhibitor ("COX-2 agent") causes no clinically meaningful inhibition of COX-1, over the whole range of doses used and concentrations achieved in clinical usage.

This working classification quite rightly emphasizes the paramount importance of studying clinically relevant concentrations.

Incidentally, after Sir John Vane had brought to light the mechanism of action of NSAIDs in 1971 (11), it was consistently observed that plasma and tissue concentrations of NSAIDs needed to obtain detectable anti-inflammatory (COX-2 driven) effects *in vivo* were higher than those needed to inhibit (undifferentiated) cyclooxygenase *in vitro* with non selective models. The first reasonable explanation for this discrepancy came from Needleman and his group in 1990, who hypothesized the existence of 2 different cyclooxygenases (1).

The importance of considering various dose levels is illustrated by two existing NSAIDs which were found to manifest some COX-2 preferential inhibition (4).

In various assays, *meloxicam* has been estimated to be between 3- and 77-fold selective for COX-2. When the whole blood concentration-inhibition curves are analyzed, it would be expected that meloxicam, 7.5 mg/day, inhibits COX-2 by 55-75% and COX-1 by 10%. With 15 mg/day, an inhibition of COX-2 by 80-90% would be expected, accompagnied by a 15-30% inhibition of COX-1.

Nimesulide was found to be 5 to 16-fold selective for COX-2. When similar simulations are performed at the recommended doses of 100 mg given twice daily, a significant inhibition ($> 50\%$) of COX-1 occurs and COX-2 preference is lost. This is a consequence of a too steep concentration-inhibition curve, in addition to a rather weak COX-2 preference.

Clinically, nimesulide seems to induce ulcer complications as commonly as standard NSAIDs, and definite inflammatory conditions such as rheumatoid arthritis, are beyond its efficacy range.

Accordingly it must be stressed that preferential COX-2 inhibition *in vitro* may translate into a COX-1 sparing effect *in vivo*, provided the plasma concentration-inhibition curve is flat enough so that steady-state levels are continuously maintained above the inhibitory concentrations for COX-2, but below the inhibitory concentrations for COX-1.

For practical purposes, referring to the working classification proposed above : category (b) includes the standard NSAIDs some of which are slightly more active on COX-1 than on COX-2 ; category (c) includes mainly meloxicam, a preferential COX-2 inhibitor ; category (d) includes highly selective, newly developed NSAIDs, which we shall now consider, as well as meloxicam, from a clinical point of view.

V. Clinical studies

1. *Meloxicam*

In a double-blind study in healthy males, meloxicam 7.5 mg caused no more mucosal injury than placebo over 23 days. However, a higher daily dose of meloxicam (15 mg) as recommended for treating rheumatoid arthritis, caused levels of mucosal injury intermediate between placebo and piroxicam 20 mg (12). This is consistent with the reduction in COX-2 preference known to occur with higher doses of meloxicam, as shown above.

The Melissa (Meloxicam Large-scale International Study Safety Assessment) was a double-blind, randomized, prospective trial, conducted over 28 days in patients with exacerbation of hip, knee, hand or spine osteoarthritis (13). Meloxicam 7.5 mg was given to 4635 patients and diclofenac 100 mg slow release was given to 4688 patients. Significantly ($p < 0.001$) fewer GI adverse effects were reported by patients receiving meloxicam (13%) compared to those receiving diclofenac (19%). Significantly ($p < 0.01$) more patients discontinued meloxicam than diclofenac because of a lack of efficacy.

The Select (Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies) trial was identical to the Melissa study in design and patients, except for the comparator drug, which was piroxicam 20 mg a day (14). The outcome was similar.

It should be noted that meloxicam 7.5 mg most probably represents a lower effective dose than diclofenac0 100 mg or piroxicam 20 mg. Accordingly, the Melissa and Select results, both obtained with osteoarthritis, can by no means be extrapolated to the 15 mg meloxicam dose, which would be certainly needed to treat conditions such as rheumatoid arthritis (15).

2. *Celecoxib* (SC 58635 - Celebrex™)

This drug is quoted as being 375-fold selective for COX-2. Clinical efficacy and safety have already been extensively investigated. One such study (16) included :

(a) An osteoarthritis trial randomizing 297 patients who received celecoxib (40 mg twice daily, 100 mg twice daily or 200 mg twice daily) or placebo for 2 weeks. All 3 dosages were different from placebo in the efficacy assessments ;
(b) A rheumatoid arthritis trial randomizing 330 patients who received celecoxib (40 mg twice daily, 200 mg twice daily, or 400 mg twice daily) or placebo for 4 weeks. The 2 higher dosage groups differed significantly from placebo in all efficacy assessments ;
(c) An upper GI study randomizing 128 healthy subjects who received celecoxib 100 mg twice daily, celecoxib 200 mg twice daily, naproxen 500 mg twice daily, or placebo for 1 week. At the two dosage levels, celecoxib produced no ulcers and was indistinguishable from placebo. In the naproxen group, 19% of subjects developed gastric ulcers ($p < 0.047$), which is comparable to findings of other 1-week endoscopic studies, in which 500-1000 mg/day naproxen induced gastric ulcers at incidences of 8-40% ;
(d) An assessment of platelet effects. Six healthy male subjects received celecoxib 400 mg twice daily for six days. After a 7-day washout period, they received a single 650 mg dose of aspirin. No clinically meaningful effect of celecoxib on platelet aggregation or thromboxane B_2 levels was found at this high therapeutic dose, in contrast to the significant decreases in these measures with aspirin. Since platelet prostaglandin metabolism and thromboxane B_2 production are mediated only by COX-1, these results suggest that celecoxib at 400 mg daily has no *in vivo* effect on platelet COX-1.

Celebrex™ is supplied in the USA as 100 and 200 mg capsules. The recommended dose for osteoarthritis is 100 mg twice a day and for rheumatoid arthritis 200 mg twice a day. These doses have an equivalent efficacy to naproxen 500 mg or diclofenac 75 mg, both twice daily (15).

3. *Rofecoxib* (MK 0966 - Vioxx™)

Rofecoxib is another designer drug which is so much more COX-2 selective that loss of selectivity at higher doses is unlikely to occur. The selectivity ratio of rofecoxib has been measured above 800 in human cell lines. In the whole blood *ex vivo* assay, an IC_{50} for COX-1 could not be calculated because inhibition was not seen with doses up to 1000 mg. Available data from osteoarthritis studies showed rofecoxib at 12.5 or 25 mg per day to be as effective as ibuprofen 2400 mg a day or diclofenac 150 mg a day.

In doses of 250 mg per day (10 - 20 times the likely recommended clinical dose) rofecoxib had no effect on bleeding time, and caused levels of gastric mucosal injury that were similar to placebo and less than with ibuprofen 2400 mg over 7 days (15).

With such promising data, it can be reasonably hoped that highly selective COX-2 inhibitors will provide a major therapeutic breakthrough.

VI. Pending issues

1. *Gastrointestinal safety of COX-2 agents*

a) COX-2 induction has been demonstrated in *H pylori* gastritis and in inflammatory bowel disease. The COX-2 that is induced in *H pylori* gastritis probably remains a minor contributor to protective prostaglandin synthesis. The enzyme's contribution in ulcerative colitis may be greater (15). Individual COX-2 agents will have to be shown to be safe in these conditions.

b) COX-2 is induced at the rim of gastric ulcers in humans. In animal studies, COX-2 inhibitors retarded ulcer healing. Consequently, in patients with classical NSAID-associated ulcers, healing with active agents will have to be studied when these patients are switched to COX-2 inhibitors.

2. *Vascular disease and COX-2 agents*

Preservation of normal platelet function, as described above with selective COX-2 inhibitors, is a doubtless advance for maintaining the effective haemostasis required in case of GI bleeding and for surgical and other invasive procedures, but in the setting of vascular insufficiency, the therapeutic aims are obviously different. Low-dose aspirin's unique cardiovascular protective effects are mediated through COX-1 inhibition while vasodilation is mainly promoted via COX-1 induced prostacyclin (PGI_2) production, although it may become COX-2 driven in hypoxia (17).

Consequently, selective COX-2 inhibitors do not seem to be the best choice in this wide group of patients with vascular insufficiency.

3. *COX-2 agents and renal function*

Conventional NSAIDs are widely known to induce clinically significant creatinine elevations, salt and water retention, hyponatraemia and hyperkaliaemia. These adverse reactions are particularly prone to occur in patients with volume depletion, hypotension, congestive heart failure, ascitis, diuretic therapy and intrinsic renal disease.

Prostaglandins, mainly COX-1 driven, have a significant modulatory role on a variety of renal events including renal blood flow (PGI_2 and PGE_2), water and salt reabsorption (PGE_2), renin production (PGI_2 and PGE_2). Regulation through COX-2 has been observed in the macula densa following salt deprivation.

Specific studies will be needed to determine whether selective COX-2 inhibitors will share some or all of the above adverse reactions. Clinical trials with celecoxib have shown renal effects similar to those observed with standard NSAIDs.

4. *Efficacy of selective COX-2 inhibitors*

Clinical trials should be carefully diversified and all subtypes of arthritic disorders should be specifically targeted, especially taking into account important biological data on the detection and expression of COX-1/COX-2 in synovial cells and fluids.

One such study (18) found the expression of COX-2 to be elevated in a disease-related pattern in the synovial tissue from patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis in comparison with osteoarthritis samples, and was especially high in ankylosing spondylitis synovial tissue. Consequently the latter diseases may become the gold standard of therapeutic performance, osteoarthritis being at the opposite end of the spectrum, and providing much less clinically meaningful data.

Another study (19) found both COX-1 and COX-2 isoforms expressed by synovial fluid cells taken from patients with crystal-induced arthritis, rheumatoid arthritis and psoriatic arthritis, raising the point of keeping some COX-1 inhibitory potency in the novel NSAIDs.

VII. Conclusions

1) The reality of the COX concept is now clinically well confirmed, and its future applications appear promising. One should, however, remain cautious on several issues. Indeed, the paradigm that COX-1 is exclusively committed to physiologic homeostasis and that COX-2 is entirely involved in inflammation is an obvious oversimplification.

2) Only highly selective (rather than preferential) COX-2 inhibitors will be able to break the prostaglandin-dependent link between efficacy and gastrotoxicity.

3) The efficacy of these COX-2 agents should be tested throughout the full spectrum of arthritis, ankylosing spondylitis (AS) possibly becoming the challenging clinical model. Indeed, NSAIDs is the corner stone for treating AS, for which no convincing disease modifying drug is available.

4) Further clinical studies and experience is required to establish the safety of COX-2 agents both in the normal and diseased GI tract.

5) Little is known about the possible renal adverse effects of COX-2 agents. Will many of them share the all-too-common drawbacks of standard NSAIDs ?

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