The role of COX inhibitors in various physiological systems

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Abstract

This article gives an overview of the physiology of the COX enzymes, selectivity of NSAIDs and efficacy of COX-2 selective inhibitors in comparison to nonselective ones.

Many articles focus on the cardiovascular side-effects of COX-2 inhibitors, but in this paper we describe the effects of COX inhibition in a number of other physiological systems, for example the bones and soft tissues, kidneys, lungs and the female reproductive tract. In particular we look at the gastrointestinal tract, where factors such as H. pylori infection and duration of NSAID use may influence clinical outcomes.

Furthermore, we investigate the potential role of COX inhibition in the treatment of Alzheimer’s disease and cancer. Lastly, we address the controversy of some COX-2 inhibitors possibly being cardioprotective and look at their safety in combination with aspirin.

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the cyclo-oxygenase (COX) enzyme, which is responsible for prostaglandin H2 (PGH2) synthesis. Inhibition of PG results in pain relief and reduction of inflammation. However, the majority of NSAIDs inhibit PGs found all over the body and not only at the location of the inflammation, causing side effects like gastrointestinal (GI) and renal toxicity, as well as impairment of platelet function.

The COX enzyme exists in two main isoforms, namely COX-1 and COX-2. Conventionally it was thought that inhibition of COX-2 is responsible for the anti-inflammatory effect, whereas COX-1 inhibition is responsible for the adverse events. Traditional NSAIDs are non selective and block both COX-1 and COX-2 enzymes, which results in the anti-inflammatory effect, but with potential adverse effects. Selective COX-2 inhibitors or “COXIBs”, e.g. celecoxib, lumiracoxib and parecoxib, have comparable anti-inflammatory effects to the nonselective inhibitors, but apparently with less GI toxicity.

However, in recent years this differentiation in terms of side-effects has been questioned. Some of the COX-2 inhibitors, e.g. rofecoxib and valdecoxib have been withdrawn from the market due to concerns about adverse cardiovascular events and serious anaphylactic reactions, respectively. Lumiracoxib has also been withdrawn from the South-African market, due to serious liver complications.

In 2005 the FDA concluded that in accurately selected and informed patients the benefits of celecoxib outweigh the possible risks and therefore this drug should remain in the market. However, the following actions are required for all NSAIDs:

• A boxed warning on the label with regards to the cardiovascular (CV) and GI risks, including a contraindication for use in patients immediately post operative from coronary artery bypass grafting (CABG).
• Patients should be encouraged to use the lowest effective dose for the shortest duration.
• A medication guide should be dispensed with the drug.

In May 2006 the South African Medicines Control Council required that standard information related to CV and GI safety is included in package inserts for all NSAIDs and COX-2 inhibitors.
Physiology of the COX enzymes

A number of PGs are catalysed via COX-1 and COX-2 enzymes from arachidonic acid, which is found throughout the body. The range of prostaglandins synthesised by cells expressing COX-1 or COX-2 is influenced by the presence of diverse downstream enzymes in the particular tissue. There are several PGs, designated by letters A to I with several subgroups indicated by numbers, e.g. PGE2, PGF2α and PGI2.

The COX-1 enzyme (the housekeeping enzyme) is found in most tissues and serves regular physiological function, but could be upregulated in particular cell types. The COX-2 enzyme is found in the vascular endothelium, brain, kidney, bone and female reproductive system and is also involved in certain physiological processes. However, it is induced by inflammatory stimuli such as bacterial endotoxin and cytokines. For example, this upregulation of COX-2 in arthritis contributes to the classical symptoms of rheumatoid arthritis (RA). Increased levels of COX-2 have also been seen in diseases such as Alzheimer's disease (AD), systemic lupus erythematosus, colon, breast and pancreatic cancer, as well as diabetic neuropathy and premature labour.

The NSAIDs in therapeutic use have all been shown to inhibit COX, resulting in a significant reduction in PG synthesis. Figure 1 depicts some of the functional effects related to inhibition of COX-1 and/or COX-2.

COX-3 is a recently identified splice variant/isoenzyme of COX-1 and, more suitably, may have been named COX-1b. It was initially reported to be expressed in canine cerebral cortex. In humans COX-3 mRNA is found in highest concentrations in the brain and heart. However, it could possibly be that COX-3 is not applicable to humans, as it appears we may be unlikely to express this enzyme, because of a nucleotide difference between humans and canines. Therefore, although the COX-3 signal may be found in humans, this could not directly result in COX-3 protein synthesis. Warner and colleague concluded that only two genes for COX enzymes (COX-1 and COX-2) exist in humans.

Selectivity

NSAIDs do not have the same pharmacological profile, but differ in terms of COX-2/COX-1 selectivity ratios. The COXIBs express at least a 200- to 300-fold selectivity for blocking COX-2 over COX-1 at the defined therapeutic dose. Celecoxib is the least selective of the COX-2 inhibitors; it is only slightly more selective than diclofenac. Lumiracoxib is the most COX-2 selective, followed by rofecoxib and etoricoxib.

Some older NSAIDs are relatively COX-2 selective at low doses. For example meloxicam, which is available in doses of 7.5 mg and 15 mg, blocks the activity of COX-2 in low doses, but has a more profound effect on COX-1 in higher doses. At a dose of 15 mg an increase in serious GI side effects is seen compared to 7.5 mg.

In some experimental systems, nabumetone appears to more effectively block COX-2 than COX-1. It may be less likely to induce gastric ulcers than other NSAIDs. However, relative inhibition of COX-2 decreases and the risk of ulcer disease increases with the use of higher doses of nabumetone. Since 6-MNA, the active metabolite of nabumetone, is only a weak inhibitor of COX at low doses, the relative gastric protection observed with nabumetone may be due to the neutral state of the prodrug formulation rather than COX-2 selectivity.

Although conventional NSAIDs are mostly not selective for COX-2, some, e.g. diclofenac, are similar to celecoxib and meloxicam in laboratory findings of COX-2 selectivity. However, human pharmacokinetics such as a longer plasma half life or higher doses used in practice may make laboratory evaluation of selectivity irrelevant. Therefore, an emphasis on overall clinical benefit of each drug seems appropriate.

Efficacy

COX-2 inhibitors are generally found to be equally effective as compared to traditional NSAIDs. Refer to Table I for studies that compared the efficacy of COX-2 inhibitors with traditional NSAIDs.

In a meta-analysis of 14 trials including patients with osteoarthritis (OA) and RA, COXIBs were directly compared over 2–13 weeks. Seven trials compared rofecoxib (25 mg/day) with either celecoxib (200 mg/day) or valdecoxib (10 mg/day). The tolerability and efficacy of rofecoxib appeared to be similar to both celecoxib and valdecoxib, but due to limited base evidence and potentially non-equivalent doses, these results must be interpreted with caution. The other trials compared lumiracoxib (200–800 mg/day) with celecoxib (200–400 mg/day) or rofecoxib (25 mg/day). The efficacy of lumiracoxib compared to celecoxib and rofecoxib seems to be dose dependant and there was no significant difference with regards to safety and tolerability.

COX inhibition and Alzheimer's disease (AD)

Evidence of COX-2 containing inflammatory mediators and activated microglia found around AD lesions suggest the possibility that chronic inflammation could directly cause neural damage. There is also a link between N-methyl-D-aspartate (NMDA)-mediated neural activity, COX-2 induction and cell death.

It is hypothesised that NSAIDs may modify the risk of dementia and protect against cognitive decline. The antithrombotic effect of some PGs may be important for protection against AD. For example, de la Torre suggested that the development of torturous and flow-impeded
capillaries in the brain is the cause of AD. This would seemingly encourage intravascular coagulation, resulting in ischaemic damage to the brain that could lead to the development of AD. It follows that reduction in the synthesis of the protective PGs may have deleterious effects on cognitive performance.

Epidemiologic studies concluded that NSAID users have half the risk of acquiring AD compared to non-NSAID users. This was especially true for more distant use (i.e. years before dementia symptoms would normally appear), as compared to use in people with neuropathy already present.

The results of a 12-month trial of rofecoxib and naproxen, which found no slowing of cognitive decline in mild-moderate AD patients, support the above observation.

The ADAPT (Alzheimer’s Disease Antiinflammatory Prevention Trial) evaluated the effects of naproxen and celecoxib on cognitive function in older adults with a family history of AD. A total of 2528 patients enrolled in the 4 year trial and 2117 contributed follow-up cognitive measures. Patients randomly received celecoxib (200 mg twice a day), naproxen sodium (220 mg twice a day) or placebo. Seven cognitive function tests and a global summary score were measured annually. The conclusion was that neither celecoxib, nor naproxen preserves or improves cognitive function.

More clinical trials with different NSAIDs, e.g. ibuprofen which was commonly used in observational studies, and carefully timed exposure to these drugs are needed before the role of COX inhibition in AD is clarified.

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COX inhibition and cancer

Because of COX-2 expression in neoplasms, there is a hypothesis that COX-2 inhibition may be useful in the treatment or prevention of various cancers.2,5

COX may possibly play an essential role in the regulation of angiogenesis related to neoplastic tumour cells. Therefore, COXIBs may inhibit the growth of blood vessels into developing tumours.2

The upregulation of COX-2 has been noticed in oesophageal and pancreatic cancer; blocking COX-2 is associated with a reduction in proliferation and an increase in apoptosis (programmed cell death) of these cancer cell lines. Notably, rofecoxib blocks cellular proliferation in humans with Barrett’s oesophagus.6

Several studies have demonstrated a 40-50% reduction in the risk of colorectal cancer in patients who use aspirin and other NSAIDs, for example sulindac, celecoxib and rofecoxib.2,4,6 Clinical trials have clearly shown that NSAIDs cause regression of pre-existing adenomas in patients with familial adenomatous polyposis (FAP).2,6 The FAP trial with 83 patients showed that celecoxib 400 mg daily reduced rectal polyps by 28%.4

However, the APPROVe trial evaluating the efficacy of rofecoxib in preventing the recurrence of colorectal polyps, was prematurely stopped after investigators found that patients taking 25 mg rofecoxib a day had double the risk of thromboembolic events compared to those taking placebo.5,7

The APC trial enrolling 3600 patients over 5 years to see whether celecoxib could prevent colon cancer in patients, who previously had colon polyps removed, was also prematurely halted. Compared to placebo, patients who took 400 mg celecoxib per day had 2.5 times as many strokes, heart attacks and heart deaths. However, in a second cancer study namely PreSAP, no increased risk of cardiac problems was found.7

Overall, there are good preliminary results in terms of adenoma prevention with COXIBs. Despite the CV safety issues, celecoxib also has FDA registration for familial multiple polyposis syndrome.4,15

COX-2 expression also appears to be involved in liver, lung and breast cancer and the development of teratocarcinomas. In animal studies, blocking of COX-2 is associated with a reduction in liver metastases from colon cancer, but there are no positive outcomes in humans yet.6

Whether NSAIDs inhibit tumour progression only by blocking PG synthesis is debatable. Several studies done in cell culture models have indicated that NSAIDs can act through a mechanism independent of their ability to block COX.2,8

Table I: Efficacy of COX-2 inhibitors compared to traditional NSAIDs3,11,12,13

<table>
<thead>
<tr>
<th>Study type</th>
<th>Comparators</th>
<th>Clinical efficacy of COXIBs vs NSAIDs</th>
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</thead>
<tbody>
<tr>
<td>Celecoxib 200–800 mg/day</td>
<td>40 RCTs with a median sample size of 655 patients with OA or RA</td>
<td>Naproxen, diclofenac, ibuprofen</td>
</tr>
<tr>
<td>Celecoxib 100 mg twice a day</td>
<td>6-week RCT with 246 patients with AS</td>
<td>Ketoprofen 100 mg bd</td>
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<tr>
<td>Celecoxib 200–400 mg daily</td>
<td>12-week RCT with 458 patients with AS</td>
<td>Diclofenac SR 75 mg bd</td>
</tr>
<tr>
<td>Etoricoxib 60–120 mg/day</td>
<td>7 relatively small RCTs in patients with OA or RA</td>
<td>Naproxen, diclofenac, and ibuprofen</td>
</tr>
<tr>
<td>Etoricoxib 90 and 120 mg</td>
<td>52-week RCT with 387 AS patients</td>
<td>Naproxen 1000 mg</td>
</tr>
<tr>
<td>Lumaracoxib 100–1200 mg/day</td>
<td>15 RCTs with a median sample size of 893 patients with OA or RA</td>
<td>Naproxen, diclofenac, or ibuprofen</td>
</tr>
<tr>
<td>Meloxicam 7.5–22.5 mg/day</td>
<td>16 RCTs with 22886 participants with OA or RA</td>
<td>Naproxen, diclofenac, nabumetone or piroxicam</td>
</tr>
<tr>
<td>Rofecoxib 12.5–50 mg/day</td>
<td>23 RCTs with a median sample size of 673 patients with OA or RA</td>
<td>Naproxen, ibuprofen, nabumetone or diclofenac with misoprostol</td>
</tr>
<tr>
<td>Valdecoxib 10–80 mg/day</td>
<td>11 RCTs with a total of 9293 participants with OA or RA</td>
<td>Naproxen, diclofenac, or ibuprofen</td>
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</tbody>
</table>

OA – Osteoarthritis; RA – Rheumatoid arthritis; RCT – Randomised controlled trial; AS – Ankylosing Spondylitis; bd – twice a day
COX inhibition and the gastrointestinal (GI) tract

Serious GI events like bleeding or perforation from peptic ulcers take place in up to 2% of patients taking NSAIDs, but are mostly asymptomatic. On the other hand, endoscopically confirmed ulcers occur in one quarter of people who take nonselective NSAIDs like ibuprofen, but less frequently in COXIB users. Only limited data links ulcers on endoscopy with complications like upper gut bleeding or perforation. This may possibly be because the gut mucosa adapts to noxious insults like NSAIDs.

COX-2 inhibitors provide protection against serious GI adverse effects, but this protective effect differs radically across the individual drugs, concomitant aspirin and period of use. 3

Refer to Table II for studies related to the GI adverse effects of COX-2 inhibitors.

The risk of serious GI toxicity seems to be comparable between NSAIDs and COXIBs, despite the duration of previous NSAID use, but cumulative risk is likely to be greater with longer term use. Some studies demonstrate a higher risk of GI complications earlier during NSAID treatment. 3,5,16 The CLASS study has shown that GI events were rare with diclofenac after a period of 3 months of treatment, but after the second 6 months of treatment the incidence of ulcer complications was higher with celecoxib than with ibuprofen or diclofenac. 3,16 Overall, after a year of observation there were no significant differences of ulcer complications between the 3 drugs. 3,5

Helicobacter pylori infection and NSAIDs are the two most important factors related to peptic ulcer disease, but it is uncertain whether NSAIDs and H. pylori together might increase ulcer risk. Some studies have shown that first time NSAID use increases risk only in people with H. pylori infection. Post hoc analysis of the VIGOR and CLASS studies does not confirm an obvious association between signs of infection and ulcer complications. 2 Other studies have shown that H. pylori infection reduces NSAID risk; maybe because H. pylori increases prostaglandins, i.e. COX-2 expression found with Helicobacter pylori may contribute to tissue repair. 3,6

Based on this, concerns have been raised that the inhibition of COX-2 may reduce beneficial inflammation and cause damage. 2,3,5,9,19 This may explain why in some studies the use of COXIBs was related to higher ulceration rates than placebo. 4,16,19 Furthermore it was found that oesophageal ulcer healing is delayed by blocking COX-2 because of reduced ulceration-induced oesophageal epithelial cell proliferation. 6

Nevertheless, the apparent favourable GI tolerability, at least in the short term, and widespread availability of COXIBs have caused a change in clinical practice. 3,19 As such, the cost of prescription NSAIDs in the United Kingdom has increased by one quarter since 2004 due to the use of COX-2 selective drugs. 3

Pharmacoeconomic studies prove that cost-effectiveness is encouraging when COX-2 inhibitors are limited to high-risk patients, and when the decrease in the risk of severe GI side effects is large. 5

However, costs can also be decreased when a traditional NSAID (e.g. ibuprofen or diclofenac) is used in combination with a proton-pump inhibitor (PPI), instead of using a COX-2 inhibitor alone. 3,5 In one study, diclofenac in combination with omeprazole was shown to be as safe as celecoxib in patients with a history of gastric ulcer bleeds. 5,6 Note that the PPI is not expected to give protection in the lower GI tract, but inflammation, ulcers and bleeding in the small intestine and colon are much less common than in the upper GI tract. 3,5

COX inhibition in bone and soft tissues

The role of PGs in bone metabolism is complex and conflicting. For example, PG stimulates bone resorption in vitro, but in human and animal studies PG stimulates bone formation. Collagen synthesis by osteoblasts can either be stimulated or inhibited by PGs. 7 Thus, PGs play an essential role in bone repair and normal bone homeostasis. 2,20

Animal studies have shown that selective COX-2 inhibition:

- Impairs ligament and fracture healing
- Limits glomerular capillary repair after glomerulonephritis
- Reduces bone ingrowth 4,6,20

It has also been reported in animal studies that bone healing after spinal fusion as well as fracture healing is more dependant on COX-1 activity rather than COX-2. 6

In an observational study, limited evidence supported a causal relationship between NSAIDs and nonhealing of fractures. However, in a retrospective study of tibial fractures, NSAIDs were not a significant risk factor for nonunion. Generally, the extensive use of NSAIDs by patients with fractures has not manifested a clinical problem with nonunion. This is possibly due to the difference in the doses of NSAIDs between animals and humans or the different biology of human fractures. 4 A slight increase in bone density has in fact been seen. 6

Unfortunately there are hardly any good studies done in human NSAID users and sufficient studies will have to be very large, because nonunion is an unusual event with modern treatment regimens. 2,6

It is unclear whether the COX-enzymes are required for dermal wound healing. Animal studies have shown that COX-2 inhibition may possibly decrease the initial inflammatory phase of epidermal wound healing and lessen formation of scar tissue, without decreasing tensile strength or disrupting reepithelialisation. 6

COX inhibition and the reproductive tract

Over the years it has been well recognised that PGs are involved in ovulation, fertilisation and embryo implantation. 2,6 Ovulation goes together with the induction of PG synthesis as
### Table II: Example of studies investigating the GI effect of COX-2 inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Medication</th>
<th>Outcome regarding GI adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vioxx Gastrointestinal Outcomes Research (VIGOR) trial</td>
<td>Double-blind, prospective RCT including 8 076 RA patients</td>
<td>Median follow up of 9 months</td>
<td>Rofecoxib (50 mg daily) versus naproxen (1000 mg daily); patients were not allowed to use aspirin</td>
<td>Serious GI events were significantly less in patients receiving rofecoxib compared to patients receiving naproxen</td>
</tr>
<tr>
<td>Therapeutic Arthritis Research and Gastrointestinal Event Trail (TARGET) study</td>
<td>Double-blind RCT including &gt;18 000 patients with OA</td>
<td>1 year</td>
<td>Lumiracoxib (400 mg daily) was compared to naproxen (500 mg bd) or ibuprofen (800 mg tds); patients were allowed to use aspirin</td>
<td>Serious GI events were significantly less in the lumiracoxib arm, only in patients who did not use concurrent aspirin</td>
</tr>
<tr>
<td>Successive Celecoxib Efficacy and Safety Study (SUCCESS-I)</td>
<td>Double-blind RCT including 13274 patients with OA</td>
<td>12 weeks</td>
<td>8800 patients randomly received celecoxib (100 or 200 mg bd) and 4394 received diclofenac (50 mg bd) or naproxen (500 mg bd); patients were allowed to take aspirin</td>
<td>The number of clinically significant ulcers was equal in both groups, despite the larger size of the celecoxib group; there were fewer complications only in patients not taking concomitant aspirin</td>
</tr>
<tr>
<td>Surveillance endoscopy</td>
<td>RCT including 688 patients with RA</td>
<td>12 weeks</td>
<td>Celecoxib, naproxen or placebo; there is no mention whether aspirin was allowed or not</td>
<td>Endoscopically determined gastroduodenal ulcers among patients taking celecoxib was similar to placebo and significantly lower than that with naproxen</td>
</tr>
<tr>
<td>Celecoxib Long term Arthritis Safety Study (CLASS)</td>
<td>Double-blind RCT involving 8059 OA and RA patients</td>
<td>1 year</td>
<td>Celecoxib (400 mg twice a day), ibuprofen (800 mg tds) or diclofenac (75 mg bd); patients were allowed to use up to 325 mg aspirin daily</td>
<td>Celecoxib was associated with reduced incidence of symptomatic ulcers and ulcer complications compared to the nonselective NSAIDs at 6 months; however, at 1 year there was no statistically significant reduction in ulcers and their complications</td>
</tr>
<tr>
<td>Endoscopy study</td>
<td>Double-blind, parallel-group study with 680 patients</td>
<td>12 weeks</td>
<td>Etoricoxib (120 mg daily), ibuprofen (800 mg tds) or placebo; there is no information on aspirin use</td>
<td>Incidence of ulcers was significantly higher in the ibuprofen group</td>
</tr>
<tr>
<td>Combined analysis of upper GI events</td>
<td>10 Phase II/III trials in patients with OA, RA and chronic low back pain</td>
<td>Maximum 792 days treatment</td>
<td>Etoricoxib (60, 90 or 120 mg daily) versus naproxen, ibuprofen or diclofenac; there is no information on aspirin use</td>
<td>The incidence of adverse upper GI events was reduced by +/- 50% in etoricoxib users; results were mainly driven by naproxen</td>
</tr>
<tr>
<td>Cardiovascular safety and gastrointestinal tolerability of etoricoxib vs diclofenac in a randomised controlled clinical trial (the MEDAL study)</td>
<td>Double-blind, RCT including 23 504 patients with OA or RA</td>
<td>Mean duration from 19.4 to 20.8 months</td>
<td>Etoricoxib (60 or 90 mg daily) and diclofenac (75 mg bd); patients were allowed to use low dose aspirin</td>
<td>Etoricoxib had a more favourable GI tolerability profile compared to diclofenac, but there was no difference in complicated events; aspirin use did not influence results significantly</td>
</tr>
</tbody>
</table>

OA – Osteoarthritis; RA – Rheumatoid arthritis; RCT – Randomised controlled trial; bd – twice a day; tds – three times a day
a result of LH surge. COX-2 induction is needed for successful follicle rupture, possibly due to involvement in activating proteolytic enzymes necessary for this process. Rofecoxib has an unfavourable effect on ovulation, resulting in delayed follicular rupture without upsetting the peripheral hormonal cycle.

As the COX-1 gene is not strongly inducible, it seems that COX-1 mediates the early stages of labour, uterine contractions and early phases of cervical dilation. COX-2 is upregulated by the action of proinflammatory cytokines from structures such as the foetal membranes and may generate the PGs that maintain myometrial contractility and cervical ripening, eventually resulting in expulsion of the foetus. COX-2 is induced during human labour while the COX-1 isomere is not.

Human studies have shown that indomethacin and other NSAIDs, as well as the COX-2 inhibitor nimesulide, decrease preterm labour.

**COX inhibition and the kidneys**

A number of in vitro and animal studies point towards the prominent role of COX-2 in renal development and function. COX-2 generated PGs may be important moderators of renin production and tubuloglomerular feedback.

In rabbits, selective COX-2 inhibition results in an increased pressor effect of angiotensin-II and decreased blood flow in the renal medulla, with subsequent reduced urine output and sodium excretion.

Despite these observations, clinical trials with celecoxib and rofecoxib generally did not show noteworthy changes in renal function linked to treatment at the registered doses for RA and OA. The precipitation of acute renal failure seems to be confined to selected patients, such as those with heart failure, cirrhosis, diabetic nephropathy, volume and salt depletion and hypercalcaemia. These findings suggest that COXIBs should be avoided in patients with underlying conditions.

However, conventional NSAIDs may also adversely affect renal function in at-risk patients and currently there is no evidence that the renal safety of the COXIBs is different from that of the nonselective COX inhibitors, or from each other.

**COX inhibition and the lungs**

Asthma and associated diseases are typified by excessive proliferation of airway cells, which mediate bronchoconstriction. Some patients experience symptoms after taking aspirin or conventional NSAIDs, most likely due to an increase in leukotriene production as a result of COX inhibition.

Aspirin-sensitive asthmatics express COX-2 in their respiratory tracts, but clinical studies have shown that COX-2 inhibition is not involved in the aspirin-sensitive response of the bronchi. For example, celecoxib has been shown not to cause asthmatic exacerbations in 33 patients who previously experienced such attacks in response to two or more NSAIDs.

It seems that COX-1 inhibition releases the PG “brake” on leukotriene production, whereas COX-2 upregulation inhibits proliferation of human airway smooth muscle cells, suggesting a protective role of the latter enzyme.

**Is inhibition of COX-2 cardioprotective?**

There is controversy as to whether the cardiovascular risk of COX-2 inhibitors is a class effect, related to the mode of action, specificity or the physiological role of COX-2, or whether the CV side effects are linked to the different pharmacodynamic and pharmacokinetic properties of the various COX-2 inhibitors.

Some reports have suggested that COX-2 inhibition might in fact be cardioprotective. Two studies showed the existence of COX-2 in atherosclerotic lesions of transplanted and native coronary arteries, but not in normal ones. COX-2 expression was restricted to some well-known key players in atherogenesis, namely macrophage cells, endothelial cells within the atherosclerotic plaque and medial smooth muscle. In a study by Cipollone et al, a higher concentration of COX-2 was found in carotid plaques associated with a recent stroke or transient ischaemic attack compared to asymptomatic plaques.

COX-2 also appears to be upregulated by the same stimuli implicated in the development of atherosclerosis, including:

- Tumour necrosis factor
- Platelet-derived growth factor
- Free radicals
- Interleukin-1
- Increased anterior wall shear stress

In two small, short-term studies in patients with coronary artery disease or hypertension, celecoxib has shown significant improvement in flow-mediated vasodilatation compared to placebo. It has therefore been suggested that COX-2 inhibition can improve endothelial function and may be cardioprotective.

However, if the induction of COX-2 is viewed as a compensatory mechanism to help maintain vascular health, COX-2 should be regarded as a good player in the atherosclerotic process. It is clear that further study is required, especially direct comparisons of different COXIBs at equivalent doses, in order to evaluate their CV risk/benefit profiles.

**COX inhibitors in combination with aspirin**

In the CLASS study and other trials, similar incidences of ulcers and ulcer complications were seen among patients receiving COXIBs in combination with low dose aspirin as among patients receiving traditional NSAIDs plus aspirin. Refer to Table II. The potential GI sparing effect with selective COX-2 inhibitors may be balanced out by the toxicity of concurrent use of low dose aspirin for prevention of CV diseases.
Two possible mechanisms explaining this effect are:
- Aspirin inhibits COX-1 in the GI tract
- Aspirin allows COX-2 to manufacture gastroprotective agents like lipoxins, which help to minimise GI damage due to aspirin. This effect can be eliminated by a COXIB.  

However, the MEDAL study with etoricoxib versus diclofenac resulted in a decrease in uncomplicated GI events in the etoricoxib arm, despite the use of a PPI in combination with diclofenac and the use of aspirin in both groups. For complicated GI events there was no difference between the two groups.  

In two randomised controlled endoscopic studies where healthy volunteers were given aspirin in combination with celecoxib, naproxen or placebo, significantly fewer ulcers were found in the celecoxib group compared to naproxen. It must be noted that these two studies were of short duration (one week each) and as pointed out earlier the mere presence of ulcers on endoscopy has a weak correlation with gastric bleeding and/or perforation. 

The combined use of a COXIB and aspirin may also influence treatment decisions with regards to patients with a high CV risk. Intuitively one may think that aspirin will cancel out the negative effect of COXIBs on the CV system, however, according to the APC, APPROVe and valdecoxib CABG trials, the increased CV risk observed with COXIBs was not influenced by the use of aspirin. 

**Summary**

By blocking COX-2 both conventional NSAIDs and COXIBs reduce PG synthesis and have an equal anti-inflammatory effect. However, the other consequences of reduced PGs may differ between target tissues, depending on whether predominantly COX-1 or COX-2, or both are expressed in those cells.

The clinical effects of COXIBs and conventional NSAIDs are similar in the kidney and reproductive tract, respectively, but COX-2 selective inhibitors appear to be safer than nonselective NSAIDs in asthmatic patients. 

The COX-2 inhibitors provide protection against serious GI adverse effects, but this protection may be balanced out by long-term use and/or the toxicity of concurrent low dose aspirin. There is substantial evidence to suggest that the inhibition of COX-2 can limit the progression of colorectal cancer and Barrett’s oesophagus, however, more clinical trials are needed before the role of COX-2 in other cancers is proven. Further study is also required in Alzheimer’s disease. 

While animal studies have suggested that the inhibition of the COX-2 enzyme impairs fracture healing, clinical reports have been inconclusive. Definite data is also needed with regards to all NSAIDs and CV safety. 

Despite their cost and controversies, COX-2 inhibitors will continue to be clinically useful in a selected group of patients such as those:

- Who require NSAID treatment despite optimisation of other modalities
- With a low CV risk profile
- With a high GI bleeding risk  

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