The use of cyclo-oxygenase 2 inhibitors in South Africa

Ilse Truter, DCom, BPharm, MSc, PhD
Drug Utilisation Research Unit (DURU), Nelson Mandela Metropolitan University

Correspondence to: Ilse Truter, e-mail: ilse.truter@nmmu.ac.za

Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors are effective anti-inflammatory and analgesic agents that are used to treat a wide range of acute and chronic medical conditions. The focus of this article is specifically on COX-2 inhibitors, namely celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib and valdecoxib. Meloxicam is more COX-2 selective than traditional NSAIDs, but is not regarded as a pure COX-2 selective inhibitor generally. The COX-2 inhibitors have been surrounded by controversy since their introduction to the world market. The findings of well-known clinical trials have resulted in the subsequent withdrawal of some of these products from South African and other worldwide markets. Currently, there are three specific COX-2 inhibitors or coxibs that are available in South Africa, namely celecoxib, etoricoxib and parecoxib. Coxibs are effective analgesics, and compared with other NSAIDs, carry the lowest risk of ulcer formation and gastrointestinal upset. However, some studies suggest that they can be prothrombotic, increasing the risk of myocardial infarction, stroke and claudication. Although they have potentially serious side-effects, there is a place for COX-2 inhibitors. The benefits and risks should be carefully weighed up for each patient.

Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs for the treatment of pain and inflammation, especially for arthritis. From a historical viewpoint, the first NSAID containing therapeutic benefits was aspirin, which has now been used for more than 100 years. Overall worldwide production of approximately 50 000 tons a year reflects the importance of this substance, even today.1

NSAIDs block the biosynthesis of prostaglandins, which mediate a number of characteristic features of the body’s response to tissue injury or inflammation. Two significant outstanding effects of prostaglandins are their cytoprotective properties in the gastrointestinal tract and control of renal functions in the kidney. Like aspirin, all NSAIDs, such as ibuprofen, ketoprofen and naproxen, develop their mode of action by blocking cyclooxygenase (COX). Therefore, administration of NSAIDs, for example to treat inflammatory diseases such as osteoarthritis or rheumatoid arthritis, unavoidably leads to a lack of the prostaglandins. These are required for the abovementioned effects. As a consequence, long-term NSAID users suffer from a high incidence of gastrointestinal irritation, or in the worst cases, from life-threatening gastrointestinal ulcers and bleeding. Therefore, a major target of drug research has been the development of NSAIDs with anti-inflammatory and analgesic activity, but without the side-effects.

Overview of COX inhibition
COX enzymes mediate prostaglandin generation. The COX enzyme exists in two main isoforms, namely COX-1 and COX-2.2 COX-1 is the constitutive form, expressed in all cells (blood vessels, stomach and kidney), producing prostaglandins that maintain cellular homeostasis. If there is inflammation, the production of prostaglandins E (PGE2) and I (PGI2) is enhanced, resulting in fever, pain and inflammation. PGI2 is an inhibitor of platelet aggregation and a vasodilator. The COX-2 enzyme is mainly induced in this pathological process. Therefore, COX-2 is an inducible enzyme that generates inflammatory prostaglandins at sites of inflammation and healing. Conventional NSAIDs block both COX isoforms. COX-3 is a recently identified isoenzyme of COX-1, and more suitably, could have been named COX-1b.2 Although COX-3 is found in humans, it does not result in direct COX-3 protein synthesis.2 It may not play such an important role in humans, as it does in canines, for example.

In the stomach, COX-1 enhances mucosal perfusion, bicarbonate production and mucous production. These are all key gastric defense mechanisms. Therefore, COX-1 inhibition by conventional NSAIDs is known to cause toxic gastrointestinal effects, as well as to exert adverse renal effects [such as decreased renal perfusion, decreased glomerular filtration rate (GFR), oedema, increased blood pressure and interstitial nephritis].3 NSAIDs that non-selectively inhibit COX-1 and COX-2, as a result, predispose a patient to ulcer formation and upper gastrointestinal bleeding.
Selective COX-2 inhibitors were designed around the hypothesis that selective inhibition of the COX-2 isoform should reduce pain and inflammation, without compromising gastric mucosal integrity. They have been the subject of intense investigation in recent years. The COX inhibitors have different degrees of COX-2 selectivity.

With a decreased risk of adverse gastrointestinal effects, a class of medicine that selectively inhibits the COX-2 enzyme was introduced for analgesic purposes, and for the treatment of arthritis. Selective COX-2 inhibitors or coxibs have comparable anti-inflammatory effects to the non-selective inhibitors, but with less gastrointestinal toxicity. Coxibs are effective analgesics, and compared with other NSAIDs, have the lowest risk of ulcer formation and gastrointestinal upset. However, some studies suggest that coxibs can be prothrombotic, increasing the risk of myocardial infarction, stroke and claudication. This effect appears to be dose- and duration-related.

The coxibs express at least a 200- to 300-fold selectivity for blocking COX-2 over COX-1 at therapeutic doses. However, in recent years, this differentiation in relation to their side-effects has been questioned. The potential for reduced gastrointestinal toxicity with the use of selective COX-2 inhibitors is based on the hypothesis that inhibition of COX-1 has an effect on gastrointestinal mucosa and platelets, and this is the main cause of gastrointestinal ulcers and bleeding. Celecoxib is the least selective of the coxibs (only slightly more selective than diclofenac), while lumiracoxib is the most selective, followed by rofecoxib and etoricoxib. Rofecoxib has a more than 50-fold potency for COX-2 over COX-1. However, the order of COX-2 selectivity does not appear to explain the order of gastrointestinal toxicity (see Figure 1).

These newer selective NSAIDs or COX-2 inhibitors (rofecoxib, celecoxib, parecoxib and valdecoxib) were developed in the late 1990s, primarily because of their potentially lower incidence of gastrointestinal side-effects. There is substantial evidence to suggest that the inhibition of COX-2 can limit the progression of colorectal cancer and Barrett’s oesophagus, but more studies are needed before the role of COX-2 in other cancers is proven. It has been hypothesised that NSAIDs may modify the risk of dementia and protect against cognitive decline. The antiplatelet properties of NSAIDs may prevent or relieve Alzheimer’s disease by reducing the likelihood of ischaemic damage caused by obstruction of brain capillaries. Further studies are also required with regard to Alzheimer’s disease. Heavy promotion and marketing, coupled with direct-to-consumer advertising, led to an explosion in the use of COX-2 inhibitors worldwide.

However, recent evidence has indicated that there are major concerns regarding COX-2 inhibitors. Rofecoxib and celecoxib were the first two members of the selective COX-2 inhibitor class that were approved by the US Food and Drug Administration (FDA) in December 1998 and May 1999, respectively. The first sign that COX-2 inhibitors may increase cardiovascular risk was noted in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial. Soon thereafter, another study, the Adenomatous Polyp Prevention on Vioxx (APROVe) trial, confirmed an increased cardiovascular risk when rofecoxib was taken. This led to the withdrawal of rofecoxib from the world market in September 2004.

Since their introduction, many studies have been conducted to establish the safety of these medicines. Examples are the Celecoxib Long-term Arthritis Safety Study (CLASS) trial, the Meloxicam Large-scale International Study Safety Assessment (MELISSA), the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), Successive Celecoxib Efficacy and Safety Study (SUCCESS-1) and the PREMIER study (a randomised trial to determine the effects of multi-component lifestyle interventions on blood pressure). Subsequent to these further studies, another COX-2 inhibitor, valdecoxib (Bextra®), was withdrawn in April 2005.

**Figure 1:** Gastrointestinal toxicity versus COX-2 selectivity

---

Using data based on community-dispensed NSAIDs, the baseline incidence of peptic ulcer complications in patients taking NSAIDs is generally increased fourfold, but varies widely with different NSAIDs (as is illustrated in Figure 1), as well as with the dosages in which they are prescribed. Ibuprofen, for example, has the lowest risk.
Specific COX-2 inhibitors (coxibs) available in South Africa

The MIMS classification\(^7\) makes a distinction between selective COX-2 inhibitors (MIMS category 4.1.2) and specific COX-2 inhibitors or coxibs (MIMS category 4.1.3). Meloxicam is more COX-2 selective than traditional NSAIDs, but is not regarded as a COX-2 selective inhibitor generally. Meloxicam is classified as a selective COX-2 inhibitor only (MIMS category 4.1.2). Examples of trade names of meloxicam on the South African market include: Adco Meloxicam\(^8\), Arrow Meloxicam\(^8\), Arthrocox\(^8\), Coxflam\(^8\), Flexocam\(^8\), M-Cam\(^8\), Melflam\(^8\), Mobic\(^8\) and Zydus Meloxicam\(^8\).

Currently, three coxibs are available on the South African market (see Table I). All three have special precautions for prescribing listed.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Trade name</th>
<th>Dosage form available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Celebrex(^9)</td>
<td>100 mg, 200 mg capsules</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>Arcoxia(^9)</td>
<td>60 mg, 90 mg, 120 mg tablets</td>
</tr>
<tr>
<td>Parecoxib</td>
<td>Rayzon(^*)</td>
<td>40 mg powder for injection</td>
</tr>
</tbody>
</table>

Celecoxib, etoricoxib and parecoxib are selective inhibitors of COX-2, which is considered to be responsible for regulating production of inflammation-associated prostaglandins. These agents contain a sulphonamide moiety which may cause life-threatening hypersensitivity reactions in susceptible patients.\(^8\) Parecoxib is a prodrug of valdecoxib, and is converted to valdecoxib after parenteral administration.\(^8\)

Rofecoxib and valdecoxib were withdrawn from the market as a result of an increased risk of rare, but serious, skin reactions, as well as an increased risk of adverse cardiovascular events.\(^8\) In the case of valdecoxib, the additional risk of serious and potentially fatal skin reactions outweighed its benefits.

Although serious skin reactions also occur with the use of other COX-2 inhibitors, in the case of valdecoxib, they have been reported at higher rates.\(^8\) Rofecoxib was identified as significantly increasing the risk of myocardial infarction.\(^3\) Accumulating evidence on the cardiovascular safety of many COX-2 inhibitors has been systematically studied, and suggests a potential class effect of COX-2 inhibitors on cardiovascular risk.\(^1\) The nephrotoxic potential of COX inhibition, via either non-selective NSAIDs or selective COX-2 inhibition, has also been acknowledged, although the adverse renal effects of selective COX-2 inhibition are less clear.\(^4\)

Lumiracoxib (Prexige\(^*\)) has recently been withdrawn from the South African market, following reports of hepatotoxicity.\(^2,8\) Lumiracoxib was structurally different to other COX-2 inhibitors, and was the preferred COX-2 inhibitor for patients who had a sulphonamide allergy.

Warnings published by regulatory agencies

Since February 2005, the US FDA has required that all COX-2 inhibitors and non-selective NSAIDs carry a warning highlighting the potential for increased risk of cardiovascular events. In 2005, the FDA also reported that the benefits of celecoxib outweighed the possible risks, and that it should remain on the market.\(^2\)

In 2005, after its review of COX-2 inhibitors, the European Medicines Agency (EMEA) recommended that the following warnings must be carried on products:\(^9\)

- COX-2 inhibitors must not be used in patients with established ischaemic heart disease, and/or cerebrovascular disease, or in patients with peripheral arterial disease.
- Caution should be exercised in the prescription of COX-2 inhibitors to patients who have risk factors that predispose them to heart disease, such as hypertension, hyperlipidaemia, diabetes and smoking.
- The lowest effective dose for the shortest possible duration of treatment should be used, given the association between cardiovascular risk and exposure to COX-2 inhibitors.
- Hypersensitivity reactions are rare, but serious, and sometimes fatal skin reactions may occur. The majority of cases occur in the first month of use, and patients with a history of medicine allergies may be at greater risk.

In South Africa, the Medicines Control Council (MCC) requires labelling of all COX-2 inhibitors. Since May 2006, standard information relating to cardiovascular and gastrointestinal safety has to be included in package inserts for all NSAIDs and COX-2 inhibitors.\(^2\) The compulsory boxed warning for all COX-2 inhibitors states: “This product may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions, which may be fatal”.

Recommendations for use

For COX-2 inhibitor use, the following general recommendations are advised:\(^*\)

- COX-2 selective inhibitors do not provide protection against ischaemic cardiovascular events. These agents have been associated with an increased risk of cardiovascular events, such as myocardial infarction. COX-2 inhibitors are contraindicated in patients with ischaemic heart disease. The consumption of aspirin to attain cardiovascular protection negates the potential gastrointestinal sparing effect of the COX-2 inhibitors.\(^8\)
- NSAIDs and COX-2 inhibitors are mostly used for symptom relief, rather than disease modification. Therefore, they should only be prescribed when non-pharmacological and other lower-risk pharmacological drugs (aspirin, paracetamol and/or narcotic analgesics) have failed. If prescribed, a NSAID with a low COX-2 selectivity should be the preferred choice.
• Health care providers should assess the patient’s individualised risk:benefit ratio before prescribing a NSAID or COX-2 inhibitor. If the benefit is greater than the risk, to control symptoms, the lowest dose of these drugs for the shortest possible time should be prescribed.

• Periodically, patients should be monitored for adverse effects and the ongoing need for NSAID or COX-2 inhibitor use. Repeat prescriptions should be avoided.

From the above information, it appears that there is a select group of patients for whom COX-2 inhibitors will continue to be clinically useful, namely:  

• Patients who still require NSAID treatment, despite optimisation of other treatment choices.

• Patients with a low cardiovascular risk profile.

• Patients with a high gastrointestinal bleeding risk.

**Conclusion**

Both conventional NSAIDs and COX-2 inhibitors reduce prostaglandin synthesis, and have an anti-inflammatory effect by blocking COX-2. Despite all the studies that have been conducted so far, the COX-2 inhibitors have not been sufficiently studied in patients at risk of serious gastrointestinal events to establish that, when combined with gastroprotective agents (such as a proton-pump inhibitor or misoprostol), they offer an important safety advantage over traditional NSAIDs. It is possible that the gastrointestinal benefits of the COX-2 inhibitors are only significant in the short term. They do not have clinically meaningful advantages over traditional NSAIDs with respect to dyspepsia, nephrotoxicity, hypertension, or salt and water retention. However, they may be safe in patients with NSAID hypersensitivity, especially those with aspirin-sensitive asthma. It can be concluded that COX-2 inhibitors have a place in therapy, if used under controlled and prescription-only conditions for a specific subset of patients. However, their widespread use is not warranted.

**References**