Non-steroidal anti-inflammatory drugs: indications for use

NON-STERoidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents, with an estimated 100 million people worldwide using them regularly (Berde and Sundel, 1998). They are particularly effective for postoperative pain and for pain associated with musculo-skeletal conditions such as rheumatoid arthritis or osteoarthritis. When summarising the results of a therapeutic trial of a drug, the term ‘number needed to be treated (NNT) to prevent one adverse outcome’ is used to indicate the benefit of an active treatment over a control.

The application of this method to test the efficacy of NSAIDs has shown that diclofenac 100mg has an NNT of 1.9 and ibuprofen 400 an NNT of 2.4 compared to morphine 10mg (intramuscular injection) which has an NNT of 2.9 (Bandolier, 2002).

Although NSAIDs are effective analgesics, they are not without significant adverse side-effects: this class of drug is responsible for considerable morbidity and mortality. Tenenbaum (in Jordan and White, 2001) suggests that up to 30 per cent of regular users experience adverse gastrointestinal side-effects. Also, figures released by the National Institute for Clinical Excellence (NiCe, 2001) state that 2000 deaths occur in the UK each year related to NSAID usage.

How NSAIDs work

Following cell membrane damage, phospholipids are liberated into the body. One of these, phospholipase A₂, is converted into arachidonic acid, which is acted upon by the enzyme cyclo-oxygenase (CoX), producing prostaglandins, prostacyclin and thromboxanes.

NSAIDs are believed to exert their anti-inflammatory and analgesic actions by inhibiting the synthesis of the prostaglandins, which are responsible for inflammation and pain following tissue damage. NSAIDs inhibit action of the enzyme cyclo-oxygenase (CoX), so reducing the production of prostaglandins (Fig 1). NSAIDs not only provide analgesia through this system but also produce adverse effects because the same physiological mechanisms are responsible for protective functions within the body (Fig 2).

COX-I and COX-II

COX-I: This is always active in the body synthesising prostaglandins. These have a variety of physiological purposes, all designed to maintain normal organ function; for example, protection of the gastrointestinal tract, renal homoeostasis and platelet aggregation.

COX-II: Until 1991 it was believed that the actions of prostaglandins, both at the site of tissue damage and those involved in homoeostasis, were inseparable and were all caused by the inhibition of cyclo-oxygenase. Then the COX-II isoform was identified.

The structure of both COX-I and COX-II are similar except that COX-II has an internal pocket that gives it a larger surface area and therefore an increased binding site. Research into COX-II mechanisms has led to drug developments, with COX-II selective inhibitors having
the capability of blocking the COX-II isoform of the cyclo-oxygenase enzyme but largely sparing the COX-I isoform.

The COX-II enzyme, which is responsible for the biosynthesis of COX-II inflammatory prostaglandins (Fig 2), is predominantly inducible (normally present at low levels but has the potential to be upregulated). Under normal basal conditions it is virtually undetectable in most tissues, but injury or inflammatory stimulus can increase both peripheral and central levels of the enzyme by up to twenty-fold (Bandolier, 2000).

Rofecoxib and celecoxib are classified as COX-II-specific agents because of their higher COX-II selectivity compared to traditional NSAIDs such as diclofenac or ibuprofen.

Meloxicam was marketed before the COX-II gene was identified but has been found to have a high selectivity for COX-II compared to traditional NSAIDs, as does etodolac. However, these two particular drugs are not COX-II specific in the same way as rofecoxib or celecoxib, but are said to be COX-II selective.

Adverse effects of NSAIDs

- **Gastrointestinal tract:** Prostaglandins in the gastric mucosa help to maintain mucosal blood flow and barrier function. By inhibiting COX-I, NSAIDs reduce the ability of the stomach to protect itself from its acid contents, resulting in increased acid secretion. This can potentially cause erosion, ulceration, blood loss and ultimately perforation. Gastric protective agents are therefore often co-prescribed with NSAIDs with the aim of reducing the associated adverse effects of these drugs on the gastrointestinal system.

  Approximately 3-4 per cent of patients who take NSAIDs regularly also take protective agents such as proton pump inhibitors (NICE, 2001).

- **Renal:** Renal prostaglandins, mainly PGE₂, are involved in mediating blood flow and also in sodium and water re-absorption within the kidneys. Inhibition by NSAIDs can lead to toxicity, particularly in dehydrated patients. NSAIDs (including COX-II inhibitors) can reduce renal blood flow, glomerular filtration rates and urine production. In extreme cases, increased plasma volume can induce congestive cardiac failure, with pulmonary oedema and breathlessness.

- **Platelets:** Thromboxanes promote clotting by causing platelets to aggregate and blood vessels to constrict. Prostacyclin inhibits the action of platelets, dilates blood vessels and causes fibrinolysis.

  Because NSAIDs inhibit the production of thromboxanes responsible for platelet aggregation and the initiation of clotting (see Fig 1), COX-I inhibition reduces platelet aggregation and increases bleeding time. This has the potential to produce haemorrhagic complications, particularly if given to patients before surgery. In high doses, NSAIDs also inhibit the production of prostacyclin,
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**Efficacy of COX-I and COX-II inhibitors in clinical practice**

Bandolier (2000) suggests that information on the efficacy of COX-I and COX-2 inhibitors is somewhat limited. However, several studies have found that COX-II inhibitors have an equivalent efficacy to traditional NSAIDs in terms of peak visual analogue scale scores (NICE, 2001; Berde and Sundel, 1998). NICE (2001) suggests that in the absence of evidence of significant differences in anti-inflammatory efficacy between the COX-II and traditional NSAIDs, the avoidance of serious adverse effects becomes the most relevant factor when prescribing.

The therapeutic activity of NSAIDs is thought to be primarily due to the inhibition of COX-II, whereas the toxicity results from inhibition of COX-I. In theory, therefore, drugs that can inhibit COX-II but not COX-I promise to provide an analgesic effect with a reduction of the organ toxicities associated with COX-I inhibitors.

**Discussion**

Although there is some increased evidence for adverse effects by NSAIDs on the gastrointestinal system compared to placebo, with COX-II inhibitors it is significantly less than with traditional NSAIDs (NICE, 2001; Reuben and Connelly, 2000). The Celecoxib Long-term Arthritis Safety Study (CLASS) investigated 8,059 patients with either osteoarthritis or rheumatoid arthritis randomised to take celecoxib, ibuprofen or diclofenac over a 12-month period. The trial initially demonstrated favourable results, showing that at six months there were fewer reported gastrointestinal complications with celecoxib than with diclofenac or ibuprofen. However, much controversy surrounds the study because the publication of the less favourable 12-month outcomes did not demonstrate a reduction in adverse gastrointestinal events with the COX-II inhibitor. A possible explanation could be that co-administration of aspirin was allowed during the trial (CLASS Advisory Committee, 2001).

A significant implication for practice derived from the CLASS study is that patients receiving aspirin as a prophylactic measure against adverse vascular events (thrombotic cerebrovascular or cardiovascular disease) will probably not derive any gastrointestinal safety advantage from COX-II selective inhibitors. Clearly, further research is required.

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**TABLE 1. GUIDANCE ON THE USE OF COX-II SELECTIVE INHIBITORS (NICE, 2001)**

<table>
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<th>High-risk factors:</th>
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<tr>
<td>■ Over 65 years of age</td>
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<td>■ Previous clinical history of gastrointestinal tract ulcer, bleeding or gastro-duodenal perforation</td>
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<tr>
<td>■ Concomitant use of medications that are known to increase the likelihood of upper gastrointestinal tract adverse events, i.e. steroids</td>
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<tr>
<td>■ Presence of serious co-morbidity (cardiovascular disease, renal impairment)</td>
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<tr>
<td>■ Requirements for prolonged use of maximum recommended doses of standard NSAIDs (Jordan and White, 2001).</td>
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**Pain response:** Following trauma or an inflammatory stimulus causing cell membrane damage, prostaglandins (E2) are released which synthesise nociceptors (pain receptors). This stimulation increases COX-I enzyme levels up to four-fold (Bandolier, 2000). Traditional or conventional NSAIDs such as diclofenac or ibuprofen inhibit both COX-I and COX-II enzymes.

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**Benefits of COX-II selective inhibitors**

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  - Reduced risk of gastrointestinal adverse effects
  - Reduced risk of cardiovascular adverse effects
  - Reduced risk of renal adverse effects
  - Reduced cost compared to traditional NSAIDs

**Conclusions**

NICE (2001) suggests that COX-II inhibitors are not recommended for routine use but should be used instead of traditional NSAIDs for high-risk patients (Table 1).

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