Non-steroidal anti-inflammatory drugs: facts and fallacies

This article serves to review NSAIDs, their mechanism of action and adverse effects, as well as to establish the therapeutic position of the new-generation NSAIDs, the COX II selective inhibitors.

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In 1971, Sir John Vane proposed that non-steroidal anti-inflammatory drugs (NSAIDs), in particular aspirin, act through the inhibition of prostaglandin synthesis. The ubiquitous nature of prostaglandins and the discovery of their physiological properties led to the deciphering of the mysteries of common symptoms such as fever, pain and inflammation.[1,2]

NSAIDs have, over the past 30 years, become one of the most widely consumed classes of medication in the world, with more than 99 million prescriptions being filled in the USA each year.[3-5] Despite the NSAIDs being seen as a highly effective means of reducing pain and inflammation mediated by prostaglandin release, a major disadvantage relating to the use of these agents has been their ability to cause serious upper gastrointestinal complications. Reports have suggested that when comparing NSAID users with non-users, there is approximately a three- to fourfold increase in risk of ulcer bleeding or perforation.[4,6-9]

INFLAMMATORY RESPONSE

Inflammation is a defensive and protective response of the body to stress due to tissue damage, which is usually characterised by four symptoms: erythema, pain, heat and oedema.[10] Inflammation is divided into three phases: acute inflammation, the immune response, and chronic inflammation. The acute inflammatory response is initiated by tissue injury and is mediated by the release of autacoids. These autacoids include histamine, serotonin, prostaglandins and leukotrienes. The mediators of interest are the prostaglandins.

EFFECT OF PROSTAGLANDINS ON THE GASTROINTESTINAL TRACT

Normal gastrointestinal function relies on a balance between protective mechanisms and damaging peptic acid secretions. Gastric surface cells produce an adherent layer of mucus that lines the stomach. These same cells secrete bicarbonate that neutralises acid as it diffuses through the mucous layer. Submucosal blood flow also plays a key role in protecting the gastric mucosa from injury by supplying oxygen, nutrients and bicarbonate to the surface epithelium and by removing H^+ ions that have penetrated the mucous-bicarbonate and epithelial barriers. Mucosal blood flow is also essential for the development of the 'mucoid cap', a complex of mucus, fibrin and cellular debris which provides an alkaline environment for the injured epithelium so that re-epithelialisation can occur.

Virtually all cells of the gastrointestinal tract are capable of synthesising prostaglandins. Endogenous prostaglandins affect almost all known

mechanisms of mucosal defence. They inhibit acid secretion and increase mucus secretion, bicarbonate secretion and mucosal blood flow. Furthermore, prostaglandins stabilise mucosal mast cells and prevent disruption of the gastric mucosal barrier.[11,12]

NSAID MECHANISM OF ACTION

Traditional NSAIDs, e.g. diclofenac, indomethacin and piroxicam, exert their anti-inflammatory action by reversibly or irreversibly (in the case of aspirin) inhibiting the cyclo-oxygenase (COX) enzyme, responsible for converting arachidonic acid into the various forms of prostaglandins, in a non-selective manner.[5,13-16] Fig. 1 is a diagrammatic representation of the prostaglandin pathway.

Our understanding of the mode of action of the NSAIDs as inhibitors of COX has been significantly expanded by the description of different forms of this enzyme. The accumulated evidence suggests that there are at least two isoforms of the COX enzyme, namely COX I and COX II isoenzymes. COX I is a constitutive form of the enzyme which is inhibited, at least to some degree, by all the commercially available NSAIDs. COX I is thought to have an integral role in maintaining the integrity of the gastric and duodenal mucosa, regulation of renal blood flow and platelet aggregation.[16-18] The second isoform of the COX enzyme, COX II, is an inducible enzyme which, under normal circumstances, is undetectable.The expression of COX II is markedly increased during states of inflammation.As more has been learned about NSAIDs, the importance of the inhibition of prostaglandin synthesis, in particular the COX II isoenzyme, as a major mode of action is highlighted.[5,11]

By inhibiting the COX enzyme in a non-selective manner, the inflammatory process is markedly decreased; however, the regulatory physiological functions, which are also prostaglandin mediated, are inhibited by the same mechanism of action.

NSAID TOXICITY

Schoen and Vender[20] were the first to suggest that the mechanism whereby NSAIDs damage the gastrointestinal mucosa was as a result of a 'dual insult' mechanism. This mechanism of insult can be divided into two areas:

- local injury, which is pH-dependent and varies greatly among the different NSAIDs
- systemic injury, a process that is less drug-specific and does not depend on direct mucosal contact (Fig. 2).[4,11]

Local injury

Most NSAIDs are weakly acidic, lipid-soluble compounds that diffuse across cell membranes into gastric surface cells. Once inside these gastric surface cells, they are no longer lipid-soluble and therefore are unable to diffuse back into the aqueous acid. Damage to the surface cells breaks down the normal protective mechanisms and allows diffusion of acid into the submucosa, resulting in mucosal injury.[4,11]

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Systemic injury

Following Vane's hypothesis (1971) it is now generally accepted that NSAIDs inhibit the enzyme cyclo-oxygenase that transforms arachidonic acid to prostaglandins.[14,15] As has been discussed, normal gastrointestinal function relies on a balance between the protective mechanisms of prostaglandins versus the damaging effects of peptic acid secretions. Considering that

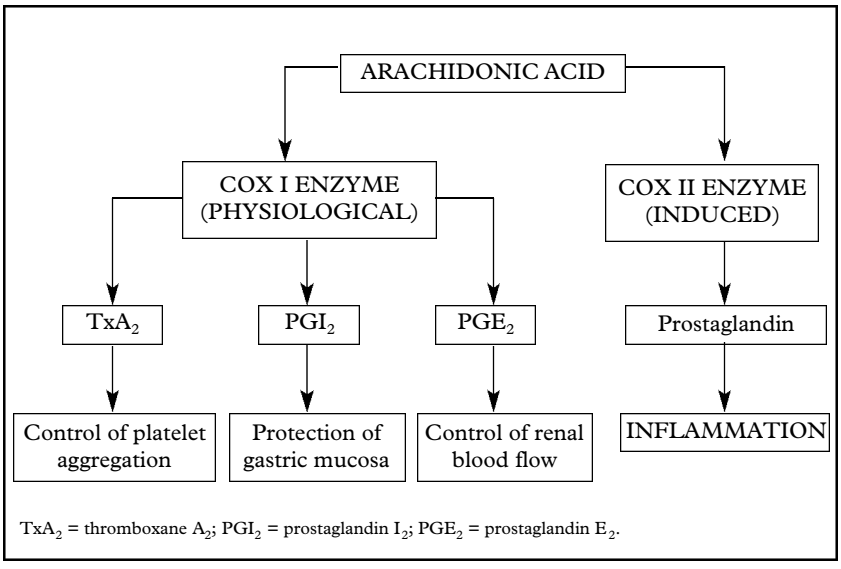

Fig. 1. Diagrammatic representation of the prostaglandin pathway.[19]

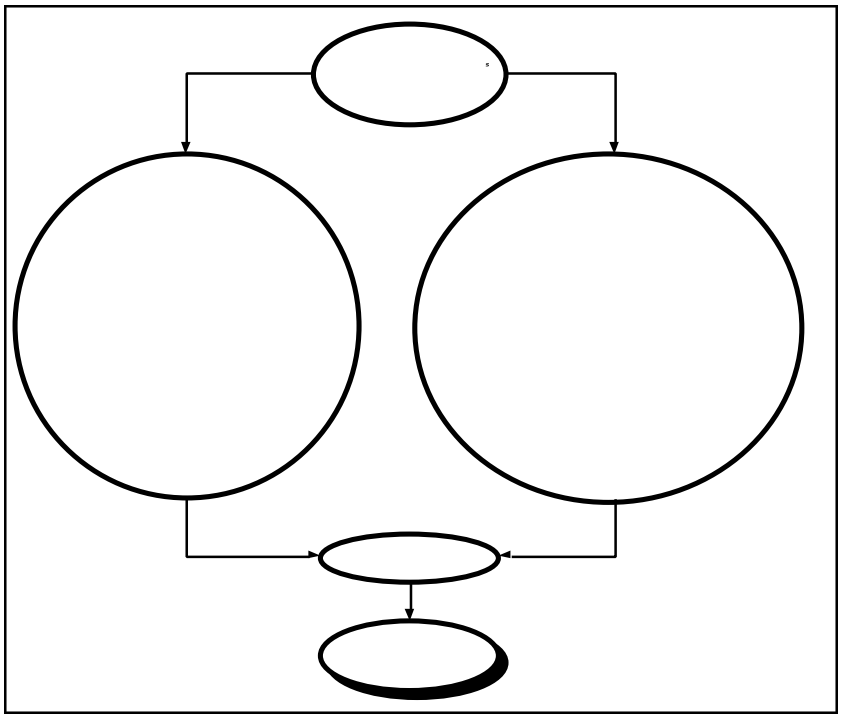

Fig. 2. A diagrammatic representation of the dual insult mechanism of NSAID-induced gastric damage involving systemic and local effects.[11]

NSAIDs are reversible inhibitors of cyclo-oxygenase, the key enzyme in prostaglandin formation, it follows that the impairment of these protective functions will allow chronic gastrointestinal injury to occur.[4]

The mechanisms by which NSAIDs induce mucosal injury are:[12]

- increased gastric acid secretion
- decreased duodenal bicarbonate output
- decreased gastric mucosal blood flow
- effect on mucous synthesis secretion via:
  - inhibited mucous synthesis
  - reduced incorporation of precursors into mucous glycoprotein
  - altered thickness of the mucous layer.

Risk factors for NSAID toxicity

Previous reports have identified five variables that pose as independent risk factors that predispose NSAID users to gastrointestinal complications:[4,8,21,22]

- increasing age (over 60 years)
- previous history of ulcer and ulcer complications
- concomitant use of corticosteroids and other ulcerogenic substances
- use of high doses of NSAIDs
- concomitant use of anticoagulant therapy.

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Apart from a greater need for generalised pain relief, this vulnerability is as a result of a combination of various physiological and pharmacokinetic factors.

Increasing age sees a reduction in the ability to biotransform and inactivate hepatically metabolised agents. This is largely as a result of a decrease in liver mass and a 40 - 45% reduction in hepatic blood flow.[16,23,24] The elderly also display markedly reduced renal function, which is often age-related.[25] Accordingly, the decreased elimination of renally excreted drugs, including NSAIDs, will result in an elevated half-life and therefore greater susceptibility to the drug's side-effect profile.[26]

COX II INHIBITORS

Gastrointestinal effects

With the ever-increasing incidence of gastrointestinal adverse effects, it has become necessary to investigate options that would provide effective treatment for inflammatory type situations, while ensuring the uncompromised effectiveness of the physiological COX I isoenzyme.The COX II selective inhibitors have emerged as an important option in the treatment of inflammatory diseases, including rheumatoid arthritis. Reports have suggested that rofecoxib and celecoxib, the two COX II selective inhibitors that are currently available, have shown comparable efficacy to that of the conventional NSAIDs and should, when used in the correct target population, i.e. those with NSAID-attributable risk, lead to improved outcomes.[17,27,28] Theoretically, COX II inhibitors should decrease inflammation by inhibiting the formation of prostaglandins responsible for causing inflammation, while leaving the COX I pathway intact, the pathway responsible for regulating the body's normal physiological function.[29]

The key issue regarding this new COX II technology is that the COX II inhibitors are only *highly selective* inhibitors of the COX II isoenzyme rather than being *specific* inhibitors.[29] Although this may appear to be a pedantic turn of phrase, it has significant therapeutic implications. The issue that presents itself in this instance is that being highly selective rather than specific inhibitors of COX II implies that despite having a greater affinity for COX II, there will still be some inhibition of the COX I isoenzyme. Studies have shown that despite maximum doses of comparator drugs being used (diclofenac 150 mg and ibuprofen 2 400 mg) the incidence of total serious adverse events (as defined by the US Food and Drug Administration) was similar in both groups (celecoxib 4.3%, NSAIDs 4.2%), as were deaths.[30]

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Renal effects

Promotional material pertaining to the renal safety of the COX II selective inhibitors has also met with some controversy. Current expert opinion is that COX II is constitutively expressed in renal tissues of all species. Therefore, this isoenzyme may be intimately involved in prostaglandin-dependent renal homeostatic processes. This assertion is borne out by recent clinical studies showing that the COX II inhibitors, rofecoxib and celecoxib, cause qualitative changes in urinary prostaglandin excretion, glomerular filtration rate and sodium retention.These reports have gone so far as to suggest that the renal effects of the COX II inhibitors may even be similar to those described for the non-selective NSAIDs and therefore should be used with caution in patients with fluid retention, heart failure and hypertension.[31,32]

THERAPEUTIC OPTIONS

Amid the hype of the potential benefits of the COX II inhibitors as well as the contradictory reports surrounding their specificity and safety profile, the intention of this review is not to overlook the significant advances that have been made with respect to COX II technology. It is true that the COX II inhibitors have a greater affinity towards the COX II isoenzyme, but it should be remembered that, at this point, there will always be a certain degree of COX I inhibition. This, as well as a few basic principles when prescribing NSAIDs, should be remembered:[30]

- Avoid NSAIDs wherever possible. Most cases of osteoarthritis require pain relief rather than NSAID therapy. Simple analgesics such as paracetamol with or without codeine should be tried. Low-dose amitriptyline can often be safely added to improve pain control.
- Use the lowest effective dose of the NSAID for the shortest possible period in cases not controlled by the above.
- For first-line treatment, use NSAIDs with a lower incidence of gastrointestinal complications, namely ibuprofen and diclofenac.

Where the use of an NSAID seems warranted, but where it is associated with unacceptable adverse effects or the risk of NSAID-associated complications is excessively high, the following should be considered:

- In the case of non-ulcer dyspepsia, therapy should be changed to an alternative NSAID as there may be a large inter-patient variability with regard to differences in tolerability of the various NSAIDs available. Failing this, a generic H_2-antagonist should be added for adequate symptom control.
- In patients with predisposing risk factors, where the risk of upper gastrointestinal complications is thought to be excessive and NSAIDs are required for adequate pain relief, a proton pump inhibitor, the prostaglandin analogue, misoprostol, or a low dose of a COX II inhibitor should be considered. If it is decided to introduce either a proton pump inhibitor or misoprostol, the cheapest effective NSAID should be chosen as the cost of prescribing a COX II inhibitor with a

8gastroprotective agent cannot be justified.

CONCLUSION

NSAIDs have been available for more than 30 years — three decades that have yielded significant therapeutic benefit for some, while others have manifested of severe adverse reactions. This uncompromising side-effect profile has resulted in the NSAID class, as a whole, being shrouded in controversy. The advent of the 'super aspirins', otherwise known as the highly selective COX II inhibitors, has certainly not escaped this tumultuous journey. Even though the COX II inhibitors have shown promise of true therapeutic advancement, it is evident that these agents are not without their shortcomings. As time has progressed since the launch of these agents onto the global pharmaceutical market, it has become increasingly evident that this sub-class of NSAIDs should be prescribed with the same caution as conventional NSAIDs. Furthermore, in the interest of cost containment, it may be considered prudent to adopt a more conservative approach when considering one's therapeutic options in treating inflammatory disorders.

References available on request.

IN A NUTSHELL

Inflammation is a defensive and protective response characterised by erythema, pain, heat and oedema.

The acute inflammatory response is initiated by tissue injury and mediated by autacoids, namely histamine, serotonin, prostaglandins and leukotrienes.

Normal gastrointestinal function depends on a balance between protective mechanisms and acid secretions.

NSAIDs upset this balance by inhibiting the COX enzyme (I and II) which convert arachidonic acid into prostaglandins.

NSAIDs which selectively inhibit the COX II enzyme have emerged as effective therapy for inflammatory diseases, while leaving the COX I pathway intact.

As they are selective rather than specific inhibitors of COX II, some inhibition of the COX I enzyme still occurs.

NSAIDs, should always be used with caution, especially in patients at risk for gastrointestinal complications, fluid retention, heart failure and hypertension.

SINGLE SUTURE

Blood pressure and cognitive impairment in heart failure patients

In an Italian study published in *Neurology* (2001; **57:** 1986-1992), cognitive impairment was found significantly more frequently among patients with heart failure than among those without heart failure (26% v. 19%). In analyses adjusted for several confounding variables, cognitive dysfunction was associated with lower systolic blood pressure (BP) among heart failure patients: systolic BP lower than 130 mmHg was found in 46% of heart failure patients with cognitive impairment and in 27% of those without impairment — a significant difference. Among patients without heart failure, there was no correlation between BP and cognitive dysfunction.

Allan S Brett, MD, writing in *Journal Watch* (8 January 2002), comments, 'Undoubtedly there are other confounding variables that were not accounted for in this study, and causal links between heart failure, cognition, and BP remain unclear. Because hypotensive drugs are a mainstay of heart failure therapy, we will face a dilemma if additional research shows that active lowering of systolic BP to below 130 mmHg increases risk for cognitive dysfunction among heart failure patients.'