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Editors:
Ade O Adebajo FRCP(Glasgow)
D John Dickson MBChB FRCP(Glasgow) FRCP(London) MRCP

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THE RELEVANCE OF COX-2 SPECIFICITY

Frank McKenna

Consultant Physician and Rheumatologist
Trafford General Hospital, Davyhulme, Manchester

- **Non-steroidal agents (NSAIDs) inhibit COX-1 and COX-2 enzymes**
- **NSAID efficacy results from COX-2 inhibition**
- **NSAID-induced gastrointestinal tract (GIT) toxicity results from COX-1 inhibition**
- **Significant gastrointestinal morbidity and mortality result from COX-1 inhibition**
- **The use of COX-2-specific drugs, which appear as effective as non-selective NSAIDs, should reduce GIT toxicity**
- **Early evidence suggests that selective COX-2 inhibition is safer**

INTRODUCTION

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been used for over a century to treat musculoskeletal pain and stiffness, but their use is limited by toxicity to the upper gastrointestinal tract (GIT). Up to a third of patients cannot tolerate NSAIDs because of dyspepsia, and there is a significant morbidity and mortality from the development of ulcers and their complications. The association between dyspepsia and the finding of endoscopic damage however is weak, with most gastric ulcers remaining silent. Surveillance studies have indicated a peptic ulcer prevalence of around 25% of all patients taking NSAIDs. Patients with a previous history of peptic ulceration, those taking either large doses of an NSAID or more than one drug and those co-ingesting NSAIDs with corticosteroids are all at increased risk from GIT toxicity, but the risks are greatest in the frail and elderly. Population studies indicate that between 1 and 2% of patients taking regular NSAIDs are admitted annually because of GIT haemorrhage or perforation, with an associated mortality of approximately 10%. From these data it can be estimated that, in the UK alone, more than 2000 deaths per annum can be directly attributed to NSAID therapy.

Pharmacological attempts at reducing NSAID-induced GIT toxicity have proved somewhat disappointing. Slow-release preparations, pro-drugs and suppositories, and even topical preparations, can still cause GIT ulceration. Co-prescription of cytoprotective agents may not always be satisfactory, and increases overall costs. Studies with H₂ antagonists indicate that, while dyspepsia is reduced, they do not reduce the risk of either ulcer development or complication rates. Misoprostol reduces the incidence of ulcers and complications (e.g. one large study found a 50% reduction in ulcer complications), but it does not fully eliminate the risks and may produce undesirable side-effects of its own. Omeprazole has also been found to reduce the incidence of ulceration, but any reduction in the rate of ulcer complications remains unclear.

DISCOVERY OF COX-1 AND COX-2

The mode of action of aspirin and other NSAIDs on the cyclooxygenase enzyme was first suggested in 1971. It was

proposed that both the toxicity and the efficacy of NSAIDs are mediated through the inhibition of prostaglandin synthesis. It is now recognised that the mechanisms responsible for maintaining gastric mucosal integrity, including mucosal blood flow, bicarbonate secretion and maintaining the mucous/bicarbonate layer, are all mediated via prostaglandins, which are generated within the mucosa following the action of cyclooxygenase on arachidonic acid.

The suggestion that cyclooxygenase was not a single enzyme was made following studies in the late 1980s, during which it was observed that dexamethasone inhibited cyclooxygenase expression following an inflammatory stimulus, but it did not affect basal prostaglandin production. Subsequent studies identified two cyclooxygenase enzymes, now referred to as COX-1 and COX-2, and the molecular configurations of both enzymes have been fully determined. COX-2 is very similar to COX-1 but has a valine rather than an isoleucine amino acid at position 523. The smaller valine at this position subtly changes the conformational arrangement of the enzyme, and opens up a side pocket not present in COX-1 which changes the specificity of the COX-2 enzyme.

COX-1 is expressed in cells in the GIT, in platelets and endothelial cells and in cells in the renal medullary collecting ducts and interstitium. The enzyme synthesises prostaglandins that regulate *normal* physiological processes, i.e. those which act to protect the gastrointestinal mucosa, to maintain renal function and to effect vascular homeostasis through platelet aggregation. This physiological regulation was referred to as 'housekeeping', and COX-1 thus referred to as the 'housekeeping' COX.

In basal conditions, COX-2 is expressed in the CNS, the renal cortex, the uterus and the prostate. Its role at these sites is currently being investigated. It is likely that renal function is at least in part dependent on the ability of COX-2 to generate prostaglandins in response to certain stimuli, and there is some evidence to suggest that COX-2 in the CNS is important in the perception of pain. However, the major role of COX-2 appears to be in the development of an inflammatory response. Thus its presence is either low or undetectable in synovial tissues from normal joints, and in many patients with osteoarthritis, but intense COX-2 expression is seen in the synovium of rheumatoid arthritis patients. Most available data suggest that the anti-inflammatory effects of NSAIDs are mediated via inhibition of COX-2 activity, whereas GI toxicity is mediated via inhibition of COX-1. Based on these observations it is probable that an NSAID which selectively inhibits COX-2, i.e. without inhibiting COX-1, would represent a potentially safer agent in respect of GIT toxicity. This report explains the

pharmaceutical attempts to develop and market agents with COX-2-selective properties.

ASSESSMENT OF COX-2 SELECTIVITY

It is well established that not all NSAIDs inhibit both enzymes to the same degree, but what is less well known is that the ranking of selectivity between the various agents varies, and is also dependent upon *the in vitro assay used to assess selectivity*, making comparison of selectivity between the agents difficult. Many of the older NSAIDs appear to inhibit COX-1 to a physiological degree, thus explaining their well-recognised GIT toxicity. Some of the newest drugs, i.e. those which were specifically chosen for development because of their selectivity profile (e.g. rofecoxib/celecoxib), are much more selective for COX-2 than for COX-1. In therapeutic concentration these drugs appear to be specific inhibitors of COX-2, and constitute a new pharmacological class termed coxibs. A number of older drugs (e.g. etodolac/meloxicam) appear partially selective for COX-2, and it has thus been proposed that these agents are called COX-2-preferential inhibitors.

It must be remembered, however, that some of the *in vitro* variability between the different assays previously discussed was, at least in part, due to the fact that the COX-2 pathway is time-dependent whereas the COX-1 pathway is not. Choosing different incubation times in the *in vitro* systems described could have given different selectivity results for the drugs tested. Another difficulty is that NSAIDs do not all exist in the stomach at the same pH, and this may represent an additional factor affecting local GIT toxicity *in vivo*. These factors dictate that, while *in vitro* test results appear to guide the likelihood of *in vivo* GIT toxicity, only prospective endoscopic and surveillance studies will determine which are the safest agents in this respect.

NEW COX-2 INHIBITORS

Celecoxib and rofecoxib were the first of the new compounds to have completed clinical trials. Celecoxib was licensed initially in the USA for the treatment of osteoarthritis and rheumatoid arthritis before receiving its European licence. Rofecoxib was initially licensed in the USA and Europe for the treatment of osteoarthritis before its licence was extended to include rheumatoid arthritis.

Large-scale clinical and endoscopic studies with both drugs have been undertaken, of up to 52 weeks' duration. Dose-ranging studies of celecoxib have indicated this drug to be as effective as standard doses of naproxen or diclofenac. Studies in osteoarthritis have indicated comparable efficacy when given once or twice daily with a dose of 200 mg daily in single or divided dose. In rheu-

matoid arthritis the effective dose is 100 or 200 mg twice daily. Rofecoxib has also been demonstrated to have similar efficacy with comparator NSAIDs including ibuprofen or diclofenac, in a dose of 12.5 or 25 mg once daily. Both compounds were better tolerated than 'traditional' comparator NSAIDs. Dyspepsia and abdominal pain have been reported less frequently with both celecoxib and rofecoxib than comparator NSAIDs, and withdrawals due to side-effects have been significantly less compared with other NSAIDs. The results of endoscopic studies have confirmed the theoretical benefit of specific inhibition of COX-2. Large-scale endoscopic studies with both compounds have found that ulceration rates from both drugs are comparable to placebo.¹ The background, placebo rate of ulceration in the studies was approximately 5%, largely related to either low-dose aspirin or *H. pylori*. There was a placebo rate of ulceration from the new agents, even in studies evaluating higher doses of the drugs. In contrast, cumulative ulceration rate from the comparator NSAIDs ranged up to 47% at 24 weeks follow-up.

If ulcers do not develop with the selective COX-2 agents, then the incidence of upper GI perforation and haemorrhage should be comparable to that in an untreated population. Results from prospective outcome studies with both compounds have confirmed a reduction in GIT complications. There has been some concern expressed following the observed increase in myocardial infarction in one study following treatment with a coxib, but this was not observed in other studies. There has also been debate concerning the degree of residual GIT risk, particularly in patients co-prescribed low dose aspirin, and

further data are required. Nevertheless a large retrospective case-linkage study (undertaken independently from the pharmaceutical companies) found there was a significant reduction in risk from the coxibs compared with standard drugs, and the risk from one of the compounds was similar to background risk.²

WHICH PATIENTS SHOULD RECEIVE COXIBS?

Until more data are available, it is advisable to be cautious when prescribing any new compounds. Nonetheless, the available data suggest that prescribing a coxib should be considered in any patient who is at high risk of NSAID GIT toxicity. NSAIDs should be avoided in the elderly and frail, but there is now the possibility that these patients can obtain worthwhile symptomatic relief of pain and stiffness, but without the considerable risks. The risk of non-GIT toxicity remains unclear. COX-2 appears to have a constitutive role in the kidney, and until more data are available the same caution should be considered as when prescribing NSAIDs to patients with cardiac and renal disease and to patients with asthma. If the promise from the initial experience with the coxibs is fulfilled, it is likely that this new class of drugs will replace most and possibly all of our current NSAIDs within the first decade of the millennium.

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ADDENDUM (July 2005)

Since the publication of this report, there has been significant controversy regarding this group of drugs. Other compounds have been developed and some have been withdrawn. Initial controversy related to the risk/benefit ratio of COX-2 inhibitors in reducing the risk of GI complications compared with non-selective NSAIDs. The results of prospective outcome studies and case-controlled studies when taken as a whole indicate that COX-2 inhibitors are not without risk, but the risk is less than that from non-selective drugs. However, there has been concern that 'channelling' of treatment – treating patients with significant risk factors with COX-2 inhibitors – has caused toxicity in patients who would not have received anti-inflammatory drug therapy.

Since the observation of an increased rate of cardiovascular events in VIGOR, the prospective outcome study with rofecoxib, there have been a number of studies addressing the potential cardiac toxicity of

these drugs. At the time of writing this is an evolving field. Rofecoxib has been withdrawn because of further evidence of a link between rofecoxib and vascular events, particularly in high dose. A number of large population studies have identified an association between most anti-inflammatory drugs and cardiac events independent of COX-2 selectivity. The mechanism may be through salt and water retention and increase in blood pressure. Valdecoxib has been withdrawn because of a risk of serious mucocutaneous reactions (in approximately 1 per 150,000 patients).

Current recommendations are to avoid non-selective NSAIDs in patients with risk factors for GI complications and to avoid COX-2 inhibitors in those with known vascular disease. The US Food and Drug Administration (FDA) has given a similar warning for NSAIDs and vascular disease and, as further data become available, it is likely that this will also be a recommendation in Europe.