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COX-1 and COX-2 inhibitors

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By inhibiting prostaglandin synthesis, non-steroidal anti-inflammatory drugs (NSAIDs) cause mucosal damage, ulceration and ulcer complication throughout the gastrointestinal tract. The recognition that there are two cyclo-oxygenase enzymes, one predominating at sites of inflammation (COX-2) and one constitutively expressed in the gastrointestinal tract (COX-1), has led to the important therapeutic development of COX-2 inhibitors. COX-2 is phylogenetically more primitive that COX-1 and, while very similar, has critical differences, particularly the existence of a small pocket half way down the active enzyme site. A number of drugs achieve selectivity by binding to this pocket, including presumptively rofecoxib and celecoxib. Others, such as meloxicam, may inhibit COX-2 by different mechanisms.

Truly selective COX-2 inhibitors have been shown to have no effect on gastric mucosal prostaglandin synthesis, to cause no acute injury, and no chronic ulceration compared to placebo. Rofecoxib has, in a prospective systematic evaluation involving 8076 patients, been shown to reduce clinically significant ulcers, ulcer complications and gastrointestinal bleeding significantly compared to naproxen. Outcomes data for celecoxib have also been published although differences from the combined comparator agents (diclofenac and ibuprofen) did not reach statistical significance.

Use of aspirin in the class study has shown that the benefits of COX-2 inhibitors may be reduced by aspirin use. The VIGOR study has raised the possibility that some NSAIDs, particularly naproxen, may protect against vascular disease compared to COX-2 inhibitors (or placebo).

Key words: non-steroidal anti-inflammatory drugs (NSAIDs); cyclo-oxygenase (COX); selective COX-2 inhibitors; ulcer; stomach; duodenum; outcomes; ulcer complications; rofecoxib; celecoxib; cardiovascular coronary artery disease; coronary thrombosis; rheumatoid arthritis; osteoarthritis.

Although non-steroidal anti-inflammatory drugs (NSAIDs) damage the entire gastrointestinal tract in humans, the main recognized pathology is in the stomach and duodenum. By contrast, in rodents, non-aspirin NSAIDs ultimately cause more damage and ulceration in the small intestine, particularly the terminal ileum. Growing evidence shows that small-bowel ulceration, bleeding with consequent anaemia and perforation also occur in humans. In the colon, NSAIDs cause erosive damage and ulceration, provoke diverticular perforation and induce relapse of ulcerative (and probably Crohn's) colitis.

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NSAIDS AND CYCLO-OXYGENASE INHIBITION

NSAIDs have a number of potentially toxic affects on the gastrointestinal tract. The property that is common to all those capable of doing damage is an ability to inhibit prostaglandin synthesis.[1] This seems important because prostaglandins are central in protection against a wide variety of luminal insults.[2] Defence mechanisms subserved by prostaglandins include maintenance of mucosal blood flow, secretion of bicarbonate and mucus, maintenance of a protective waxy hydrophobic surface layer and possibly more direct but less understood 'cytoprotection' of epithelial and edothelial cells, possibly as a result of histo-dilution by permeating fluids.[3,4] In addition, prostaglandins secreted by myofibroblasts appear to co-ordinate epithelial cell secretion[5], again potentially protecting by a process of dilution within the lumen. Prostaglandins derived from macrophages (and other sources) are capable of down-regulating lymphocyte inflammatory responses[6] and may mediate oral tolerance to luminal antigens.[7,8]

Inhibition of prostaglandin synthesis thus may predispose to injury by a wide variety of luminal insults, including acid, bile salts and antigens, albeit probably by different mechanisms. By limiting prostaglandin synthesis, NSAIDs abrogate these defensive reactions to such stimuli.

CYCLO-OXYGENASE ISOENZYMES

Inhibition of prostaglandin synthesis is, of course, the central mechanism by which NSAIDs reduce inflammation and pain in arthritis and other inflammatory conditions. For many years, this led to a nihilistic perception that there could be no therapeutic gain without the pain of gastrointestinal toxicity. This was changed by the discovery that there are (at least) two cyclo-oxygenase (COX) enzymes: a house-keeping enzyme, COX-1, constitutively expressed throughout the body and of particular importance for gastrointestinal protection, and an inducible cyclo-oxygenase, COX-2, expression of which is enhanced by cytokines, growth factors and other inflammatory ulcerogenic stimuli.[9–12] This recognition opened the way to development of selective inhibitors of the inducible cyclo-oxygenase that, in theory, would leave gastrointestinal COX-1 and thereby mucosal defensive reactions untouched.

Such is the importance of NSAIDs in symptom control that this recognition stimulated the development of a range of selective COX-2 inhibitors that has gone from the initial recognition of COX-2 to widespread availability backed up by large outcomes studies in under 10 years. Initially, drugs were screened (see below) for COX-2 selectivity on a pragmatic basis, and the drugs celecoxib and rofecoxib[13–16] were discovered by this process. Subsequent elucidation of the three-dimensional structure of first COX-1 and later COX-2[16–19] has shown how similar these enzymes are, how potentially difficult it might be to achieve selectivity and, therefore, remarkably, how fortuitous the pragmatic discovery of these drugs has been.

Both enzymes contain an active catalytic site that consists of a long hairpin molecule in roughly the shape of a prostaglandin molecule that is responsible for the initial synthesis of the endoperoxide prostaglandin PGG_2 and PGH_2 (Figure 1). The channel is largely lipophilic but amphiphilic helices bind the enzyme to the upper leaves of the endoplasmic reticulum linking the active site to an EGF-like domain. When injury occurs, precursor fatty acids such as arachidonic acid are sucked into the large lipophilic channel where a tyrosine at position 385 carries a radical from a nearby haem molecule to achieve cyclicization. Both COX-1 and COX-2 have a polar arginine

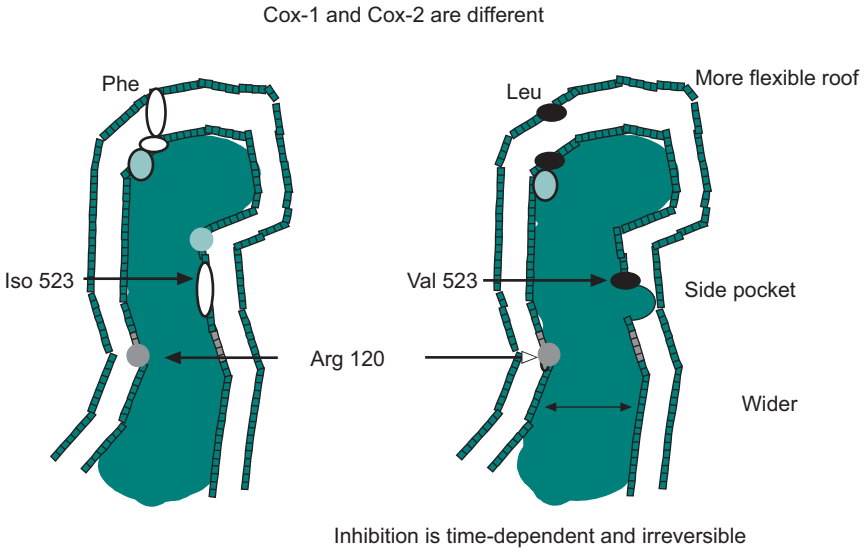

Figure 1. Differences between constitutive cyclo-oxygenase (COX)-1 and inducible COX-2. Based on Hawkey CJ, 1999 *Lancet* **353**:307–314 and reproduced with permission.

molecule at position 120, half way down the channel, and non-selective inhibitors can block both enzymes at this point by simple stearic hindrance.

There is a high degree of homology between COX-1 and COX-2: 61% of amino acids are identical and 84% are similar. In the upper active site there is >90% homology. Only a limited number of sites with the potential for selective exploitation exist. Of particular importance is a substitution at position 523 between isoleucine (in COX-1) and valine (in COX-2). The single methyl group difference is sufficient to create extra space in the active site and this has become recognized as the COX-2 pocket. It is at this site that rofecoxib, celecoxib and other related tri-cyclic enzymes appear to act. These drugs are too bulky to access COX-1 easily and hence selectivity is achieved. Another difference is substitution of leucine (in COX-2) for phenylalanine (in COX-1), which leads to greater flexibility of the roof of the active site in COX-2. It is possible that chemically dissimilar drugs such as meloxicam may act here.

Another difference between COX-1 and COX-2 is that binding of NSAIDs to COX-1 is by reversible hydrogen-bonding and inhibition by simple stearic hindrance. The effect of COX-2 inhibitors is time-dependent, and studies of fluorescence quenching suggest that inhibition depends upon an active process leading to closure of the lower enzyme site.[19–21] This may trap the inhibitor, resulting in a meta-stable transitional state and, essentially, irreversible binding. It is said that failure to recognize the time-dependence of COX-2 inhibition led to the selectivity of Dup 697 not to be recognized.

AVAILABLE COX-2-SELECTIVE DRUGS

Essentially two groups of drugs have been shown to have COX-2 selectivity. One group, designated by the World Health Organization as coxibs, include celecoxib and rofecoxib, tri-cyclic drugs that have been shown to, or are believed to, access the COX-2

pocket.[14–16] Another group of drugs that are structurally dissimilar are previously developed NSAIDs that were retrospectively found to be COX-2-selective. Drugs within this group include etodalac, meloxicam and nimesulide.[22–26] Because coxibs were known to be selective when they were developed, their clinical evaluation has been from the standpoint of their COX-2 selectivity and focused on showing their gastrointestinal safety from conventional NSAIDs in a systematic way. Conversely, drugs retrospectively found to be COX-2 inhibitors have inevitably not been evaluated for selective COX-2-related properties to such rigorous paradigms. Consequently, although it is probable that they share some of the safety features of coxibs the amount of supporting evidence is less.

EVALUATION OF COX-2 SELECTIVITY

A variety of methods have been used to show COX-2 selectivity. Many early studies used isolated enzyme systems and found selectivities in the hundred- or thousand-fold range.[13] A consensus emerged that whole-cell systems were preferable, at least for the pragmatic evaluation of selectivities, because they would reflect protein binding and transcellular drug distribution.[27] The assays most widely used to compare drugs are, or have been, developed from the whole blood assay described by Patrignani and colleagues.[28] In this assay, whole blood is either allowed to clot under standardized conditions, with production of thromboxane from platelets (COX-1 assay), or incubated for 24 hours with lipopolysaccharide to induce COX-2 (COX-2 assay, Figure 2). Since these two assays have totally different time courses (and differences may therefore arise because of differences in drug stability) and because there is a delay to COX-2 activation, a modification of this assay (the William Harvey modified assay) using pre-stimulated human A-549 monocytic cells to measure COX-2 activity, has been developed.[29]

Figure 3 shows the selectivity of a range of drugs assessed in the modified William Harvey assay. As can mostly be seen, of the drugs compared in this study, rofecoxib was the most selective although more selective drugs have subsequently emerged.[30]

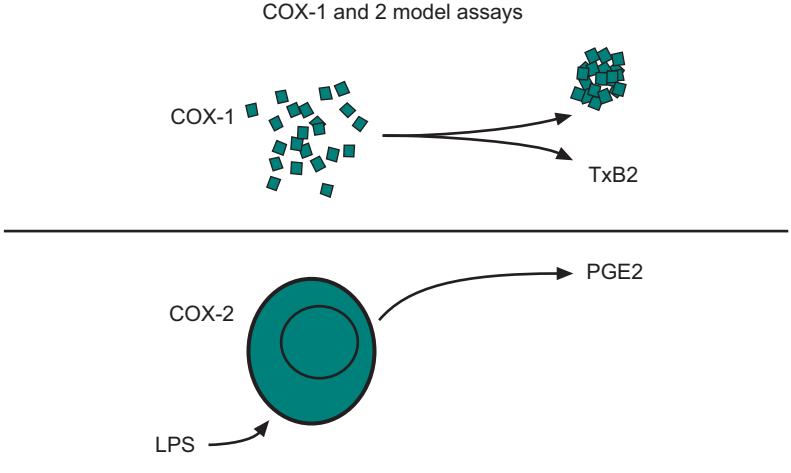

Figure 2. Schematic representation of COX-1 and COX-2 synthesis in the whole-blood selectivity assay.

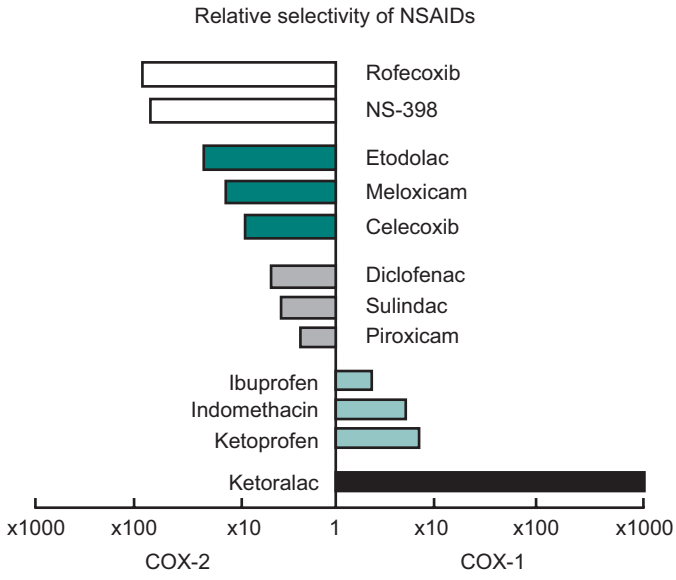

Figure 3. Relative selectivity of some pharmacological agents. Derived from data in Warner et al 1999 (*Proceedings of the National Academy of Sciences of the USA* **96**: 7563–7568) with permission.

Perhaps surprisingly, celecoxib showed less selectivity than that seen with meloxicam or etodalac. Although ibuprofen is an NSAID of low toxicity, this and other assays have shown that it is somewhat COX-1-selective; it seems likely that its low toxicity may more reflect the low doses at which it tends to be used in European countries.

ROFECOXIB

Acute studies

As well as being selective in the whole-blood and other assays, rofecoxib has also been shown directly to spare gastric mucosal prostaglandin synthesis at supra-therapeutic doses (up to 50 mg daily) in humans[31,32] (Figure 4). By comparison, naproxen 500 mg bid led to approximately 70% inhibition. This may explain why rofecoxib at a very high dose (250 mg) caused no acute injury to the gastroduodenal mucosa compared to placebo (Figure 5).[33] High doses of rofecoxib (50 mg) also lacked indomethacin's ability to enhance intestinal permeability[34] and ibuprofen's ability to introduce whole-gut chronic gastrointestinal bleeding.[35]

Chronic patient studies

In large, therapeutic studies in patients, rofecoxib 12.5 mg and 25 mg daily has been shown to be as effective as ibuprofen 2.4 g daily or diclofenac 150 mg daily.[36–38] The effect of rofecoxib 25 mg and the supratherapeutic dose of 50 mg daily on endoscopically detected ulceration have been compared with ibuprofen 2.4 g daily in two large studies of identical design in osteoarthritis patients.[39,40] Over 3 months, neither dose of rofecoxib caused any significant increase in ulceration compared to placebo (4.7

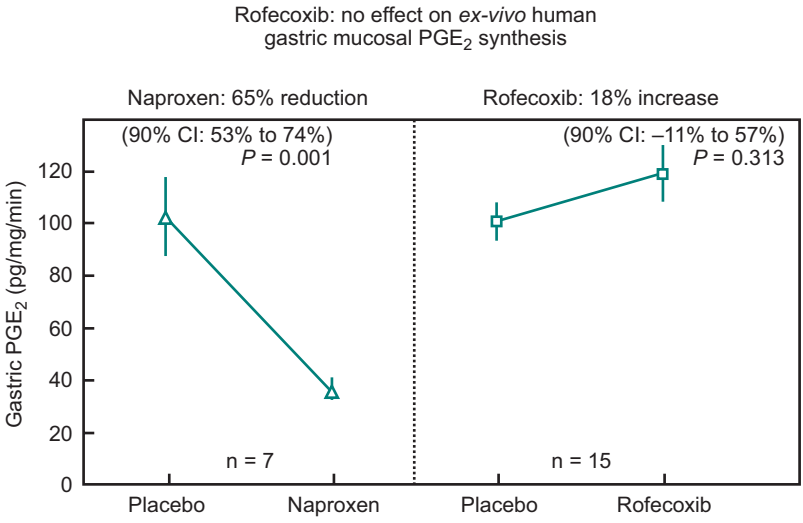

Figure 4. Inhibition of human gastric mucosal PGE $_2$ synthesis by naproxen 1g daily but not by rofecoxib 50 mg daily. Reproduced from Wight et al 2001, *Gastroenterology*.

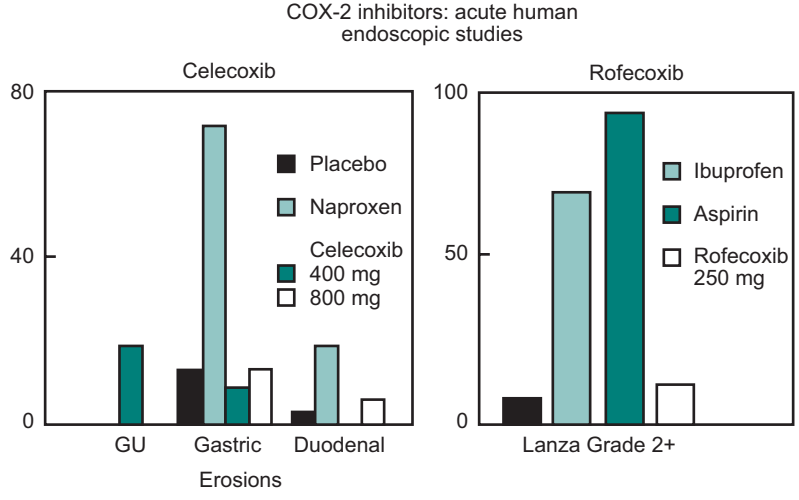

Figure 5. Acute endoscopic studies of celecoxib and rofecoxib. Data derived from Lanza et al 1999, *Alimentary Pharmacology & Therapeutics* **13**: 761–767, with permission.

and 8.1% versus 7.3%) and, for rofecoxib 25 mg, the comparison with placebo met pre-specified criteria for equivalence (Figure 6). Over 3 and 6 months the incidence of endoscopic ulcers in patients taking ibuprofen 2.4g daily was four times higher than with rofecoxib, rising from 28.5% at 3 months to 46.4% at 6 months.

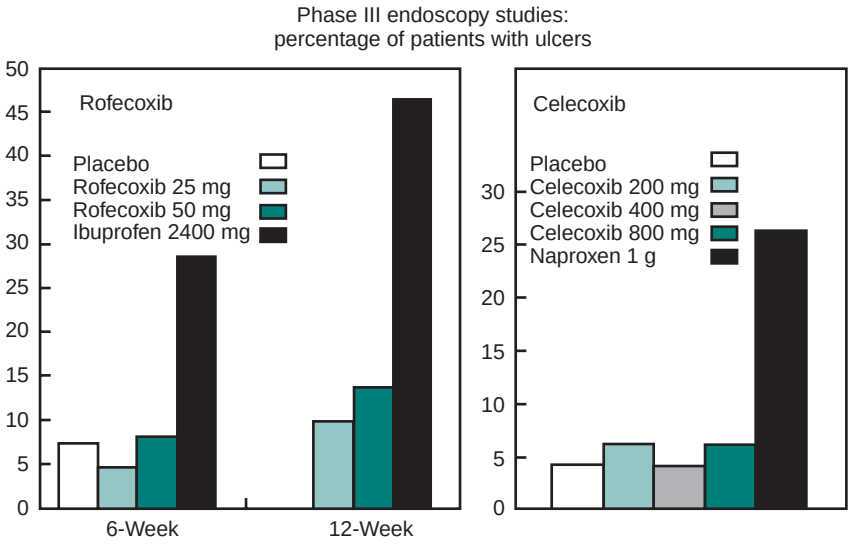

Figure 6. Phase III endoscopic studies of rofecoxib and celecoxib. The left-hand panel shows combined data of two studies with rofecoxib, derived from Hawkey (2000, *Arthritis and Rheumatism* **43**: 370–377), with permission. The right hand panel shows some data derived from Simon et al (1999, *JAMA* **282**: 1921–1928) with permission.

The effect of rofecoxib on ulcer 'outcomes'

There has been some scepticism about endoscopic studies despite evidence that endoscopic ulcers and even erosions are predictive of clinical outcomes.[41] In an effort to achieve a deletion of the labelling traditionally given to NSAIDs that warns of ulcer complications, a large study, comparing the development of clinically important ulcers with rofecoxib 50 mg and naproxen 500 mg bid has been carried out.[42] In the VIGOR study, 8076 patients with rheumatoid arthritis were randomized to receive either the supratherapeutic dose of rofecoxib or a standard dose of naproxen (Table 1). Recruited patients were not endoscoped routinely during the study but only if clinical developments required this. The primary endpoint of the study was clinical upper GI events (perforation, obstruction, bleeding or symptomatic ulcer). The secondary endpoints were complicated upper gastrointestinal events (perforation, obstruction and major upper gastrointestinal bleeding). An independent blinded adjudication committee evaluated the validity of reported endpoints. In addition, an analysis of all episodes of GI bleeding, whether confirmed or unconfirmed, and whether upper or lower, was carried out.

In this study there were 177 confirmed upper GI clinical events and 53 complications (of which 43 were ulcer complications). As shown in Figure 7, the use of rofecoxib was associated with a reduction in all upper GI events, in complicated events and in gastrointestinal bleeding. An analysis of the effect of rofecoxib in patients with and without growing independent risk factors was carried out (data presented to FDA February 8th 2001).[43] This showed that patients under 65 without a past history, who were negative for *Helicobacter pylori* and not on steroids, had 5.1 events per 100 patient-years on naproxen and 2.6 per 100 patient-years on rofecoxib (51% reduction). In those without such risk factors, the event rate was 1.9 per 100 patient-years on

Table I. VIGOR and CLASS compared.

	VIGOR Rofecoxib 50 mg	CLASS Celecoxib 400 mg bid
Patients	8076 RA	c. 8059 OA (72%) + RA
Aspirin	No	⩽325 mg (21%)
NSAIDs	Naproxen 1g	Diclofenac 150 mg Ibuprofen 2.4 g
Duration	9.2 (13)	c. 9 (13)
Primary endpoint	Clinically significant UGI events	Complicated ulcers
Secondary endpoint	Complicated events	Clinically significant ulcers
Analysis	ITT (Life table)	Crude, censored (3 days –6 months)

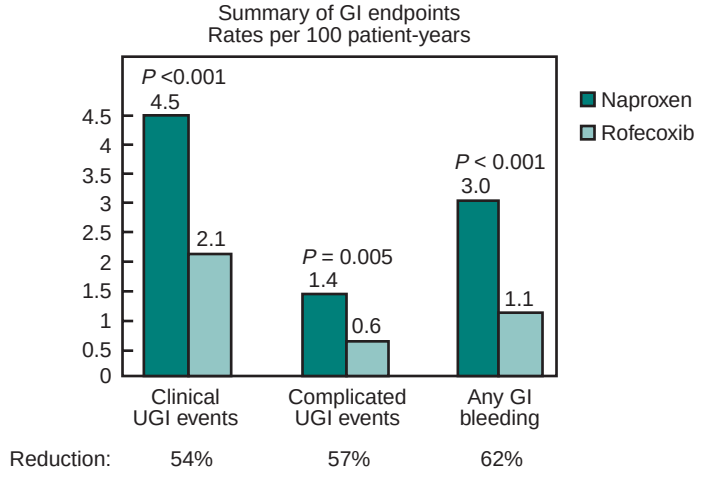

Figure 7. Reduction in gastrointestinal endpoints with rofecoxib 50 mg daily compared to naproxen 1g daily.

naproxen and 0.2 per 100 patient-years on rofecoxib (88% reduction, although with wide confidence intervals). In this study there was also a reduction in the number of discontinuations for dyspepsia, abdominal pain and epigastric discomfort.

CELECOXIB

Acute studies

Although celecoxib has been shown to be selective in recombinant enzyme and whole-blood assays (Figure 3), there are no data on its ability to spare gastric prostaglandin synthesis in humans. Nevertheless, high doses of celecoxib have been shown not to cause any more acute gastroduodenal injury than placebo (Figure 5).[44,45] There are no reports of the effects of celecoxib on intestinal permeability or chronic blood loss.

Chronic patient studies

Unlike rofecoxib, celecoxib has been subject to a full phase III evaluation for efficacy in both rheumatoid arthritis and osteoarthritis.[16,45–48] The main comparator drugs have

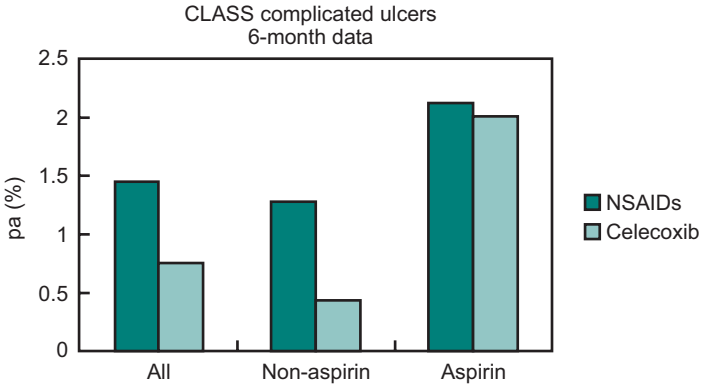

Figure 8. Reduction in complicated ulcers with celecoxib 400 mg bid, compared to ibuprofen 2.4 g daily or diclofenac 150 mg daily. The effect in patients not using aspirin is statistically significant. The effect in patients using aspirin is not.

been diclofenac (150 mg daily) and naproxen (1 g daily). These studies have shown no significant difference between celecoxib and non-selective NSAIDs in efficacy.

In six studies, the effect of celecoxib on gastroduodenal ulceration over periods of up to 6 months has also been evaluated.[45,48] In some of these studies sequential endoscopy was conducted whereas others evaluated endoscopic findings at the end of the trial. In five of the six studies, celecoxib showed significantly less mucosal injury than the active NSAID and did not differ significantly from placebo (Figure 6).

Outcomes study of celecoxib

Like rofecoxib, celecoxib has been evaluated for its ability to reduce the rate of development of clinically significant ulcers (Table 1).[49] The Celecoxib Largescale Assessment of Safety Study (CLASS) was similar in size and design to the Vioxx In Gastrointestinal Outcomes Research (VIGOR) study, but with some differences. Patients with both osteoarthritis and rheumatoid arthritis were studied, ulcer complications were the primary endpoint, and although the study lasted for a median of 9 months, only data over the period of 3 days to 6 months were included in the trial publication. Full data have recently been made available in the context of FDA Advisory Board hearings on February 7th 2001.

Overall, results reported for celecoxib in the paper describing the CLASS study were similar to those seen with rofecoxib in the VIGOR study (Figure 8). The reduction in upper GI complications (from 1.5 to 0.76%), the primary endpoint, fell short of statistical significance ($P = 0.09$). The reduction in all ulcers was statistically significant. As with rofecoxib, the overall incidence of GI symptoms was significantly lower in patients taking celecoxib than in those taking the comparator NSAID. Also reported was a lower incidence of anaemia, fewer abnormalities in liver function tests and a reduction in the overall incidence of renal adverse effects.

However, these published data have to be interpreted with caution in the light of the full trial data reviewed by the FDA Advisory Board meeting. These data show no reduction in ulcer complications with celecoxib (crude 52 week rate 0.43%) compared to diclofenac (0.50%) or ibuprofen (0.55%, $P = 0.450$) over 1 year. However, the

reduction in all ulcer events remained significant (crude rate 1.05% with celecoxib), principally due to a difference from ibuprofen (1.76%) rather than diclofenac (1.30%).

Differences between celecoxib and comparators may have failed to emerge because use of aspirin in 21% of patients appeared to abrogate any benefits of celecoxib (Figure 8). Among patients not taking aspirin, differences in all ulcer events were more pronounced compared to ibuprofen (crude 53 week rate 0.68% versus 1.78%), although not diclofenac (0.64%). Among these patients there was a significant reduction in ulcer complications over 26 weeks ($P = 0.037$) and a trend ($P = 0.185$) to reduction over 52 weeks, again attributable to differences between celecoxib and ibuprofen rather than diclofenac.

SERENDIPITOUS COX-2-SELECTIVE DRUGS

Meloxicam, etodalac and nimesulide have all been found in whole-blood assays to have selectivity comparable to that of celecoxib[29], although less than that of rofecoxib. They may also be as safe as celecoxib but the evidence supporting such a proposition is less well developed. These drugs have been subjected to neither a programme of endoscopic analysis as large as that for the coxibs, nor evaluation in prospective outcomes studies, although some post-marketing data have been published. It has also become clear that diclofenac is slightly COX-2-selective, perhaps about twofold.[29] As diclofenac has been a comparator NSAID in many studies, there is a wide body of evidence to show that it is associated with more gastrointestinal toxicity than celecoxib and rofecoxib, which may help to define how much COX-2 selectivity is needed to avoid such toxicity.

ETODALAC

In vitro and ex vivo studies using recombinant or whole-blood assays have consistently suggested that etodalac has moderate COX-2 selectivity, possibly similar to that of celecoxib.[22,29] Two studies have shown that etodalac lacks the ability of naproxen to inhibit ex vivo gastric mucosal prostaglandin synthesis.[50,51] These studies have also shown that this is associated with a reduction in acute and chronic gastrointestinal injury, in both volunteers[52] and patients.[53] In studies lasting between 3 months and 3 years, the incidence of ulcers presenting clinically tended to be lower, amounting to two in 694 patients on etodalac 300–1000 mg per day compared to 15 in 689 on naproxen 1 g daily, piroxicam 20 mg daily or ibuprofen 2.4 g daily.[54–57] There have been no prospective or ad hoc studies of the effect of etodalac usage on presentation with ulcer complications. There has been insufficient use of etodalac for assessment of its toxicity to emerge from epidemiological studies that have investigated the risks of individual NSAIDs.[58,59]

NIMESULIDE

Nimesulide possesses a structure which may allow access to the COX-2 binding site.[60] In vivo and ex vivo whole-blood and recombinant enzyme assays suggest that nimesulide possesses moderate COX-2 selectivity, comparable to that seen with celecoxib, meloxicam or diclofenac.[22,61–63]

Ex vivo studies suggested that nimesulide had little effect on gastric mucosal prostaglandin synthesis in vitro[64] but such studies could reflect failure to achieve tissue penetration. However, after dosing in volunteers, nimesulide was shown to have no effect on prostaglandin synthesis compared to naproxen.[65] In a small volunteer study there were suggestions that nimesulide caused less acute injury than naproxen.[66] However, there is no systematic body of post-marketing data or prospective study of GI complications with nimesulide. Epidemiological studies do not necessarily support the proposition that use of nimesulide is associated with reduced ulcer complications.[67] It is possible that therapeutic doses of nimesulide are too high for selectivity to be evident.[68] However, nimesulide appears to lack the ability of naproxen to cause small-bowel injury in rats and humans.[26]

MELOXICAM

Meloxicam has a structure that does not predict an ability to access the COX-2 pocket. Nevertheless, in vitro and ex vivo studies have fairly consistently shown COX-2 selectivity comparable to that of celecoxib, etodalac and nimesulide[22,29,61] although selectivity is not complete.[69,70] Presumably meloxicam inhibits the COX-2 enzyme by a different mechanism, possibly exploiting increased flexibility of the inner shell of the roof of the enzyme.

In one study, meloxicam did not inhibit human gastric mucosal prostaglandin synthesis.[71] However, the comparator drug piroxicam had no effect either, raising questions about the validity of the method. In acute studies, meloxicam 7.5 mg (but not 15 mg) causes significantly less injury than piroxicam 20 mg.[72] In a second study[73], there was a trend towards less mucosal injury with meloxicam 15 mg than with piroxicam 20 mg. A review of early patient studies[74] found significantly fewer upper GI perforations, ulceration or bleeding with meloxicam 7.5 mg or 15 mg than with piroxicam or naproxen; the differences from diclofenac 100 mg were not significant. Later studies have tended to confirm a slight trend to reduced ulcer events with meloxicam compared to comparators, including piroxicam and diclofenac.[75–80] However, these studies and a meta-analysis[81] have emphasized particularly the improved symptomatic tolerability of meloxicam compared to comparators. It is possible that a lower rate of dyspepsia might blunt evaluation of the true ulcerated patients on meloxicam.

In a recent large, non-randomized observational study, meloxicam was associated with reduced symptoms and GI bleeding compared to comparator NSAIDs (diclofenac, ibuprofen, piroxicam or indomethacin).[82] A nested case–control study of the UK general practice research database (GPRD), while not showing any increase in gastrointestinal problems with meloxicam compared to diclofenac, naproxen, or piroxicam, was probably too small to establish whether meloxicam was or was not better than these comparators. As with nimesulide, it is possible that meloxicam loses COX-2 selectivity, particularly at higher doses.[61]

COMPARISONS OF COXIBS WITH ANALGESIC DRUGS

A meta-analysis of analgesics used in standardized dental pain studies suggested that COX-2 inhibitors could represent optimal control of acute pain, with the number needed to treat to avoid one episode of dental pain being lower than that with other drugs (A. Moore, personal communication). This is principally because COX-2

inhibitors appear to be more effective than paracetamol and better tolerated than NSAIDs and opiate analgesics such as tramadol. Direct comparisons of COX-2 inhibitors with paracetamol are emerging and, despite earlier assertions that paracetamol is as effective as NSAIDs (usually based on small studies)[83–85], these studies show, not surprisingly, better efficacy than paracetamol.[86]

RENAL EFFECTS

COX-2 plays a complex and important role in renal pathophysiology[87–93] that is not fully understood. Adverse effects of non-specific NSAIDs include, particularly, decreased sodium excretion, decreased potassium excretion, and reduced renal perfusion[90,94], and emerging evidence suggests some if not all of these effects are shared by selective COX-2 inhibitors. This is not surprising given the central role that COX-2 appears to play in renal function. COX-2 is expressed, constitutively in macula densa, and in the thick ascending limb of Henle[93] where it is steroid-suppressible.[95] COX-2 is also expressed in renal microvessels. COX-2 has potentially opposite effects on salt and water retention and renal blood flow in different sites of the kidney and may vary by model. In the macula densa, COX-2 appears to play an important role in the release of renin in response to salt deprivation.[96] Elsewhere, such as in the thick ascending limb of Henle, mono-oxygenators are also expressed and can metabolize arachidonic acid to 20-HETE.[92] 20-HETE has a powerful vasoconstricting action that is partly abrogated by the ability of COX-2 on pre-glomerular microvessels to provide an alternative pathway (to prostaglandins) or to metabolize 20-HETE (to vasodilator 20-hydroxy prostaglandins).[97] Cyclo-oxygenase inhibition results in substantial increases in 20-HETE, especially in patients on a low-salt diet, and this effect predominates so that cyclo-oxygenase inhibition leads to fluid retention despite paradoxically interfering with renin release.

What is not clear is whether COX-1 or COX-2 products contribute most to renal blood flow and creatinine clearance or whether this varies with sodium status. Acute pathophysiological studies have shown that under conditions of sodium restriction (when COX-2 is induced) subjects respond to COX-2 inhibition in a way that is similar to that seen with nonselective NSAIDs, with transiently reduced sodium excretion and a persistent reduction in glomerular filtration rate.[89,98] Under higher sodium conditions, COX-1 may contribute more to renal blood flow and glomerular filtration.[99]

Certainly, in patient studies there is an increased rate of fluid retention compared to placebo, with both selective and non-selective COX inhibitors.[90,100] In most studies, the proportion of patients experiencing such problems has been similar to that seen with non-selective NSAIDs, although in the CLASS study a reduced incidence on celecoxib compared to diclofenac or ibuprofen was reported. It is not clear whether this reflects effective dose or the non-linear characteristics of celecoxib absorption or some other mechanism.

CARDIOVASCULAR EFFECTS OF COX-2 INHIBITORS

Early concerns that selective blockade of COX-2 might result in patients not attaining putative incidental cardiovascular benefits of NSAIDs were reinforced with the discovery that COX-2 was an important source of prostacyclin and that both celecoxib

and rofecoxib lead to reductions in total body production of prostacyclin as measured by urinary excretion of metabolites.[99,101] However, early studies showed no excess of cardiovascular events, and in fact in one study there appeared to be a significant reduction in myocardial infarction with rofecoxib compared to ibuprofen, diclofenac or nabumetone.[102,103]

However, by contrast, in the VIGOR study there was a significantly higher level of myocardial infarction in patients taking rofecoxib compared to naproxen.[42] Such a difference was not seen between celecoxib and ibuprofen/diclofenac in the CLASS study.[49] The results have proved controversial and difficult to disentangle. Because the comparison was not a pre-specified hypothesized one, and the result in the VIGOR study differed from results in phase III studies, it may have occurred by chance. Alternatively, it could have reflected a reduced myocardial infarction rate on naproxen. Certainly some data suggest that naproxen differs from other NSAIDs in causing sufficient inhibition of platelet thromboxane synthesis to have an aspirin-like effect over the 24-hour period of dosing[104] (data presented on rofecoxib to FDA, February 8th 2001). Non-evaluated data presented at a recent FDA hearing suggest a relative risk of 0.6 for myocardial infarction associated with naproxen use. Significant differences in myocardial infarction rates between celecoxib and comparator NSAIDs were not seen in the CLASS study, although absolute rates were very similar to those seen in patients on rofecoxib in the VIGOR study. This may have been firstly because aspirin use was allowed (and seen in 21% of patients) and secondly because the comparator NSAIDs (ibuprofen and diclofenac) are not sufficiently powerful or prolonged as inhibitors of platelet thromboxane to exert an aspirin-like effect[105] (data presented on rofecoxib to FDA, February 8th 2001). This is an important finding that requires further evaluation. The therapeutic implications are that patients who require aspirin should have it but (as seen in the CLASS study) some or all of the advantages of COX-2 inhibitors may then be lost. An alternative but as yet unexplored strategy is that naproxen could be used in such patients.

CELECOXIB OR ROFECOXIB: WHICH IS BEST?

Both drugs appear to have very good gastroduodenal safety. Competitive controversy has tended to focus on non-GI issues. Neither drug is particularly soluble, and both have a moderately long t-max.[16,106,107] In addition, absorption kinetics with celecoxib are not fully dose proportional.[108] The potential acute efficacy disadvantages of modest absorption can be overcome by using higher doses, and rofecoxib 50 mg has been shown to have an analgesic efficacy in models of dental pain, and for relief of pain in dysmenorrhoea, in osteoarthritis and post-operatively.[109–112] There is a lesser body of evidence favouring celecoxib which, unlike rofecoxib, has not attained a license for acute pain. Differences in effective dose may account for the results of one study that shows rofecoxib 50 mg to be substantially and significantly more effective than celecoxib 200 mg as treatment for dental pain.[112]

Differences in effective dose may also account for emerging differences in efficacy and adverse effects of marketed doses of the two drugs. Intriguingly, two studies of similar design have resulted in essentially complementary findings in comparisons of rofecoxib and celecoxib. In a study sponsored by Merck, rofecoxib 25 mg daily was shown to be significantly more effective in osteoarthritis than celecoxib 200 mg daily, and 12.5 daily was numerically better than celecoxib.[86] Conversely, in a Pfizer-sponsored study of the same doses, rofecoxib 25 mg daily caused more hypertension than did celecoxib 200 mg

daily (personal communication, Uznam Azaz). Given the importance of COX-2 in renal function, it seems implausible that one inhibitor, at equally effective doses, would cause fluid retention while the other would not. It seems more likely that the two marketed doses of rofecoxib may be somewhat more potent than the two marketed doses of celecoxib and that mechanism-related adverse effects are dose-dependent. An additional factor could be the relatively poor absorption of celecoxib (with non-liver-absorption characteristics) which may make it more difficult to achieve levels impacting on renal function. More experience is necessary to define equally potent doses of celecoxib and rofecoxib before such issues can be resolved.

To these differences must be added the data recently presented to the FDA (February 7th, 2001) which showed that there were no differences in the study's primary endpoint of ulcer complications over the full duration of the trial. While the study may well have failed to demonstrate a true effect, because of inadequate power and design flaws, the more clear-cut result of the VIGOR study must give greater confidence in the GI safety of this more selective COX-2 inhibitor.

WHICH COX-2 INHIBITOR TO SELECT?

There is little doubt that rofecoxib probably has none of the gastrointestinal toxicity of non-selective NSAIDs and that, despite the inconclusive results of the CLASS study, toxicity is substantially reduced with celecoxib as well. There is a significant chance that a similar consideration applies to those drugs that have been serendipitously discovered to be COX-2 selective, but the evidence for this is much more limited. In particular, while the strategy with celecoxib and rofecoxib has been to test supra-therapeutic doses of the drugs against normal doses of NSAIDs because the issue to be established was well defined, the pragmatic testing of meloxicam, nimesulide and etodalac has been quite different. In a number of studies where GI safety has been shown compared to that of non-selective comparators, relatively low doses have been used and dropouts for lack of efficacy have tended to be higher for both meloxicam and nimesulide[76,79], while there is good direct evidence that some selectivity is lost at higher doses.[113] Thus, while the latter drugs tend to be somewhat less expensive than the coxibs, the evidence for their safety is as yet much less secure.

WHO SHOULD RECEIVE COX-2 INHIBITORS?

A truism has grown up that it is patients at high risk who should be treated with COX-2 inhibitors. This may not be rational. While the absolute reductions in such patients are somewhat (though not greatly) higher than the absolute reductions in low-risk patients, substantial risk, probably attributable to risk factors, remains. By contrast, when low-risk patients use COX-2 inhibitors, limited data suggest that their risk of ulcer disease becomes virtually nil:[114] data presented on celecoxib to FDA on February 7th 2001[43] and data presented on rofecoxib to FDA on February 8th 2001 (Laine, 2001 FDA). In consequence, such patients may need no other monitoring or therapy while high-risk patients may need additional measures such as eradication of *Helicobacter pylori* (where relevant) or co-therapy with proton pump inhibitors. Pragmatic trials are needed to resolve whether use of COX-2 inhibitors or use of co-therapy are better strategies with and without non-drug-related risk factors.

Practice points

- COX-2 inhibitors should be considered for all patients requiring analgesia. Safety improvements are similar for those at high and low risk
- patients with additional risk factors may need additional or alternative strategies
- acid suppression may be needed in addition or instead of COX-2 inhibitors in patients taking (low-dose) aspirin and with active and possibly previous ulceration
- to minimize GI side-effects, cardiovascular prophylaxis should involve no more than 75/82.5 mg of aspirin and should be restricted to patients with existing vascular disease

Research agenda

- direct comparisons of individual COX-2 inhibitors
- evaluation of COX-2 inhibitors to determine whether they have any effect on inflammatory bowel disease
- comparison of COX-2 inhibitors with non-selective NSAIDs and proton pump inhibitors, for their effects on dyspepsia, endoscopic ulceration, ulcer complications and critical vascular and gastrointestinal events

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