Leading article

COX-1 and COX-2 products in the gut: therapeutic impact of COX-2 inhibitors

Despite the considerable range of newly identified disease modifying approaches to the control of the inflammatory process reported over the past 10–20 years, only a few have yet gained widespread clinical acceptance. In contrast, the very recent advent of the class of anti-inflammatory agents termed COX-2 selective inhibitors is already having a significant impact on current clinical prescribing practice and market share in those territories that they are available.

That these COX-2 selective inhibitors have become so successful within the same year of their launch attests to the perceived need for novel agents that can control the signs and symptoms of inflammatory diseases, but with minimal risk of gastrointestinal side effects. Extensive epidemiological studies have well documented the so-called stealth epidemic of the gastropathy with non-steroidal anti-inflammatory drugs (NSAIDs) that has developed over the period since the non-aspirin NSAIDs were introduced.[1 2] The massive growth of the market for such products, which has involved different patients populations and the prescription of high doses, has led to the current substantial problem of some 103 000 hospitalisations and 16 500 deaths per year in the USA alone. The impact of such events on health care budgets is therefore substantial, and the risk of serious side effects from these agents is an important consideration in long term anti-inflammatory therapy, especially in the elderly. Individual assessment of personal risk from taking NSAIDs can be obtained from a questionnaire accessed at www.seniors.org/score.

This initial success of the COX-2 selective agents, unprecedented in the area of anti-inflammatory analgesics, has probably arisen from the general perception that they are a superior form of non-steroidal anti-inflammatory drug rather than a completely novel therapeutic approach of unknown clinical consequences. Moreover, the very reasonable scientific rationale proposed for their enhanced safety has been backed up by relatively extensive and well conducted clinical trials that have addressed the important pharmacological features of these agents. These factors have allowed their rapid appraisal and subsequent registration by regulatory bodies with minimal delay.

The development of the scientific rationale for the efficacy and safety of these agents covers some 30 years, beginning with the identification of cyclo-oxygenase (COX) inhibition by aspirin and the other classical non-steroidal anti-inflammatory drugs in 1971 by John Vane, as a mechanism of both their anti-inflammatory analgesic actions and their side effects on the gut.[3] This was followed 10 years later by identification of site selective inhibition of COX as a rational basis for the development of less gut injurious anti-inflammatory agents.[4] The beginning of the 1990s saw the molecular identification and characterisation of two isoforms of COX, upon which the current focus for selective inhibitors of the COX-2 isoform is based.[5–7] A decade later, the initial regulatory approval of celecoxib (Celebrex; Searle), the first specially designed selective COX-2 inhibitor, was granted in the USA, followed rapidly by its launch onto the market in early 1999. It has subsequently gained marketing authorisation in many different territories, with approval in the UK in May 2000, being launched by Pharmacia/Pfizer. Within a few months of the commercialisation of celecoxib, another selective COX-2 inhibitor, rofecoxib (Vioxx; Merck), was approved and launched in the USA, and was similarly approved in the UK in June 1999.

The present article reviews the background to the development of these gut sparing anti-inflammatory agents, as well as their therapeutic promise.

Role of COX-1 products

Early experimental studies established that the endogenous metabolites of arachidonic acid, prostaglandins, formed via the cyclo-oxygenase enzyme, now called COX-1, were involved as local physiological mediators or modulators of gastric mucosal function.[8] Prostaglandins of the E and I series, PGE_2 and prostacyclin, respectively, are formed by gastric mucosal tissue.[8] These prostanoids can inhibit gastric acid secretion, stimulate gastric bicarbonate and mucus secretion, as well as affecting sodium and chloride ionic flux across the injured mucosa. In addition, these prostanoids induce vasodilatation in the mucosal microcirculation, as well as preventing the leucocyte-endothelial adhesion and vascular stasis induced by damaging agents.[8]

This early interest in the physiological and potential therapeutic properties of the prostanoids established that such endogenous prostanoids had potent antiulcer properties. Indeed, administration of these prostanoids or their synthetic analogues protected the gastric mucosa from damage by a wide range of injurious insults.[9] This so-called cytoprotective property[9] is probably a consequence of a range of beneficial pharmacological and biochemical activities acting in concert.[8 10] As prostanoids exert such potent actions on gastric function and integrity, it is not surprising that alterations in local prostaglandin formation, particularly following COX-1 inhibition, have been implicated as a mechanism underlying gastric damage and disease. However, such hypotheses involving prostanoid inhibition needed to be reconciled with earlier concepts of how these agents bring about gastric mucosal injury.

Studies in the mid-1960s indicated that topical administration of aspirin and salicylate cause local irritancy with disruption of the epithelial barrier, which was considered the major pathological process.[11] Such topical actions, however, appear to be unrelated to COX inhibition.[12] Indeed, the biochemical basis for these topical actions remains to be fully established but probably involves local accumulation of these agents in mucosal tissue and interference with cellular metabolism, including inhibition of oxidative phosphorylation in the barrier cells.[12] Experimental studies further identified a synergistic interaction

Abbreviations used in this paper: COX, cyclo-oxygenase; NSAIDs, non-steroidal anti-inflammatory drugs; iNOS, inducible nitric oxide synthase; FAP, familial adenomatous polypopsis.

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between these events, with extensive damage being elicited by topical irritants when prostanoid biosynthesis was inhibited.[12]

It has become apparent that inhibition of COX-1 is a critical step in the development of gastric injury and ulceration by the classical non-steroidal anti-inflammatory agents. The cascade of events that follows inhibition of COX-1, and the reduction in constitutive prostanoids, appear to involve actions on the microcirculation that affect blood flow and promote the adhesion of white cells to the microvascular endothelium, with subsequent release of local injurious mediators.[12–14] Such events arising from cellular injury deep in the mucosa would lead to erosion and eventual ulceration. It is also possible that prostanoid inhibition may additionally affect the integrity of the superficial epithelial through actions on the overlying protective mucus bicarbonate layer.[8] COX-1 inhibition may also affect the surface active phospholipids that regulate the hydrophobicity of the mucosa, a property that repels the influx of hydrogen ions into the mucosa.[15] These adverse events following prostanoid inhibition would assume greater importance in the presence of a topical irritant that evokes injury through COX independent mechanisms.

Site selective actions of inhibitors

In addition to their extensively described beneficial protective and physiological roles in the gut, prostanoids, particularly of the E series, were well known to have pro-inflammatory and hyperalgesic actions, and to be found at the site of inflammation. The suggestion that site selective inhibition of prostanoid production would produce anti-inflammatory agents with less gastrointestinal toxicity was made some 20 years ago.[4] In those early experimental studies on the differential inhibition of cyclo-oxygenase, it was demonstrated that prostanoid production in inflammatory sites could be inhibited without affecting prostanoid generation in the gastric mucosa. Moreover, those anti-inflammatory agents that were selective inhibitors of prostanoid biosynthesis in the inflammatory areas did not provoke gastric mucosal injury. Such findings predicted that differential enzymes were involved in the production of prostanoids at these distinct sites. It was therefore proposed that the development of anti-inflammatory agents that fail to inhibit cyclo-oxygenase in the gastric mucosa would be a rational approach to obtaining clinically well tolerated drugs.[4]

The biochemical rationale for the development of COX-2 selective drugs arose some 10 years later from an understanding of the molecular biology of cyclo-oxygenase, with the identification of two distinct isoforms.[5–7] These seminal studies have indeed emphasised the important of molecular techniques in enzyme targeting and drug design. The COX-1 isoform present in the gastrointestinal mucosa, renal systems, and platelets was identified as a constitutive enzyme. The prostanoids synthesised by this COX-1 enzyme control many physiological functions including microvascular blood flow, platelet aggregation, renal tubular functions, as well as regulation of gastric acid production and mucosal integrity. The second isoform, COX-2, was found to be inducible, being expressed within 4–24 hours in a number of cell systems following challenge with inflammatory mediators such as interleukin-1, lipopolysaccharide, and various mitogens. This isoform, which apparently can also occur constitutively in some tissues and under certain situations, is considered to be the primary source of the proinflammatory prostanoids,[5–7 16] making it an appropriate target for drug development.

Although the human COX-1 gene is larger than that of COX-2, being 8.3 and 22 kilobases, respectively, there is 61% homology between the expressed enzyme isoforms. Structural analysis has revealed a highly conserved upper active site, with only two residue changes between the isoforms, and a less conserved lower active site. The only key primary sequence difference in the immediate vicinity of the active site is residue 523, which in COX-1 is isoleucine and in COX-2 is the smaller substituent, valine.[16] Both isoforms, which are membrane associated, have a molecular weight of 70 kDa and are of the same length, but with different N and C terminal regions. COX-2 has been characterised as an early response gene, with a number of regulatory factors having been identified, and which can be downregulated by corticosteroids.[5–7 16]

Determination of COX selectivity

Early reports on the inhibitory action of a number of experimental agents indicated that discrimination between the COX enzyme isoforms could be obtained, although the degree of such selectivity greatly depended on the assay and experimental conditions used. The source of enzymes from human, animal, or recombinant material, type of preparation such as whole cells, subcellular fractions or purified enzyme, the nature of the cell or cell line, and the stimulus for COX-2 induction all had a significant bearing on the selectivity ratio between COX-1 and COX-2.[16 17] Most workers now accept that studies using human blood as a source of enzyme give a reliable and relevant index of activity.[16 17] Recent refinements have involved incubation of heparinised blood with the drugs for one hour followed by challenge with the calcium ionophore A23187 to stimulate thromboxane production (COX-1) or transfer to a human cell line preinduced to express COX-2.[18] Using this methodology, the selectivity ratio for commonly used NSAIDs exhibiting some discrimination for the COX-2 isoform in vitro was nimesulide <celecoxib <meloxicam <etodolac <rofecoxib.

The pharmacokinetic behaviour of the drug in vivo, together with its potency, will however have an important influence on the degree of selectivity that would be achieved in vivo on clinical dosing.[18] This is exemplified by studies with meloxicam that showed that a dose of 7–15 mg in volunteers for seven days caused an overall 30% inhibition of thromboxane production in clotting blood, as an index of COX-1 inhibition.[19] It is likely that separation between COX-1 and COX-2 inhibition is enhanced at the lower doses of meloxicam and probably with other inhibitors, such as nimesulide and etodolac, anti-inflammatory agents already in clinical use and now redefined, along with meloxicam, as preferential COX-2 inhibitors.

It is evident that the human whole blood assay, adapted for use ex vivo, following administration of the drug to humans provides useful surrogate markers for COX-1 and COX-2 activity. However, determination of COX-2 activity at the inflammatory sites, especially in humans, with a number of inhibitors would support these assumptions but such approaches require the development of appropriate methodology. Similarly, determination of inhibition of COX-1 activity in human gastrointestinal biopsy tissue with a range of agents would also be of substantial interest to allow comparison with indirect whole blood assay systems. A number of studies with the preferential COX-2 inhibitors on gastroduodenal COX activity have been conducted. Thus therapeutic doses of etodolac did not suppress gastric or duodenal prostanoid biosynthesis and had a favourable gastrointestinal side effect profile.[20] Studies using nimesulide have also reported less suppression of gastric mucosal prostanoid production ex vivo, as well as thromboxane production in whole blood, than the standard NSAID naproxen but was more potent than naproxen on COX-2 dependent PGE_2 production in whole

blood.[21] A comparative ex vivo evaluation of the actions of the new selective COX-2 inhibitors on gastroduodenal COX-1 activity in human tissue after administration is therefore awaited with interest.

Effects on the intestine

In addition to the actions of COX-1 inhibitors on the gastric or duodenal mucosa, such agents promote damage in the small and large intestine in experimental studies.[22 23] Moreover, oral ingestion of aspirin, ibuprofen, or indomethacin by healthy volunteers and patients increased the permeability of the small intestine to radiolabelled markers.[24] This effect was also observed after rectal administration of these agents, indicating that this was a systemic action and not just a reflection of local irritation. In addition, in studies in patients receiving non-steroid anti-inflammatory drugs for the treatment of rheumatoid arthritis or osteoarthritis, more than 60% exhibited blood and protein loss with demonstrable inflammation of the small intestine.[25]

As in the gastric mucosa, local irritant actions on the intestinal mucosa involving inhibition of oxidative phosphorylation and COX inhibition have been proposed to explain the injurious actions.[23 25] Experimental studies also suggest a role for the inducible isoform of nitric oxide synthase (iNOS) that can generate sustained cytotoxic levels of nitric oxide.[26] Thus the slow onset of intestinal lesions following these NSAIDs appears to involve the ingress of gut bacteria stimulating iNOS expression. The early events that give rise to the breach in the mucosal defence mechanisms, allowing ingress of gut bacteria, appear to involve inhibition of COX-1.[26]

Evidence so far from experimental and clinical studies on faecal blood loss as an index of haemorrhagic injury in the gut has suggested that COX-2 inhibitors do not provoke intestinal injury, a finding supported by the use of specific permeability markers.[27] Thus whereas gastroduodenal injury from standard NSAIDs can be attenuated by the use of acid suppressors, particularly proton pump inhibitors, and by mucosal protective agents[28] which are unlikely to be effective against intestinal injury, the COX-2 selective agents appear to provide a more comprehensive reduction in gastrointestinal damage.

Gastrointestinal cancer

One aspect currently attracting much attention is the involvement of COX-2 products in the promotion of cancer. A number of epidemiological studies have shown that prolonged use of aspirin and other NSAIDs is associated with a reduced relative risk of colorectal carcinoma.[29–31] For example, a recent population based survey for a period of five years or more, of 104 277 patients aged 65 years or over, indicated that long term NSAID use halved the risk of colon cancer.[32] In another large scale population based survey, users of NSAIDs were shown to have a significantly reduced risk of oesophageal and gastric carcinoma.[33]

Studies have demonstrated that COX-2 is over expressed in 85% of primary colorectal carcinomas and in cell lines derived from such cancers.[30 34 35] Over expression of COX-2 appears to alter the phenotype of intestinal epithelial cells and increases their carcinogenic potential, thus offering an appropriate therapeutic target for COX-2 inhibitors.

The mechanism of action of NSAIDs in the modulation of tumour growth, however, has been extensively debated since the original findings with non-selective NSAIDs. Actions on cycle arrest and apoptosis which may underlie this action have been demonstrated in colonic cell lines and animal models.[30 34–36] Early experimental studies have shown the beneficial actions of potent NSAIDs such as flubiprofen on cancer growth, response to therapy, and survival in animal models.[37] Subsequent clinical studies in 1983 indicated that the NSAID sulindac was effective in reducing the number of colonic polyps in Gardiner's syndrome[38] although this agent is not considered a potent inhibitor of cyclo-oxygenase. Thus cyclo-oxygenase independent mechanisms have been postulated for the actions of sulindac and related agents but further work will be needed to identify the molecular and biochemical basis of any such actions. Aspirin has been shown to be active in preventing spontaneous intestinal adenomas in genetically prone mice.[39] Preferential COX-2 inhibitors share the antitumour properties of more traditional NSAIDs, with meloxicam inhibiting the growth of colorectal tumour cells in vitro[40] and nimesulide reducing the development of precancerous polyps in genetically predisposed mice.[41] Moreover, in recent studies, celecoxib has shown protective activity in chemically induced tumours in mice.[42]

Such findings prompted the clinical evaluation of selective COX-2 inhibitors in precancerous conditions such as familial adenomatous polypopsis (FAP). Following priority review by the FDA of data from phase III studies on regression and reduction of colorectal polyps in FAP patients in December 1999, celecoxib has become the first approved drug for this indication. This disease is a precursor of colonic cancer in these people, and approval was based on a 28% reduction in polyp number in a double blind study in 83 patients compared with 5% reduction with placebo. The efficacy of celecoxib in treating colon cancer is being evaluated in a phase III study while its usefulness in a number of other cancer types, including Barrett's oesophagus and sporadic adenomatous colonic polyps, is also being explored. Similar studies with rofecoxib are known to be underway and it is anticipated that if all of these studies with COX-2 inhibitors reveal a beneficial action, this class of drug will be increasing used, either alone or in combination with cytotoxic agents, in the chemotherapeutic control of such cancers.

Clinical data with COX-2 inhibitors

A number of trials have been conducted over the past 10 years that generally support the favourable side effect profile of COX-2 preferential compounds. Thus a meta-analysis of controlled trials with nimesulide indicated that it had a better risk-benefit ratio than the standard NSAIDs.[43] In a comparative study in 200 patients with osteoarthritis over a three month period, there was no difference between the incidence and severity of gastrointestinal side effects with two COX-2 preferential drugs, nimesulide and etodolac.[44] In a number of studies, etodolac showed reduced side effects on the gut compared with standard NSAIDs.[45] In a three year therapy period in 1446 patients, etodolac had comparable efficacy and incidence as ibuprofen, accepted as a well tolerated NSAID in the clinic.[46]

Evaluation of the US patient insurance claims over a nine month period indicated that etodolac had a similar gastrointestinal safety profile as nabumetone[47] while in an earlier study in 91 osteoarthritis patients both drugs had comparable efficacy and were well tolerated.[48] In another comparative study, comparable efficacy and safety were also reported with nabumentone and the clinically used agent aceclofenac.[49] It is of interest that COX-2 selectivity in vivo of these two latter compounds is unclear, both requiring metabolic activation to inhibit the COX enzymes.[18 50] It is thus feasible that the safety profile of nabumetone and aceclofenac depend not solely on COX-2 selectivity but on other factors, including lack of local topical irritancy.

In the MELISSA trial in 10 000 patients with osteoarthritis and the SELECT trial involving 9286 patients with osteoarthritis, a significantly reduced incidence of side effects was noted in the meloxicam group compared with the comparators diclofenac and piroxicam, respectively. These studies showed comparable clinical efficacy but with a lower incidence of gastrointestinal complications with meloxicam, and again supported the concept that preferential inhibition of COX-2 is a therapeutically viable proposition.[51 52]

This clinical promise was indeed upheld by the selective COX-2 inhibitors. Celecoxib was approved for the treatment of rheumatoid arthritis and osteoarthritis by the FDA, based on submitted findings from 5285 patients in controlled trials. In a study in 665 patients with rheumatoid arthritis over a 24 week period, it produced comparable sustained management of pain and inflammation as the comparator diclofenac. However, gastroduodenal ulceration was detected in only 4% of patients receiving celecoxib in contrast with 15% in the diclofenac group, with a threefold greater withdrawal from diclofenac treatment because of gastrointestinal side effects.[53] In a 12 week study in osteoarthritic patients, celecoxib and naproxen had equal efficacy and were both well tolerated.[54] In a further 12 week study in 1149 rheumatoid patients, both celecoxib and naproxen improved the signs and symptoms of arthritis. The incidence of endoscopically assessed gastroduodenal ulceration over the dose range of celecoxib used (4–6%) was the same as the placebo group, and was substantially less than that observed in the naproxen group (26%).[55]

In addition to anti-inflammatory utilities in osteoarthritis, the COX-2 selective rofecoxib has been approved by the FDA for the treatment of acute pain in adults, dysmenorrhoea, and osteoarthritis, based on preclinical efficacy[56] and findings from clinical studies.[57] The analgesic properties of COX-2 inhibitors had been a controversial issue in the early development of these agents although preclinical data with both celecoxib and rofecoxib supported an analgesic action.[56 58] The clinical studies in analgesia paradigms clearly puts this issue to rest, yet it is apparent that these agents do not offer the pain relief profile of strong or narcotic analgesics.

In a study on the efficacy of a single dose regimen in post-dental pain in 151 patients, rofecoxib had comparable analgesic effects, onset of action, and peak degree of pain relief as ibuprofen.[57] This agent also demonstrated efficacy as an anti-inflammatory agent in a number of clinical studies with once daily treatment. In a comparison of eight studies involving 5435 patients with osteoarthritis, rofecoxib was associated with an overall significantly lower incidence of upper gastrointestinal tract bleeding than the comparator NSAIDs, including diclofenac and ibuprofen.[59] In a further study in 742 patient with osteoarthritis, using ibuprofen as the comparator, the incidence of ulcers was evaluated over a 24 week treatment period.[60] The cumulative number of ulcers in the rofecoxib group was significantly lower than that with the higher dose of ibuprofen (7.3% and 28%, respectively) at 12 weeks, being equivalent to the placebo group, while at 24 weeks the ulcer rate with the higher dose of rofecoxib (50 mg) was 14.7% compared with 45.8% in the ibuprofen group.[60]

Conclusions

Following the successful launch of celecoxib and rofecoxib in the USA and other territories over the past 12 months, the pharmaceutical industry still appears to have considerable interest in further developing the COX-2 selectivity concept for the identification of novel anti-inflammatory analgesics. Indeed, at a recent William Harvey Research Conference (Lisbon, October, 1999) on the potential for COX-2 specific agents, some 18 pharmaceutical companies were represented. Proof of principle has come from a range of experimental models and clinical studies which demonstrate the clinical efficacy of these agents as anti-inflammatory and analgesic agents, with little or no gastrointestinal irritancy.

With the full recognition of the potential commercial success of these agents, celecoxib having captured some 22% of the prescription market for antiarthritic therapy in the USA in its first quarter year sales, renewed efforts on COX-2 inhibitors from most pharmaceutical companies in the inflammatory arena are anticipated. Because of the size and fragmentation of the current use of NSAIDs, we may expect to see a range of COX-2 agents with different, or slightly different, pharmacological or pharmacokinetic profiles become available. It will, however, be very important that these agents are as rigorously evaluated as the recently launched agents, to ensure that unexpected and atypical side effects do not emerge from structural variants. Any such adverse events would create significant resistance to use of this class of NSAIDs by clinical practitioners and patients alike. The continued success of the COX-2 concept will of course depend on the clinical performance of the products in general practice, outside tightly regulated and assessed clinic trials, with acceptance by the patient being the final arbitrator.

It is clear, however, that these COX-2 selective agents cannot be classed as "super aspirins" as their therapeutic actions as anti-inflammatory analgesics demonstrated so far do not surpass those of aspirin or the classical NSAIDs. Moreover, COX-2 inhibitors would not be suitable for some key indications for which aspirin is used, particularly in the prevention of platelet aggregation and cardiovascular disease, a fact that must be emphasised to the prescribing community. Recent clinical pharmacology data from McAdam and colleagues have also suggested that there is a reduction in prostacyclin metabolites with COX-2 inhibitors[61] which theoretically could have an adverse cardiovascular and prothrombotic potential. Indeed, it will be important for future studies with COX-2 inhibitors in patients at cardiovascular risk to establish the relative benefit/risk ratio for cardiovascular or gastrointestinal adverse events if they continue with low dose aspirin to inhibit preferentially COX-1 derived platelet thromboxane production.

It is not known how the selective COX-2 inhibitor drugs will behave on more prolonged high dose administration over several years, especially under the conditions prevailing in patients with chronic inflammatory conditions or in the elderly. In addition, it is not known if such prolonged suppression of COX-2 will affect physiological responses as this enzyme can be expressed constitutively. Thus COX-2 appears to be involved in the healing of experimental peptic ulcers and in the process of angiogenesis, at least in experimental models.[62 63] Although the existing clinical data with these agents do not suggest a major problem over that anticipated with other NSAIDs, it is not yet known from direct studies whether COX-2 selective inhibitors will affect ulcer healing in patients with pre-existing gastric or duodenal lesions.

In addition, whether such agents, in common with other NSAIDs, would be counterindicated in patients with inflammatory bowel diseases has not been established in appropriate clinical studies. Exacerbation with a range of COX-2 selective inhibitors in experimental colonic inflammation has been reported,[64] and such agents do not appear to offer anti-inflammatory benefit in colitic models.[65] However, the possibility that selective COX-2 inhibitors could also have a use in other major therapeutic areas such

as in colon cancer, as well as in Alzheimer's disease, has continued the interest in the identification and development of highly selective COX-2 inhibitors.

The anticipated reduction in risk with COX-2 selective anti-inflammatory drugs has significant implications for health economics, with a potentially substantial reduced requirement for additional health care costs for those iatrogenic diseases associated with the classical NSAIDs. A remaining question is whether such currently available agents have sufficient selectivity between the isoforms to exploit fully any differential therapeutic benefit. Thus it is clear that both the key players have already progressed back up and follow up compound into late stage developments plans, and are ready to expand and defend their territory if required. Thus Merck have a highly selective inhibitor MK-663 in phase III development and preliminary data in some 600 osteoarthritis patients have shown it to be effective, and with adverse events comparable with placebo. Searle and Pfizer are developing valdecoxib, reported to be a highly selective COX-2 inhibitor, while their other compound, paraecoxib, is being positioned as an injectable post-surgical analgesic.

It is not yet known whether such high specificity in novel COX-2 inhibitors will be associated with greater clinical efficacy or a superior side effect profile than the existing COX-2 inhibitors. Indeed, as many of the clinical studies with celecoxib and rofecoxib report levels of gastrointestinal injury close to that of placebo is not clear how improvements with newer COX-2 inhibitors will be established, other than their performance in long term studies. Furthermore, although in some in vitro assays rofecoxib appears to have greater selectivity than celecoxib, whether the two latter agents will be distinguishable from each other in large scale head-to-head clinical trials, or perhaps more importantly in general practice, by their efficacy or side effect profile will be of major significance.

It is possible that any newer more selective agents will receive the endorsement, so far withheld by regulatory agencies such as the FDA for the two launched products, that selective COX-2 inhibiting agents represent a new class of anti-inflammatory agent. Thus these agents are still not exempt from the standard warning of possible gastrointestinal side effects required of all NSAIDs in the package insert and in the summary of product characteristics. Only with extensive clinical evaluation of the next generation of highly selective agents that would warrant the term specific COX-2 inhibitors would any additional therapeutic advantage of such a degree of enzyme discrimination be identified. Until then, the therapeutic promise and cost-benefit relationship of the currently available COX-2 inhibitors, derived from such humble 19th century beginnings as the salicylates, will continue to be under close scrutiny.

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