THE COX CONTROVERSY: VIEWPOINT 2

New dogmas or old?

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Recent experimental studies may undermine our understanding of the gastrointestinal side effects of non-steroidal anti-inflammatory drugs and cast a shadow on the original concept that underpins the development of the recent addition to the clinical anti-inflammatory armamentarium, the COX-2 selective inhibitors. But is this just a passing cloud or a total eclipse of the COX theory?

Just when we had thought that the problems with understanding the gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs) had all been solved, along comes experimental data that apparently undermines the whole concept. Thus as Bjarnason and colleagues¹ discuss in the accompanying viewpoint 1 in this issue of *Gut* [see page 1376], experimental studies using isoform selective cyclooxygenase (COX) inhibitors and COX gene deleted rodents have cast a shadow on the original concept that underpins the development of the recent addition to the clinical anti-inflammatory armamentarium, the COX-2 selective inhibitors. The question we must ask is whether this is just a passing cloud or a total eclipse of the COX theory?

The mechanistic interpretation of the experimental data may indeed reveal inadequacies or even flaws in the working concept. However, as pointed out, these would not affect the clinical findings or therapeutic benefit of COX-2 inhibitors as anti-inflammatory and analgesic agents in terms of the more favourable gastrointestinal side effect profile seen in most, but it should be said not all, of the published clinical studies.^{2–4} Irrespective of that being the case, we must all agree it is still important from a scientific and academic viewpoint to understand more fully the role of COX inhibition in the pathogenesis of such side effects. So, where did we all go wrong in our thinking, if indeed we really did?

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It is of course very important, as Bjarnason *et al* point out,¹ to consider the historical perspectives behind the development of any scientific concept. Interpretation of the information on such historical milestones will however depend on the direction from which one is approaching them. Some insight may also be gained by looking closely at the older maps of the area.

An early stage in the understanding of the biochemical actions that could be exerted by

NSAIDs came from the work of Whitehouse and Haslam some 40 years ago, who proposed that these drugs in high concentrations can uncouple oxidative phosphorylation.⁵ Such work was subsequently used to formulate early theories of the biochemical and toxicological basis of the local irritancy of these drugs.^{6,7} It is gratifying therefore that this early work has been reconfirmed by Bjarnason *et al* and forms an essential part of their own new dogma.^{8,9}

With the discovery by Vane and colleagues in 1971 that aspirin and NSAIDs prevent the production of prostaglandins by inhibiting COX,¹⁰ a general hypothesis on the mechanism of their therapeutic actions and side effects was developed, although caveats to the universal applicability were clearly recognised at that time by this group. It was apparent for example that such COX inhibition could not be the sole process by which NSAIDs provoked gastric mucosal injury.^{7,11}

Indeed, the well established gastric barrier breaking action of salicylates identified in the 1960s by Davenport¹² was always considered likely to be independent of COX inhibition as these actions were shared by diverse irritants such as ethanol, detergents, and bile salts. These topical irritant actions, particularly shown by the chemically acidic NSAIDs, which disrupt the gastric epithelial cell barrier and allow the back diffusion of acid into the mucosa, were considered to result from their physicochemical properties interacting with the surface phospholipids.¹³ Local changes in epithelial oxidative respiration followed their accumulation in these cells.⁶

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It was very clear that such topical gastric effects would largely, if not exclusively, occur only after oral administration. Moreover, it was known that many of the newer NSAIDs available at that time could provoke injury via the parenteral route, suggesting that other biochemical mechanisms must also operate, with COX inhibition being a likely contender. Thus the concept of synergistic interactions between topical irritancy and COX inhibition in mucosal injury was developed in the late 1970s.⁷ This working theory can thus explain why orally ingested low dose aspirin in cardiovascular therapy can still give rise to worrisome gastric damage on long term usage, as the minimal

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; NO, nitric oxide; iNOS, inducible nitric oxide synthase; AS, ankylosing spondylitis.

topical effects can synergise with the consequences of local or systemic COX inhibition.¹⁴

It also became apparent from early work that site selectivity of COX inhibition could be achieved, which could also influence the gastric side effect profile. Thus sodium salicylate and an experimental COX and lipoxygenase dual inhibitor did not inhibit gastric mucosal COX and did not provoke mucosal injury although these agents did inhibit prostanoid production at inflammatory sites where they exerted anti-inflammatory actions.⁷ It was predicted that anti-inflammatory COX inhibitors that had an attenuated ability to inhibit COX in the mucosa, or had reduced topical irritant activity, would yield novel NSAIDs displaying a lower propensity to damage the stomach, while agents having both attributes would be considerably superior.^{7 11} Such work was the precursor to the COX selectivity concept developed some 10 years later.

The experimental work with the newly identified selective COX-2 inhibitors, including celecoxib and rofecoxib, supported the concept that inhibition of the constitutive COX-1 isoform was a necessary component of the initiation of gastric damage.^{15 16} Hence it was considered that COX-2 selective agents would be essentially free of such actions while retaining anti-inflammatory properties as a consequence of reducing proinflammatory prostanoids synthesised by the inducible COX-2 isoform. Indeed, in the preclinical models, the COX-2 selective agents had a superior safety profile on the gut compared with the other NSAIDs.^{15 16} This was borne out in many clinical trials, particularly those using endoscopic techniques.¹⁷⁻¹⁹ This work did not exclude however that mitigation of other factors such as topical irritation by these essentially chemically non-acidic new agents could also contribute, especially when the agents were compared with standard NSAIDs given orally. In addition, the inability of the COX-2 selective inhibitors to affect platelet function,⁴ unlike the NSAIDs that also inhibit COX-1, may also reduce the potential for microbleeding in the gut although this lack of activity is also considered to be a risk factor in coexisting cardiovascular disease.

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The first real challenge to the working concept on the mechanism underlying the safety profile of the COX-2 inhibitors came from studies that indicted that neither selective inhibitors of either the COX-1 or COX-2 isoforms themselves provoked acute gastric injury in the rat after a single dose although a combination of these agents did.²⁰ Whereas the original working hypothesis dictated that inhibition of COX-1 was the key COX related event in the initiation of mucosal injury, it was now proposed that inhibition of both COX isoforms were required. Acute inhibition of COX-1 resulted in reduction in gastric blood flow, a mechanism long proposed to underlie the gastric injury by NSAIDs,¹¹ while acute inhibition of COX-2 evoked adhesion of white cells in the intestinal microcirculation, considered to be involved in the initiation of gut injury, both events being required for gross mucosal injury to manifest.²⁰ Clearly, however, the net effect on gastric damage with a COX-2 inhibitor that did not inhibit COX-1 would be the same regardless of whether the earlier or later concept was operational.

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If one turns to the small intestinal injury with NSAIDs,²¹ experimental findings in the rat from some 20 years ago again

indicated that COX inhibition could not be the sole factor in this complex pathology. Thus profound COX inhibition with aspirin itself did not regularly cause such subacute injury, in contrast with agents such as indomethacin.²² It would appear that enterohepatic recirculation of many NSAIDs allows a more prolonged contact with the intestinal mucosa, so local irritant effects may be of relevance in these slowly evolving lesions, especially in rodents.^{9 23} Recent detailed studies in mice using COX-1 and COX-2 inhibitors and COX knockout mice have now suggested that as in the gastric mucosa, inhibition of both isoforms is required for the development of the characteristic jejunal lesions seen over 48 hours with NSAIDs.²⁴

Early vascular changes are evident in the small intestine following NSAIDs but it is not clear if these are solely the result of acute COX inhibition.²⁵ Studies with antibacterial agents have shown that the ingress of luminal bacteria is involved in this enteropathy,^{23 26} confirming early work with germ free animals.²¹ Thus an early breach in the intestinal barrier defence with subsequent translocation of the bacteria and release of endotoxin gives rise to expression of the nitric oxide (NO) synthase isoform, inducible nitric oxide synthase (iNOS).²⁶ The NO so formed appears to combine with the oxygen moiety, superoxide, to form the highly reactive and cytotoxic species, peroxynitrite, which is responsible for the further development of the fulminant intestinal lesions following the initial challenge with the NSAID.^{27 28}

Are the COX-2 selective inhibitors considered completely free of such actions on the small intestine? The answer is quite simply, no. Indeed, the preclinical and safety data of the submissions to the Food and Drug Administration (see www.fda.gov/cder/approval/index.htm) for the first generation COX-2 inhibitors, celecoxib and rofecoxib, or to the European Medicines Evaluation Agency (see www.emea.eu.int/) for the second generation compound, valdecoxib, all record intestinal pathology, including perforation and inflammation from longer term toxicological studies in rodents at high doses. This has been recognised by many regulatory authorities in their assessment of the requirements for drug labelling, package inserts, and the listed summary of the product characteristics.

Bjarnason *et al* report that in COX-2 knockout mice, ileocaecal lesions can also be detected, as also found with a three month treatment with COX-2 inhibitors and indeed other NSAIDs.^{1 24} The pathological processes underlying these gut lesions have not been identified but would appear to be independent of any local irritant action in those animals not receiving NSAIDs. It has been mooted that as low grade inflammatory lesions have been detected in the ileum and caecum of patients with ankylosing spondylitis (AS), many of whom take NSAIDs, that prolonged COX-2 inhibition may have contributed to their aetiology.¹ However, inflammation is found in the duodenum as well as in the colon of AS patients, a region not usually associated with NSAID induced injury, while translocating gut bacteria have been implicated in this gut inflammation which is also accompanied by iNOS expression.²⁹ These patients take a wide range of pharmacologically active agents, including the so-called disease modifying antirheumatic drugs and corticosteroids. Thus it will be important to establish if there is any difference between the treatment cohorts for the incidence and time to occurrence of these lesions in a disease which, like other inflammatory bowel diseases, also has an important immune component.

Are these jejunal or ileocaecal lesions observed with COX-2 inhibitors in rodents cause for great concern? While the pathological basis for such enteropathy should indeed be explored vigorously and its possible occurrence in humans carefully monitored, it must be remembered that one single anti-inflammatory dose of many clinically used NSAIDs such as indomethacin or diclofenac will cause a high incidence of mortality in rodents after three days due to intestinal lesions and perforation.^{21 22 28} This extreme toxicological reaction in rodents obviously is not observed in the clinical setting,

although standard NSAIDs, unlike the COX-2 inhibitors, cause acute changes in intestinal permeability in humans.³⁰ Moreover, NSAIDs cause a high incidence of small intestinal side effects in longer term studies. Thus some 40% of serious gastrointestinal adverse events in rheumatoid arthritic patients during a median of a nine month treatment period with naproxen were associated with the small bowel, while treatment with rofecoxib caused only half this incidence of these intestinal adverse events.³¹

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Although clearly not the sole process in gut injury produced by NSAIDs, the data so far support a key role for COX inhibition, albeit COX-1 or a combination of COX-1 and COX-2, in the complex pathological events. These processes also appear to involve some form of local irritation in both the stomach and intestine with the standard NSAIDs, and such effects are substantially enhanced by concurrent COX inhibition. As with all good biological concepts, evolution of thought and knowledge demands that virtually none are left as their originators had designed and it is the hallmark of the scientific process that we should challenge the prevailing dogma. Even then, we are still left with a paradigm that COX inhibition is involved with this form of iatrogenic gut diseases. We thus appear to be heading back to the comfort of the older dogmas but now restyled with refined information on the involvement of the various biochemical actions of NSAIDs.

Building on the therapeutic, and no doubt commercial, success of the earlier COX-2 selective inhibitors, coxibs, already launched in this century, second generation drugs in this class are rapidly emerging, while analysis of their side effect profile, particularly as related to cardiovascular adverse events, are being carefully monitored.⁴ Other controversial areas with these agents concern the possible physiological roles of the COX-2 isoform products, including renal actions and in angiogenesis, and such queries need to be resolved.

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Confirmation of long term benefits to patients in terms of reduced gastrointestinal side effects compared with standard NSAIDs for equivalent anti-inflammatory and pain management activity, or even in the emerging oncological utilities, will be required to sustain the additional costs of therapy with these agents. Whatever the mechanism of any reduced gut pathology of these coxibs, a clinically acceptable general safety profile is likely to be the major key determinant to the continued success and growth of such agents in a fiercely contested anti-inflammatory arena, despite new, old, or indeed no COX dogma.

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