THE COX CONTROVERSY: VIEWPOINT 1

NSAIDs: the Emperor's new dogma?

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Gut 2003;52:1376-1378

The spectacular marketing success of the selective cyclooxygenase 2 (COX-2) inhibitors is largely based on efficacy comparable with conventional non-steroidal anti-inflammatory drugs (NSAIDs) with vastly improved gastrointestinal safety. The additional key to the marketing success is the purity and simplicity of the message—that is, COX-1 inhibition causes the gastrointestinal side effects of NSAIDs (COX-1 dogma) while COX-2 blocking confers the therapeutic benefits (COX-2 dogma). Adherence to the COX dogmas with development of COX-2 selective agents has undoubtedly benefited many patients, but ironically their scientific basis is now seriously challenged by experimentation.

action and pathogenesis of NSAID induced gastrointestinal damage come from the experimental animal receiving large doses of the drug short term.

"Discovery of the mode of action of conventional NSAIDs in the 1970s led to the dogma that all the beneficial and adverse affects of aspirin and NSAIDs were due to COX inhibition (COX hypothesis)"

Discovery of the mode of action of conventional NSAIDs in the 1970s⁹ led to the dogma that all the beneficial and adverse affects of aspirin and NSAIDs were due to COX inhibition (COX hypothesis).¹⁰ Only a handful of investigators dared to challenge this doctrine which equated gastric damage with inhibition of gastric COX and decreased levels of protective mucosal prostaglandins. These investigators introduced the term "topical" toxicity to describe a prostaglandin independent component to the damage that required a luminal to mucosal drug contact.^{11 12} The basis for this adjustment came in part from rodent experiments that showed that gastric mucosal prostaglandins could be decreased by over 90% by rectal or intravenous administration of conventional NSAIDs without causing stomach damage.^{13 14} Furthermore, short term gastric damage seemed to correlate better with the degree of acidity of the particular NSAID than its effect to decrease mucosal prostaglandins.¹² It is now apparent that this "topical" effect is due to their physicochemical properties (they are lipid soluble weak acids) allowing NSAIDs to interact with surface membrane phospholipids¹⁵ and uncouple mitochondrial oxidative phosphorylation.¹⁶ Experimentally a compelling case could be made for the idea that the gastrointestinal damage was set off by a combination of COX inhibition and the "topical" effect.¹⁷ Nevertheless, based on the fact that misoprostol conferred protection against NSAID induced gastric damage^{5 18} and that administration of an antibody to COX led to gastric damage in the rabbit,¹⁹ COX inhibition alone was considered by most to be the sole explanation for the damage.

"The facts may yet turn this biological fairytale into a pantomime"

The COX adherents had their coronation with the discovery of the two isoforms of COX (1 and

The spectacular marketing success of the selective cyclooxygenase 2 (COX-2) inhibitors celecoxib and rofecoxib is largely based on the "fulfilled" promise of efficacy, equal to conventional non-steroidal anti-inflammatory drugs (NSAIDs), with vastly improved gastrointestinal safety.¹ Certainly, these drugs cause very little if any gastric damage in short and long term endoscopy studies,² or small bowel damage³ in the short term in humans. Furthermore, the large outcome studies show a 50–60% reduction in serious complication rates of gastric ulcers (perforation and clinically evident bleeding)⁴ which is comparable with the beneficial effect of misoprostol when coprescribed with conventional NSAIDs.⁵ The additional key to the marketing success is the purity and simplicity of the message—that is, COX-1 inhibition causes the gastrointestinal side effects of NSAIDs (COX-1 dogma) while COX-2 blocking confers the therapeutic benefits (COX-2 dogma).¹ Rejoice!

Despite this undoubted success, a faint rumble of discontent is growing regarding the possible renal, central nervous, reproductive, and cardiovascular^{6–8} side effects as COX-2 is constitutively expressed in these tissues. The incidence of these side effects is very unlikely to outweigh the benefits of the improved gastrointestinal tolerability. It is more likely that the interest in these side effects will be driven by some pharmaceutical companies in order to gain a marketing advantage over their competitors.

More interestingly, it seems that the idea leading to the improved gastrointestinal tolerability of COX-2 selective agents was scientifically flawed. In order to appreciate this fully it is important to look at certain historical milestones in the development of NSAIDs. It is also important to emphasise that almost all data on the mode of

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Accepted for publication 15 April 2003

2) in the 1990s. Simplicity and order was maintained with the celebrated new COX-1 and -2 dogma.^{1,20} The delivery of efficacy and improved safety of rofecoxib and celecoxib (both are non-acidic) in humans was the proof of concept. However, the facts may yet turn this biological fairytale into a pantomime.

Studies show that mice that lack the COX-1 enzyme (COX-1^{-/-}) only have 1–3% of the gastrointestinal mucosal prostaglandin levels as wild-type animals (COX-1^{+/+}), yet they do not develop spontaneous gastrointestinal lesions.^{21,22} This is not by itself a threat to the COX-1 dogma as upregulatory compensatory mechanisms can be postulated.^{20,23} However, selective COX-1 inhibition (with SC-560) in COX-1^{+/+} mice²² or rats^{24–27} does not lead to any gastrointestinal damage (despite >95% decreases in mucosal prostaglandin levels). Classical NSAID-like gastrointestinal lesions are however seen when there is dual inhibition or absence of the two COX enzymes,^{22,24,26,27} and adding in the “topical” effect increases this damage.

When the COX-1^{-/-} mice were developed, the same group produced COX-2^{-/-} animals.²⁸ The first description of these animals and a detailed gastrointestinal study²² concur that some COX-2^{-/-} animals die from peritoneal sepsis. This is now known to be due to ileocaecal perforation.²² Indeed, about half of COX-2^{-/-} animals have evidence of increased intestinal permeability and inflammation without detectable changes in mucosal prostaglandin levels.²² Many of these develop ileocaecal ulcers that differ both in their location and histopathological appearance from the acute damage seen in animals receiving conventional NSAIDs short term.²² Again, this unexpected finding (for the COX believers) might be attributed to some dysregulation of compensatory pathways except for the fact that selective COX-2 inhibitors given long term cause the same damage in COX-2^{+/+} animals.²² Interestingly, another long term study, assessing the effects of long term low dose indomethacin, showed very similar ileocaecal pathology.²⁹

We are therefore left with the conclusions that gastric and mid small intestinal damage (NSAID enteropathy) is set off by a synergistic action of two or more of the biochemical actions common to all conventional NSAIDs (COX-1+COX-2 inhibition, COX-1 inhibition+“topical” effect, etc). Selective inhibition or absence of COX-1 or -2 alone has no significant pathophysiological consequences at these sites, hence the success of the COX-2 selective agents rofecoxib and celecoxib, neither of whom has a “topical” effect. Furthermore, a practical consequence of this “new” pathogenic information is that it explains why low dose aspirin (that causes very little gastric damage while inhibiting gastric COX significantly³⁰) coadministered with celecoxib causes similar gastric damage to conventional NSAIDs.³¹

“If the facts don't fit the theory, change the facts”

What then of ileocaecal damage, which is distinctively different from NSAID enteropathy, which seems to be driven by long term COX-2 absence or inhibition? Do we simply ignore the above data as it does not conform to our preconceived belief in the COX-1 or -2 dogma (“If the facts don't fit the theory, change the facts”, Albert Einstein), or does it warrant detailed investigation in humans? At present, there are no studies that specifically assess possible ileocolonic damage caused by COX-2 selective agents in humans. Extensive ileocolonoscopy studies have however been carried out in patients with spondylarthropathy, especially reactive arthritis and ankylosing spondylitis, all of whom were on or had received conventional NSAIDs long term.³² Thirty to 70% of these patients have macro- and microscopic ileitis with a variable proportion of patients having concurrent caecal or colonic inflammation.^{33,34} Some studies suggest that this inflammation may represent subclinical Crohn's disease.^{32,34}

However, it is interesting that the prevalence of the lesions and the microscopic features are very similar to those found in mice subjected to long term COX-2 inhibition or absence. Is it possible that the spondylarthropathic ileocaecitis presents iatrogenic COX-2 driven damage as described in animals? If so then the most worrying aspect is that the severity and prognosis of the spondylarthropathy is in part dependent on the histopathological features of this inflammation.^{35,36}

If a story appears to be too good to be true, especially when it involves complex biological processes, it is probably flawed or even plain wrong (“unless you're a scientist, it's much more important for a theory to be shapely, than for it to be true”, Christopher Hampton). Adherence to the COX dogmas with development of COX-2 selective agents has undoubtedly benefited many patients, but ironically their scientific basis is now seriously challenged by experimentation.

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