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Understanding the COX-2/ NSAID Dilemma

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"FACTS ARE STUBBORN THINGS, BUT STATISTICS ARE MORE PLIABLE" — Mark Twain

In the beginning there was salicylate, and that begat acetylsalicylic acid (ASA; aspirin), and that begat non-salicylate NSAIDs, and more NSAIDs and more until there were 100, and that begat selective cyclo-oxygenase (COX)-2 NSAIDs; and then there was celebrating in the land.

If only the story could end there, but we now know that we have not solved the safety issues confounding this whole group of drugs since the beginning.

Those of us who decried the intolerance and gastric toxicity of aspirin almost a half century ago are now singing a different tune.[1,2] With headlines daily reporting the dangers and morbidity of the NSAID/COX-2 successors to aspirin, not to mention their exorbitant costs, the recent centennial celebration of the discovery of aspirin also marked a great irony.[3-5] For now, aspirin is again one of the most used drugs, but mostly to prevent cardiovascular thrombotic complications. Yet, its sole remaining non-acetylated analogue, salsalate, through complete sparing of prostaglandin, is absent such end-organ and homeostatic toxicities.[6] This 'ancient' drug was first approved in 1932 and is now found with difficulty on the dusty back shelves of some pharmacies, and is only prescribed by knowledgeable rheumatologists with good memories. And yet, paradoxically, it is our evermore sophisticated basic research that ferreted out the human price of disrupting prostaglandin metabolism.[7] This can potentially disrupt gastroprotective mechanisms that, in unfavourable host-risk circumstances, lead to serious gastropathy. Prostaglandin dysregulation may also impact on thrombotic mechanisms, thus precipitating cardiovascular complications.[8] The balance between isoenzyme COX-1 and COX-2 (and possibly a COX-3 isoenzyme) is not only related to a 'safe constitutional role' but also to pain and inflammation inhibition. This is importantly amplified by long-term full-dose use. Thus, the pharmacokinetic dysregulation can synergise with the pharmacodynamic vulnerabilities of the host.[9]

Rheumatology practice now differentiates minimally clinically important differences (MCID) in treatment from really important differences (RID). Although COX-2/NSAIDs are limited to the MCID category, they have proven highly useful for arthritis and common pain. However, they do have a limited ceiling for analgesia, never found to exceed the therapeutic dosage of aspirin, though far better tolerated. Importantly, opioids are reserved for more significant levels of pain and are also end-organ non-toxic.[10] Finally, topical therapies, sparing systemic adverse effects, are recommended for local therapy, including newer topical NSAIDs.[11,12]

Yet, historically, NSAID dangers were reported from the first experiences almost a half century ago.[2,13] We, and then others, indicated the most common of the serious problems was gastrointestinal, and indeed gave the name 'NSAID gastropathy' to differentiate it from peptic ulcer disease.[2] Despite the discovery of *Helicobacter pylori* ulcers since, NSAID gastropathy stands separate. It is best prevented, not treated, since not using NSAIDs in those at higher risk simply obviates this drug-specific problem. And so, for that matter, will be the case

in other NSAID-related attendant end-organ and thrombotic events.

The issue of NSAID safety has been conflated by the surreptitious discovery in a large hodge-podge of epidemiological studies of the various outcomes of long-term COX-2/NSAIDs on cardiovascular thrombotic events (myocardial infarction, stroke).[5,14,15] Case control, cohort and observational studies as a basis for 'cherry-picking' unexpected other outcomes should be subject to careful scrutiny and rigorous follow-up protocols. Instead, these have been a direct-to-media basis for media hyperbole (i.e. COX-2 therapy: three times the risk for heart attacks and stroke!). Investigators have suggested that age of cohort and chronicity of dose administration could not mitigate this risk.[5] Yet, this is contrary to the known 'background noise' of co-disease, and length of exposure and biohandling issues (i.e. the elderly, the chronically ill).[16]

In conclusion, this is not to suggest that the media frenzy over the NSAID/COX-2 debacle that has resulted in the withdrawal of two of the three major COX-2 agents and the strong labelling of 'black box' warnings for the remainder in the US, should harken the end of COX-2/NSAIDs as an important prescription and over-the-counter common therapy. For they have indeed enjoyed a deserved useful clinical role. We may live in the 'information age', but information is not synonymous with knowledge. The many COX-2/NSAIDs seem to have unique subsets of responders to justify choices based on properly monitored and documented outcomes. Evidence-based, randomised controlled trials (absent long-term drug exposure) are not positioned well to identify these one-by-one differences. Nor, for that matter, do they recognise safety issues critical to long-term NSAID use. Therefore, until better postmarketing surveillance becomes a reality, the following guide could be useful:

- generally avoid long-term NSAID use in the very elderly and debilitated;
- continue to use COX-2/NSAIDs sensibly and selectively based on sound clinical judgement and judicious monitoring;
- consider topical therapy for local non-systemic problems;
- consider pure analgesics adjusted to pain level and on a co-therapy basis to minimise duration and dosage of NSAID exposure;
- individualise such usage based on good clinical judgement and judicious monitoring.

This judgement must be in harmony with both sound empirical experience and evidence-based outcomes without suspect pliable statistical results. And, thus, you fulfill your Hippocratic Oath to "first do no harm", but also relieve pain and suffering.

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