COX 1 and 2 : The cyclo-oxygenase systems
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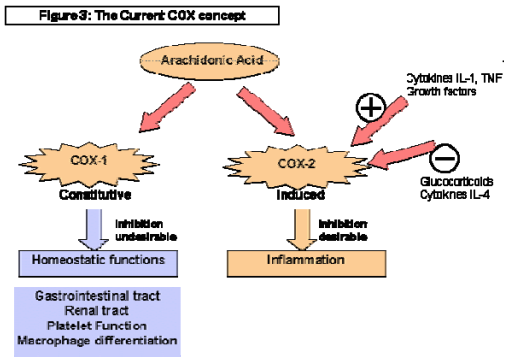
Whilst many NSAID's - Non-steroidal anti-inflammatory drugs, are considered to have equivalent efficacy, there is now no doubt that NSAID's have different side effect profiles The explosion of knowledge about the different cyclooxygenase enzymes has given us a more fundamental understanding of the actions and side effects of these drugs.

Fries et al showed with The Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) database, of over 17 000 patients in 37 centres in the US and Canada, that there is considerable morbidity and mortality from arthritis. They confirm, as have other researchers, that NSAID's are not all the same but rather, have different toxicity profiles. They illustrated appropriately, that the disease modifying drugs (DMARDs), used in the therapy of inflammatory arthritis, have an acceptable side effect profile. They showed that the toxicity profile of these drugs used appropriately was of similar scale to the NSAID's . Therefore correct diagnosis and treatment of the underlying condition with DMARDs where appropriate, is essential. However symptomatic therapies utilizing NSAID's, have remained essential therapeutic components in the drug regimens of patients with arthritis. NSAID's remain perhaps the most widely prescribed drugs, worldwide. However they are associated with significant side effects, that complicate their use, especially in the elderly, a population group that is set to rise with the advent of the maturing baby boom generation.

In the 1980's Needleman showed that COX enzyme was increased in inflamed tissue and that COX was stimulated by interleukin-1 (IL-1) on cultured human dermal fibroblasts. They showed a dose-dependent response curve. This suggested IL-1 dependent transcriptional regulation.

In 1990 he demonstrated the induction of COX by endotoxin. An increase in COX was prevented by glucocorticoids. However it was noted that dexamethasone did not affect baseline prostaglandin formation.

They therefore postulated a second COX enzyme. In 1991 the second COX isoform was cloned. This represented what is now known as COX-2. COX-1 is now known to be present in most tissues as the housekeeper enzyme. COX-2 is inducible by inflammation. It is not present at baseline, but increases in response to inflammation including arthritis. It has 60% homology with COX-1. Both have the same affinity to convert arachidonic acid to prostaglandin. COX-1 maintains normal gastric mucosa and influences kidney function. The inhibition of COX-1 is therefore undesirable. The inhibition of COX-2 on the other-hand is a desirable effect.



The concept of the COX-2 to COX-1 ratio provides us with a mechanism to assess the balance of inhibition of the inducible COX-2. Analysis of these ratios and side effects of the older

conventional non-steroidal anti-inflammatories show that the lower the ratio, the lower the COX-1 inhibition, and the lower the overall side effect profile. In the guinea pig macrophage model of Engelhardt, meloxicam had a ratio in the order of 0.33, diclofenac, 2.2 and piroxicam 33.

Figure 4 :

IC_{50} values and COX2/COX-1 ratios of different NSAIDs in guinea pig peritoneal macrophage model.
(Engelhardt et al. Journal Inflammatory Research 1995, Volume 44, Pages 422 - 429.)

NSAIDs	COX-2 IC_{50} micromol/litre	COX-1-IC_{50} micromol/litre	Ratio COX-2 / COX-1
Meloxicam	0.0019	0.00577	0.33
Diclofenac	0.0019	0.000855	2.2
Piroxicam	0.175	0.00527	33
Tenoxicam	0.322	0.201	15
Indomethacin	0.00636	0.00021	30
Teridap	47.9	0.393	122

Truly specific COX-2 inhibitors, Celecoxib (Celebrex, Pfizer corporation) , and Bextra (Pfizer corporation) are now commercially available, and others are currently being researched. Rofecoxib (Vioxx, Merck) was withdrawn by that company from commercial use due to increased risk of myocardial infarction.

Celecoxib (celebrex), the first of the new class of drugs was passed by the FDA for use in Rheumatoid and Osteoarthritis. Rofecoxib (Vioxx) has been licensed for Osteoarthritis, and pain, including dysmenorrhea and post operative pain. Development of the true COX-2 inhibitors have been well under way and have completed phase three, pre-release trials. Results from these studies show a clear reduction or even absence of gastrointestinal side effects. However, early studies showed a very slight increase in risk of myocardial infarction and recent studies showed this increase risk in a trial involving adenomatous polyp prevention after 15 month continual use. The drug was thereafter withdrawn from the market.

Celecoxib (Celebrex) for example, is 375 fold more selective for COX-2 compared to COX-1. It does not inhibit COX-1 at therapeutic doses in contrast to standard NSAID's currently available. Studies show effective benefit with no gastrointestinal adverse effects compared to placebo.

In the anticipation of the COX-2 era, many pharmaceutical companies have been positioning themselves and their existing NSAID products, as so called "preferential" COX 2 inhibitors. Such

drugs, currently available are NOT COX specific. Problems in classifying drugs as selective agents, resulted in several meetings to standardize the science of COX 2. Discussion as to what constituted true COX selectivity, has resulted in a classification of the drugs into specific versus preferential COX 2 inhibitors. It is realized that enzyme assays do not predict in-vivo selectivity. In-vivo selectivity must be seen at therapeutic concentrations and objective specificity in humans is essential. This requires therefore that a drug must show safety in endoscopy studies, platelet function must not be impaired, and a study of 3 months at minimum with at least 3 months follow up is required to show true efficacy.

Meloxicam has been released in South Africa, and is one of several so called "preferential" COX 2 inhibitors which have been developed. Specific agents which are in development have a more impressive selectivity. Meloxicam is 3 times more selective for COX 2 - compared to for, example - Celecoxib (Pfizer corporation), which is 325 times more selective. In fact analysis of the therapeutic plasma levels of Meloxicam, show these to be greater than the amounts required for inhibition of COX 1. Thus inhibition of COX 1 will occur, and side effects are therefore possible. Meloxicam is therefore NOT a specific COX 2 inhibitor.

Plasma levels of Celecoxib however, at therapeutic doses, do not exceed the levels required for COX 1 inhibition, whilst inhibiting COX 2 effectively. Studies on Celecoxib, confirm gastrointestinal side effects to be similar to placebo. The drug therefore is the first specific COX 2 inhibitor, and is the first to be so recommended by the FDA.
Rofecoxib is a COX 2 specific inhibitor which shows in - vitro evidence of sparing COX 1 whilst inhibiting COX 2. Trials confirm efficacy with reduction of endoscopic ulcers as well as serious complications of ulcers.

The overall effect, would appear to be, that the specific COX 2 relate to good gastrointestinal and renal side-effect profiles. They are major clinical advances in the management of pain and arthritis.

However apparent association with increased risk of myocardial infarction in the case of Rofecoxib has lead to a recent withdrawal of that product and a review of the entire class of drugs to evaluate safety.

Celecoxib h**as not been shown** to have this increased risk but is also under scrutiny.

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