New Cyclooxygenase Inhibitors

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Abstract

***Introduction**: The discovery of the two isoforms of cyclooxygenase (COX-1 and COX-2) has paved the way for the development of a new class of non-steroidal anti-inflammatory drugs (NSAIDs). The COX-2 inhibitors have shown comparable efficacy to the traditional NSAIDs with less gastrointestinal side effects in major clinical studies. The aims of this paper are to provide a brief historical background, pharmacology of cyclooxygenase inhibitors as well as discuss the latest update on COX-2 inhibitors. **Methods**: A MEDLINE search was performed for relevant articles from leading medical journals from 1990 to 2000. The papers reviewed include randomised controlled clinical trials, meta-analyses and review articles. **Conclusion**: The arrival of the COX-2 inhibitors into the treatment armamentarium for inflammation and analgesia has been widely accepted and welcomed. Although this new group of "wonder" drugs cause less gastrointestinal side effects, they are not renal sparing and do not have cardioprotective effects. Studies have also yet to establish its safety in NSAID-sensitive patients. In patients with chronic arthritides, cost is also an important factor to consider when prescribing these medications. Their strengths and weaknesses will become apparent with continued use.*

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Key words: Adverse effects, COX-2 inhibitors, Efficacy

Introduction

Cyclooxygenase inhibitors are non-steroidal anti-inflammatory drugs (NSAIDs). They have been used in the treatment of rheumatic diseases for several decades. The recent discovery of the cyclooxygenase isoforms, COX-1, which is known as the constitutive enzyme and COX-2 the inducible isoform, led to the development of this new class of NSAIDs known as the COX-2 inhibitors.

The rationale behind the development was the hypothesis that compounds that spare COX-1 and specifically inhibit COX-2 would lead to less toxicity particularly gastrointestinal (GI) and yet provide efficacy equal to the traditional NSAIDs.[1]

Historical Background

Salicylates were the first cyclooxygenase inhibitors ever used by man. In 1757, Reverend Edward Stone found that the extract from the bark of the willow tree contained "the cure for agues (fever)". In 1897, Hoffman, a Bayer pharmacist, developed a synthetic form of this agent, acetylsalicylic acid, better known as aspirin. He tested it on his ailing father who suffered from crippling arthritis and found that his condition improved markedly. Aspirin's use soared as a wonder drug with antipyretic, analgesic and anti-inflammatory effects.[2] The term NSAID was coined in 1949, 3 years after the discovery that corticosteroids had remarkable anti-inflammatory activity. Hence, an NSAID refers to a drug which reduces inflammation but is unrelated to steroids. Phenylbutazone was the first drug to be termed an NSAID. It was later withdrawn from use because of bone marrow toxicity. In 1965, indomethacin was the first NSAID to be discovered using the "carrageenan-induced rat paw edema model" of acute inflammation. Since then, many other compounds were identified as NSAIDs using this model. In 1971, Sir John Vane won the Nobel prize for his discovery of the mechanism of action for aspirin and NSAIDs—the inhibition of prostaglandin synthetase.[3] Masferer and colleagues[4] discovered the inducible COX-2 isoform in 1990 which is produced in pathologic situations.

Physiology of Cyclooxygenases

The enzymes involved in the synthesis of prostaglandins (PG) include phospholipase A2 which releases arachidonic acid from phospholipid membranes. Arachidonate is then metabolised by bifunctional enzyme cyclooxygenase (COX) to prostaglandin H2 (PGH2), after which stable prostaglandins are formed by a group of synthases.[5]

COX-1 is the constitutive isoform of COX and has

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distinct homeostatic functions. The gene responsible for its production has the characteristics of a housekeeping gene which is continuously transcribed and expressed in most tissues under basal conditions. Its activation leads to the production of various prostanoids which are essential for gastric cytoprotection, platelet activation, antithrombogenesis in vascular endothelium as well as renal function[6] (Fig. 1).

The inducible form of COX, COX-2 is produced by a number of cells in response to inflammatory stimuli for example, interleukin-1 and tumour necrosis factor.[4] It has a significant pathologic role in inflammation, pain and fever. It plays a role in tissue repair. Its function in other physiologic processes for example reproduction, renal function and development are not well defined as yet. Studies have found increased COX-2 expression in the GI tract following mucosal injury and specific inhibition of COX-2 delays ulcer healing in mice. Other clinical studies have shown that COX-2 inhibition led to a reduction in renal prostacyclin production in healthy elderly subjects with a significant transient decline in urinary sodium excretion (Fig. 1).

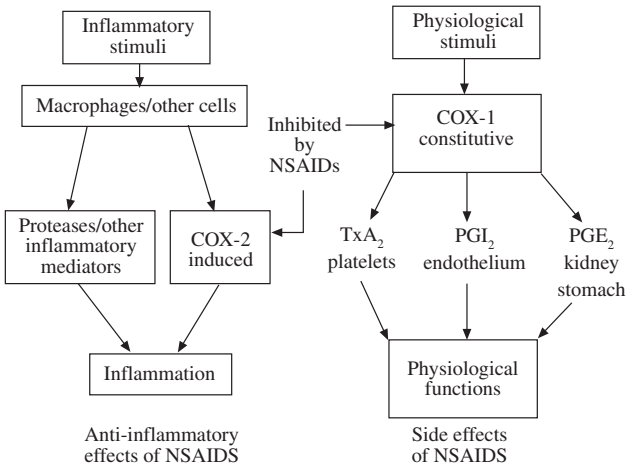

Fig. 1. Physiology of cyclooxygenases.
NSAID: non-steroidal anti-inflammatory drug

Main Adverse Effects of Standard COX Inhibitors

Gastrointestinal

The main concern about the use of non-selective COX inhibitors is that of GI toxicity. Almost 40 years elapsed before Douthwaite and Lintott[7] reported endoscopic evidence of gastric mucosal damage following the use of aspirin. In general, at least 10% to 20% of patients taking NSAIDs have dyspepsia and according to prospective data from Arthritis, Rheumatism, Aging Medical Information System (ARAMIS),[8] 13 out of every 1000 rheumatoid arthritis patients have serious GI complications when taking NSAIDs. The figure is slightly lower for patients with osteoarthritis (7.3 per 1000 patients per year). The mortality rate among hospitalised patients with NSAID-induced GI bleeding is about 5% to 10%.

In a recent meta-analysis by Hernandez-Diaz and Rodriguez,[9] the risk factors for upper GI bleeding (UGIB) include advanced age, past history of peptic ulcer disease and male gender. There was also variable risk among different NSAIDs but this was markedly attenuated when comparable daily doses were considered. Wolfe and colleagues[10] cited concomitant use of corticosteroids or anticoagulants, higher dosage of NSAIDs and the presence of serious systemic disorders as additional established risk factors for UGIB (Table I). However, many of the studies reviewed by them were based on univariate analysis and did not adjust for confounders.

Renal

In normal healthy subjects, renal prostaglandins do not have a major role in homeostasis as the basal rate of synthesis is very low. This issue becomes relevant in patients who have glomerular disease, renal insufficiency or pre-renal states like cirrhosis, cardiac failure or hypovolaemia, where renal prostaglandins are released in large quantities to preserve renal perfusion. In such settings, NSAIDs inhibit renal prostaglandin production and thus decrease renal blood flow resulting in a decline in creatinine clearance and haemodynamically-mediated renal failure. Sulindac is an example of a non-specific COX inhibitor that has some renal sparing effects as it does not inhibit renal prostaglandin E2 and prostacyclin synthesis.[11] However, some studies still caution the use of sulindac in patients with renal impairment as it has been shown to have some effects on creatinine clearance. It has been suggested that the dose of sulindac be decreased by 50% in patients

TABLE I: RISK FACTORS FOR GASTROINTESTINAL TOXICITY WITH NSAID USE

Risk factors for the development of NSAID-associated peptic ulcers

Established risk factors
· Advanced age
· History of ulcer
· Concomitant use of corticosteroids
· Higher doses of NSAIDs
· Use of more than one NSAID
· Concomitant administration of anticoagulants
· Serious systemic disorder
Possible risk factors
· Concomitant infection with *Helicobacter pylori*
· Cigarette smoking
· Consumption of alcohol

NSAID: non-steroidal anti-inflammatory drug
Adapted from Wolfe et al[10]

with a glomerular filtration rate of less than 10 mL/min.

Antithrombotic Effects

COX inhibitors decreases platelet adhesiveness via the inhibition of platelet cyclooxygenase (COX-1 pathway) due to a decrease in thromboxane A_2 production (TxA_2). It is important to note that the specific COX-2 inhibitors lack this effect on platelets.

The New Cyclooxygenase Inhibitors

Specific versus Selective COX-2 Inhibition

Several criteria must be met for a compound to be deemed as a COX-2 specific inhibitor. Firstly, the drug must exhibit specificity *in vitro*. The whole blood assay can be used to measure COX-1 and COX-2 activity *ex vivo*. Secondly, specific COX-2 inhibitors should not inhibit platelet aggregation or COX-1 over the entire range of doses.[12] Celecoxib and rofecoxib are examples of COX-2 specific inhibitors while meloxicam is COX-2 selective. The differences between this new class of cyclooxygenase inhibitors with the traditional NSAIDs are summarised in Table II.

The two main questions that need to be answered following the development of COX-2 inhibitors were firstly the clinical efficacy and secondly, the safety profile as compared to the non-specific COX inhibitors.

Meloxicam

Meloxicam is a COX-2 preferential inhibitor that has been estimated in various assays to be between 3- and 77-fold selective for COX-2. The results from efficacy studies on meloxicam appear promising. It was first marketed in Europe in 1996 for use in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

TABLE II: COMPARISON OF CHARACTERISTICS BETWEEN SPECIFIC AND NON-SPECIFIC COX INHIBITORS

Properties	Non-specific COX inhibitors	COX II specific inhibitors
Anti-inflammatory Anti-pyretic Analgesic	Yes	Yes
Gastrointestinal side-effects	Yes	Less GI erosions and ulcerations
Platelet inhibition	Yes	No
Renal side effects e.g. GFR, sodium excretion, Blood pressure	Yes	Possibly less

GFR: glomerular filtration rate; GI: gastrointestinal
Adapted from Crofford et al[24]

Following the results from two landmark trials, SELECT (Safety and Efficacy Large-Scale Evaluation of COX-inhibiting Therapies) and MELISSA (Meloxicam Large-scale International Study Safety Assessment), the gastric tolerability of meloxicam has been better defined and it has found a niche in the treatment of patients with arthritides.

In the SELECT trial,[13] over 8000 osteoarthritis patients were randomised to receive either equipotent doses of meloxicam or piroxicam. There was no significant difference in pain reduction in both groups but meloxicam had significantly less GI side effects namely dyspepsia, nausea, vomiting and abdominal pain [10.3% vs 15.4%, odds ration (OR) 0.63; P <0.001]. There was no statistical difference in the incidence of serious GI complications like perforation or bleeding between both groups. This is likely due to the small numbers.

Similar findings on GI tolerability were noted in the MELISSA trial.[14] Nine thousand two hundred and thirty-two osteoarthritis patients were randomised into 2 groups–meloxicam versus diclofenac. The average treatment period was 28 days. There was a significant reduction in GI adverse events (dyspepsia, abdominal pain, nausea, vomiting and diarrhoea) in the meloxicam group (13% vs 19%; P <0.001) but the numbers were too small to demonstrate any significant reduction in serious GI complications such as bleeding or perforation. The dose of meloxicam used in both these studies was 7.5 mg per day.

A meta-analysis of 12 randomised clinical trials by Schoenfield[15] on meloxicam versus non-selective NSAIDs revealed that the former was associated with significantly less GI adverse events (OR = 0.64; 95% CI 0.59-0.69). Patients using meloxicam experienced less dyspepsia (OR = 0.73; 95% CI 0.64-0.84), fewer perforations/ ulcerations/ bleeding (PUBs) (OR = 0.52; 95% CI 0.28-0.96) and less frequent discontinuation of NSAIDs because of adverse GI events (OR = 0.59; 95% CI 0.52-0.67). However, it is important to note that most of these trials evaluated low dose meloxicam and the results may not be generalisable at higher doses.

As of 1998, more than 1 million prescriptions have been dispensed for meloxicam in the United Kingdom alone. Forty-one per cent of 1339 suspected adverse drug reactions were of GI origin and 18% were serious—GI perforation, ulceration and/or bleeding. Most recovered with the discontinuation of meloxicam.[16]

Celecoxib

Studies have shown that celecoxib has equal efficacy to non-specific NSAIDs. Emery and colleagues[17] studied 655 patients with rheumatoid arthritis who were randomly assigned to celecoxib 200 mg bid or diclofenac SR 75 mg

bid for 24 weeks. Both drugs showed similar efficacy in terms of analgesic and anti-inflammatory activity. The incidence of gastroduodenal ulcers was significantly higher in the diclofenac group (15% vs 4%, P <0.001). The withdrawal rate for any GI-related adverse event was 3 times higher in the diclofenac group (16% vs 6%, P <0.001).

A recent meta-analysis by Goldstein and coworkers[18] of 14 randomised controlled trials (RCTs) of patients with either rheumatoid arthritis or osteoarthritis showed that the incidence of upper GI ulcer complications was 8-fold lower than non-specific NSAIDs (0.33% vs 0.03%).

The CLASS study (Celecoxib Long-Term Arthritis Safety Study)[19] revealed that celecoxib at 400 mg bid doses was associated with a significant reduction in the combined incidence of symptomatic GI ulcers and ulcer complications (0.44% vs 1.27%, P <0.04) when compared to NSAIDS (ibuprofen 800 mg tid or diclofenac 75 mg bid). However, with the concomitant use of aspirin, this difference between celecoxib and NSAID was not significant (upper GI ulcer complication rate 2.01% vs 2.12%; P = 0.92 and symptomatic ulcer 4.7% vs 6%; P = 0.49).

Rofecoxib

In a randomised double-blinded trial, 809 patients with osteoarthritis were treated with either placebo, rofecoxib 12.5 or 25 mg daily or ibuprofen 800 mg tid. The results showed that rofecoxib at both dosages had similar clinical efficacy to high dose ibuprofen.[20] Cannon and colleagues[21] studied the clinical efficacy of rofecoxib 12.5 mg or 25 mg daily versus diclofenac 50 mg tid in 784 patients with osteoarthritis and results showed that it was comparable in efficacy.

Hawkey and coworkers[22] examined the effects of rofecoxib (25 or 50 mg per day) vs ibuprofen (800 mg per day) on gastroduodenal mucosa in 775 patients with osteoarthritis. They found an improved gastric safety profile with rofecoxib (ulcer rate 5.3% and 8.8% versus 29.2% for rofecoxib 25 mg, 50 mg and ibuprofen respectively; P <0.001).

A meta-analysis by Langman and colleagues[23] of 5435 osteoarthritis patients treated with either rofecoxib or traditional NSAIDs (ibuprofen, diclofenac, nabumetone) found that the incidence of upper GI bleeding was significantly lower in the rofecoxib group (12-month cumulative incidence, 1.3% vs 1.8%; P = 0.046).

Other Issues in COX-2 Inhibitors

Apart from the highly publicised GI safety profile of COX-2 inhibitors, several pertinent aspects of COX-2 need to be addressed.

i. Anti-thrombogenesis

COX-2 specific inhibitors have no anti-platelet effects and thus patients with cardiovascular or cerebrovascular disease should be treated with aspirin concomitantly. This was highlighted by the Vioxx in Gastrointestinal Research (VIGOR) trial which has been presented in abstract form and widely discussed. It involved over 8000 patients with osteoarthritis. Subjects were randomised into two groups—one group received naproxen 500 mg bid and the other group was given rofecoxib at 12.5 or 25 mg daily. The study revealed a lower rate of clinical upper GI events but subjects in the rofecoxib group suffered a higher rate of cardiovascular events (incidence of myocardial infarctions 0.4% vs 0.1%, rofecoxib vs naproxen). However, after adjustment for baseline cardiovascular risk factors, there was a non-significant difference (0.2% vs 0.1%, rofecoxib vs naproxen). The higher rate of cardiovascular events was probably due to the fact that subjects were not allowed to take aspirin. The addition of aspirin to the regimen of treatment may alter the incidence of adverse GI events.

COX-2 is responsible for the synthesis of prostacyclin (PGI_2) under physiologic conditions. Thus, COX-2 inhibitors reduce the levels of PGI_2 and in patients with prothrombotic tendencies, the consequences may be dangerous. Crofford and coworkers[24] reported a series of 4 cases who had an underlying connective tissue disease with prothrombotic tendencies, treated with celecoxib and subsequently developed ischaemic complications. Although a causal relationship between thrombosis and COX-2 inhibitor use cannot be established on the basis of these reports, these findings do suggest the need for heightened awareness.

ii. Renal

Studies in animals and humans have shown that COX-2 has a role in renal homeostasis. Swan and colleagues[25] examined the effects of rofecoxib and indomethacin vs placebo on renal function in 75 elderly patients in a randomised, controlled trial. They found that there was a significant reduction in the glomerular filtration rate (GFR) after multiple doses of rofecoxib as compared to placebo (P <0.019). However, in another single centre study of 24 healthy elderly patients randomised to treatment with naproxen or celecoxib, the former was associated with a significant reduction in GFR (9% vs 1%; P = 0.004).[26] Both treatment groups had transient decreases in urinary sodium excretion. The numbers in this trial were small and the treatment was not double-blinded. To date, clinical trials have not convincingly demonstrated significant changes in renal function associated with treatment. However, some studies have shown that high doses of rofecoxib (50 mg) have been associated with an increased risk of lower limb oedema (6%). Until more data are available, it is advisable

to avoid the use of COX-2 inhibitors in patients with renal disease.

iii. Pregnancy

In animal models, the inhibition of COX-2 has resulted in impaired fertility. It is now evident that COX-2 may be responsible for the timing of ovulation as well as blastocyst attachment in the uterus in mice models.[27] Also, COX-2 is expressed in the fetal lamb ductus arteriosus and inhibition leads to premature closure. Hence, its use should be avoided in pregnancy.

iv. Asthma/ NSAID sensitivity

It is well known that prostaglandin E_2 (PGE_2) prevents asthma by inhibiting the production of leukotriene B4 and histamine. COX-1 inhibits PGE_2 production and thus can precipitate an acute asthmatic exacerbation. Quaratino and colleagues[28] assessed the tolerability of meloxicam in 177 patients with prior history of NSAID-sensitivity. Results showed that only 1.1% of patients experienced adverse events following meloxicam challenge. Both cases had cutaneous manifestations. Additional studies are required to determine the tolerability of COX-2 inhibitors in patients with aspirin-induced asthma and severe manifestations of NSAID-sensitivity.

v. Use in Children

Clinical trials are underway to test meloxicam in children. There is no information for rofecoxib or celecoxib.

vi. Cancer Prevention

Several studies have demonstrated a reduction in risk of colorectal adenomas and carcinoma with the use of aspirin and other NSAIDs. It has been shown that COX-2 expression is increased in colon cancer and it may also increase the metastatic potential of colon cancer cells. Unpublished data involving 83 patients with familial adenomatous polyposis (FAP) showed that the use of celecoxib led to a 28% reduction in rectal polyps. This data prompted the FDA advisory panel to approve the use of these drugs in patients with FAP.[29]

vii. Sulphur Allergy

Celecoxib has a sulfonamide moiety and its use must be avoided in patients with known allergy to sulpha drugs.

viii. Cost

A major consideration when prescribing COX-2 inhibitors is cost. With an overall modest reduction in GI adverse events, the use of such drugs should be highly individualised. The retail pharmacy in Singapore prices meloxicam 7.5 mg at S$0.75/ tablet, rofecoxib 25 mg at S$2.30/ tablet and celecoxib 200 mg at S$2.30/ tablet. A generic NSAID costs S$1.20 per week.

Conclusion

The arrival of the COX-2 inhibitors into the treatment armamentarium for inflammation and analgesia has been widely accepted and welcomed. They are as effective as standard NSAIDs and are safer on the stomach.

However, this new group of "wonder" drugs are not without side effects. They are not renal sparing and not cardioprotective. Studies have yet to establish its safety in NSAID-sensitive patients. In patients with chronic arthritides, cost is also an important factor to consider when prescribing these medications.

We look forward to future cyclooxygenase inhibitors with more COX-2 activity and hence more potent and yet still COX-1 sparing. We also hope to see the development of renal sparing COX-2 inhibitors. These new COX-2 inhibitors are a small but important step in the marathon quest towards finding the perfect NSAID—something highly effective, safe and affordable.

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