Clinical pharmacology

Serious gastrointestinal and cardiovascular events associated with non-steroidal anti-inflammatory drugs

Chronic pain is one of the commonest complaints encountered in clinical practice, and the most difficult to manage. Common causes of chronic pain include low backache, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, cancer, etc. Non-steroidal anti-inflammatory drugs (NSAIDs) form part of the armamentarium of analgesics, especially in chronic musculoskeletal pain. Non-selective NSAIDs are readily available over the counter (OTC) alone or in combination with other analgesics. All NSAIDs are equally efficacious in pain control.

NSAIDs are extensively used and are one of the commonest reasons for hospital admission due to a serious adverse event. They are associated with serious gastrointestinal (GI) tract complications such as perforation, ulceration and bleeding as well as impairment of renal function, cardiovascular disease and hypersensitivity reactions. The estimated annual incidence rate of upper GI complications is 1 - 4%.

The advent of cyclo-oxygenase (COX-2) inhibitors was to reduce the well-documented GI adverse effects associated with the use of non-selective NSAIDs. The association of NSAIDs, especially COX-2 inhibitors (coxibs) with serious cardiovascular events, however, is a major public health concern. It has led to the withdrawal of some of these agents from the market and the inclusion of a black box warning in the various package inserts by the Food and Drug Administration (FDA). Several randomised controlled trials (RCTs) (Table I) have been conducted to study the risk of serious GI and cardiovascular adverse events associated with NSAID use. This review looks at the pharmacology of the different classes of NSAIDs and their risks.

Table I. Trial names used in this review

ADAPT: Alzheimer's Disease Anti-inflammatory Prevention Trial

APC: Adenoma Prevention with Celecoxib

APPROVe: Adenomatous Polyp Prevention on Vioxx

CLASS: Celecoxib Long-term Arthritis Safety Study

MEDAL programme: Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme

PreSAP: Prevention of colorectal Spontaneous Adenomatous Polyps

TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial

VIGOR: Vioxx Gastrointestinal Outcomes Research

Pharmacology of NSAIDs

NSAIDs have analgesic, antipyretic and anti-inflammatory effects. The primary property of this class of drugs is the inhibition of COX, the enzyme responsible for conversion of arachidonic acid to prostaglandins. COX has two major iso-enzymes: COX-1 and COX-2. COX-1 is expressed constantly in most tissues producing prostaglandins responsible for GI mucosal integrity. COX-2 was thought to be induced during inflammation only, but recent evidence has shown it is expressed in healthy renal and cardiovascular tissues. Moreover, essential hypertension upregulates expression of COX-2 in the vascular tissues. Selective COX-2 inhibition reduces vascular prostacyclin synthesis without disrupting COX-1-derived thromboxane synthesis in platelets. This causes a prothrombotic state.

NSAIDs vary in their chemical structure and relative ability to block the COX iso-enzymes (Fig.1). It would seem that the more selective an agent for COX-2, the less likely to cause GI adverse events. The classification of NSAIDs and respective examples are shown in Table II. Aspirin, the prototype of NSAIDs, irreversibly inhibits platelet COX activity, while other NSAIDs are reversible inhibitors. This forms the basis for its therapeutic use as thromboprophylaxis.

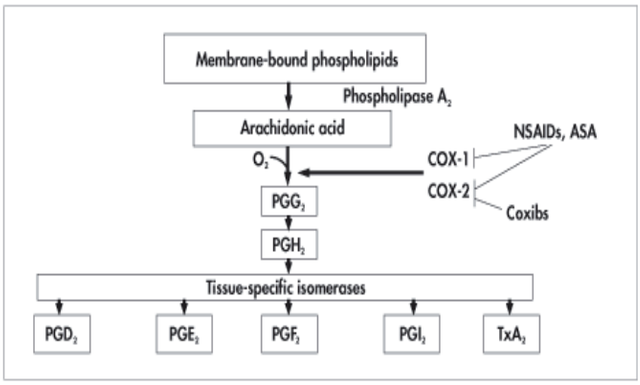

Fig. 1. Prostaglandin and thromboxane biosynthesis. PG = prostaglandin, TxA_2 = thromboxane A_2, ASA = aspirin, COX= cyclo-oxygenase.(Adapted from FitzGerald and Patrono. N Engl J Med *2001; 345: 433.)*

Table II. Classification of NSAIDs according to COX-selective properties

COX-1 selective	Non-selective	COX-2 selective
Indomethacin	Diclofenac	Celecoxib
Piroxicam	Naproxen	Etoricoxib
Lornoxicam	Ibuprofen	Parecoxib*
Tenoxicam	Nabumetone	Rofecoxib†
Ketoprofen	Sulindac	Valdecoxib†
	Ketorolac	Lumiracoxib†
	Mefenamic acid	Meloxicam

*Parenteral formulation only

†Withdrawn from the market, including South Africa.

NSAIDs and GI toxicity

Upper GI complications are defined as clinically significant bleeding, perforation, ulceration and gastric outlet obstruction. Table III outlines outcomes of upper GI complications from a few large RCTs. Results from several RCTs, whose primary objective was to measure the risk of GI events have shown that COX-2 inhibitors reduce the risk of symptomatic or endoscopic ulcers. In the Celecoxib Long-term Arthritis Safety Study (CLASS),[1] a high dose of celecoxib and standard doses of diclofenac were compared in patients with rheumatoid arthritis (RA) and osteoarthritis (OA). Results showed that for all patients, celecoxib significantly reduced

Table III. Absolute risk reduction of complicated gastrointinal events: perforation, ulceration, clinically significant bleeding, obstruction

Study, *N*, % on ASA	Median duration of follow-up (months)	Intervention	Comparison	Risk difference of annualised risk (%)	Numbers needed to treat (NNT)
CLASS	9	Celecoxib 400 mg bd	Combined NSAIDs (ibuprofen 800 mg tds or diclofenac 75 mg bd)	0.69	145
N=8 029				0.11*	900
22%				0.83**	120
VIGOR	9	Rofecoxib 50 mg od	Naproxen 500 mg bd	**0.52**	192
N=8 076					
0%					
TARGET	12	Lumiracoxib 400 mg od	Combined NSAIDs	**0.59**	170
N=18 325				0.19*	526
24%				**0.72****	139
			Ibuprofen 800 mg tds	**0.52**	192
				0.01*	1 000
				0.67**	149
			Naproxen 500 mg bd	**0.66**	151
				0.33*	303
				0.77**	129
MEDAL programme ***	Not reported (study longer > 36 months	Etoricoxib 60 or 90 mg od	Diclofenac 150 mg od	0.02	5 000
				0.00#	∞
N=34 701				0.06¶	1 667
33%				0.2β	N/A
(40% on PPI)				0.19 □	526

N = number of participants; ASA = aspirin; NNT = number needed to treat.

* Patients on aspirin.

** Patients not on aspirin.

***Pooled analysis of 3 RCTs.

Patients not on aspirin or PPIs.

¶ Patients on PPIs but not on aspirin.

β Patients on aspirin but not on PPIs.

□Patients on aspirin and PPI, N/A not applicable as higher event rate in etoricoxib group.

Last column refers to number of patients that need to be treated with a coxib for a year to prevent 1 upper GI complication, except where not applicable.

Statistically significant differences highlighted in bold ($p<0.05$)

the risk of symptomatic ulcers but there was no significant risk reduction of upper GI complications. For patients taking aspirin, this effect was lost, i.e. an absolute risk reduction of only 0.11% per annum.

The safety of rofecoxib versus naproxen was assessed in the Vioxx Gastrointestinal Outcomes Research (VIGOR)[2] trial in patients with RA who were not taking aspirin. There was a significant risk reduction for both complicated and uncomplicated GI events. The absolute risk reduction of upper GI complication was 0.52, with a numbers needed to treat (NNT) of 192 (192 patients must be treated with rofecoxib for a year to prevent 1 upper GI complication). However, due to a confirmed increased risk of cardiovascular adverse events rofecoxib was withdrawn from the market.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[3] was a large RCT in patients with arthritis. It assessed the safety of lumiracoxib versus naproxen or ibuprofen over a year. Twenty-four per cent of patients were taking aspirin. Results showed a significant reduction in complicated and uncomplicated ulcers when compared with either agent or both NSAIDs combined. For upper GI complications alone, there was no significant reduction in patients on aspirin (Table III). Because of serious hepatic adverse effects, this drug has also been withdrawn from the market.

The sponsors of MEDAL programme[4] conducted an analysis of 3 RCTs to assess the safety of etoricoxib (the newest coxib on the market) versus diclofenac in 34 701 patients with arthritis. Patients were encouraged to use proton pump inhibitors (PPIs) or aspirin as indicated. Results showed that for all patients, there were significantly fewer uncomplicated events but no reduction in complicated events. The analysis of all patients showed that the absolute risk reduction of upper GI complications was 0.02%, with a NNT of 5 000. For patients who were not on aspirin or a PPI, there was no risk reduction in upper GI complications (Table III).

Guidelines recommend concomitant use of a PPI with traditional NSAIDs or a coxib in patients at risk of GI effects. A double-blind randomised controlled trial[5] which enrolled patients at high risk for recurrent ulcer bleeding showed that a combination of a high-dose PPI (esomeprazole 20 mg twice daily) and celecoxib (200 mg twice daily) was significantly better than celecoxib alone in preventing GI complications.

NSAIDs and heart disease

Cardiovascular safety of coxibs is reported as a secondary outcome in most of the RCTs. The Anti-platelet Trialist Collaborators define a serious cardiovascular event as a composite of fatal or non-fatal myocardial

Table IV. Absolute risk reduction of cardiovascular events according to the Antiplatelet Trial Collaborators: outcome of fatal or non-fatal myocardial infarct or stroke, or vascular death

Study, *N*, % on ASA	Median duration (months)	Intervention	Comparison	Risk difference (%)	NNH
VIGOR *N*=8 076 0%	9	Rofecoxib 50 mg od	Naproxen 500 mg bd	**0.79**	127
APPROVe *N*=2 586 33%	30	Rofecoxib 25 mg od	Placebo	**1.25**	80
CLASS *N*=8 029 22%	9	Celecoxib 400 mg bd	Combined NSAIDs	0.07	1 429
			Ibuprofen 800 mg tds	0.24	417
			Diclofenac 75 mg bd	0.1	N/A
PreSAP *N*=1 561 17%	30	Celecoxib 400 mg od	Placebo	0.33	303
APC *N*=2 035 30%	>30	Celecoxib 200 mg bd	Placebo	1.6	67
		Celecoxib 400 mg bd	Placebo	2.4	42
ADAPT** *N*=2 528 56%	14 - 16	Celecoxib 200 mg bd	Naproxen 220 mg bd	1.7	N/A
		Celecoxib 200 mg bd	Placebo	0.44	227
		Naproxen 220 mg bd	Placebo	2.15	47
TARGET *N*=18 325 24%	12	Lumiracoxib 400 mg od	Combined NSAIDs	0.1	1 000
			Ibuprofen 800 mg tds	0.09	1 111
			Naproxen 500 mg bd	0.53	189

N = number of participants; ASA = aspirin; NNH= number needed to harm; od =once daily; bd = twice daily, tds = three times daily.

**Incidence given over a 3-year period.

N/A =not applicable as higher event rate in comparison group.

Last column refers to number of patients that need to be exposed to a coxib for a year (or 3 yrs in ADAPT study) to cause 1 additional cardiovascular event, except where not applicable.

Statistically significant differences highlighted in bold ($p<0.05$)

infarction, stroke or vascular death. The safety of this class of drugs was first questioned with the publication of excess cardiovascular events in the VIGOR[2] trial. Results showed that the relative risk (RR) of developing a confirmed cardiovascular event with rofecoxib compared with naproxen was 2.38 (95% confidence interval (CI), 1.39 - 4.00; p=0.002). Initially, this was thought to be due to the cardioprotective effects of naproxen. The Adenomatous Polyp Prevention on Vioxx (APPROVe)[6] trial was a placebo-controlled trial, whose aim was to prove efficacy of rofecoxib in the prevention of recurrent polyps. The study was terminated early as results showed that patients exposed to rofecoxib had a RR of developing a cardiovascular event of 1.92 (95% CI 1.19 - 3.11). The rofecoxib treatment was also significantly associated with heart failure/pulmonary oedema (RR 4.61 95% CI 1.50 - 18.83), hypertension (RR 2.02 95% CI 1.71 - 2.38), and peripheral oedema (RR 1.57 95% CI 1.17 - 2.10). This led to the voluntary withdrawal of rofecoxib from the market by the manufacturer, Merck, in 2004. Table IV shows the results (risk difference and numbers needed to harm) from a few long-term RCTs assessing cardiovascular safety of celecoxib, rofecoxib and lumiracoxib versus NSAIDs or placebo. In all studies except the VIGOR study, patients were allowed to use aspirin as indicated.

The cardiovascular safety of celecoxib has been assessed as a secondary outcome in most RCTs including the Adenoma Prevention with Celecoxib (APC)[7] and Prevention of colorectal Spontaneous Adenomatous Polyps (PreSAP),[8] which were placebo-controlled. Cardiovascular outcomes were also reported in the

ADAPT[9] and CLASS[1] trials. The aim of the ADAPT[9] trial was to assess the efficacy of celecoxib versus naproxen in the prevention of Alzheimer's disease. The APC, PreSAP and ADAPT trials were terminated early because results from APC trial showed a trend towards cardiovascular harm, which increased with the higher dose of celecoxib (Table IV) when compared with placebo. Interestingly, results from the ADAPT trial showed a significantly increased risk with naproxen (Table IV).

The safety of lumiracoxib versus ibuprofen or naproxen was assessed as the primary outcome in the TARGET[3] study. Overall results showed a trend towards harm with lumiracoxib when compared with the traditional NSAIDs. In the lumiracoxib-naproxen arm, results showed increased risk with lumiracoxib and a protective effect with naproxen (Table IV). When stratified according to aspirin use, in the lumiracoxib-ibuprofen arm, results showed a trend towards harm in low-dose aspirin users. The hypothesis is that ibuprofen interferes with antiplatelet effect of aspirin, whereas naproxen does not.

The above studies show that there is excess cardiovascular risk with all coxibs when compared with traditional NSAIDs. The risk reduction in uncomplicated GI events should be weighed against the cardiovascular risk.

In patients with cardiovascular risk, alternative analgesics should be used.

Balancing GI and cardiovascular risk

A risk assessment of each patient must be performed before prescribing traditional NSAIDs or COX-2 inhibitors. Patients with a history of recurrent peptic ulceration, the elderly, those using concomitant aspirin/warfarin/NSAIDs (OTCs)/steroids/selective serotonin reuptake inhibitors, are more prone to NSAID-induced GI side-effects. Patients with cardiovascular risk factors are more prone to cardiovascular events associated with coxibs.

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Further reading

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In a nutshell

- All NSAIDs are associated with GI risks.
- Risk appears to be related to NSAID dose.
- Low-dose aspirin combined with NSAID increases risks 2 - 4 fold.
- Enteric-coated and buffered aspirin do not reduce risk.
- Patients with established ischaemic heart disease or cerebrovascular disease should be switched from a COX-2 inhibitor to alternative analgesics.
- For all patients, the balance of GIT and CVS risk should be considered before prescribing a COX-2 inhibitor (especially those on low-dose aspirin).
- The lowest effective dose of COX-2 inhibitor and traditional NSAID should be used for the shortest possible time, if at all.