Cardiovascular Effects of Common Analgesics

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SUMMARY

The clycoxygenase (COX) enzyme forms locally active prostaglandins responsible for producing inflammation and pain. Classical non-steroidal anti-inflammatory drugs (NSAID) inhibit the COX-2 enzyme that produces inflammatory prostaglandins as well as the COX-1 enzyme that produces gastric mucosa protecting prostaglandins. By specifically inhibiting only the COX-2 enzyme, coxibs thus reduce pain but do not damage the gastric mucosa. However, COX-2 at the vascular endothelium produces antithrombotic prostaglandins, and so by inhibiting COX-2 enzyme, the coxibs promote thrombosis. Rofecoxib and valdecoxib have been withdrawn because of the adverse cardiovascular events they induce. Amongst presently available coxibs cardiovascular risk is highest with enterocoxib and lowest with celecoxib. NSAIDS also increase cardiovascular events, the risk is highest with diclofenac and lowest with naproxen. Paracetamol and corticosteroids induce hypertension, while steroids also adversely affect the heart from metabolic change as well as fluid retention. Aspirin is an anti-thrombotic agent because of its ability to inhibit the COX-1 enzyme that produces the pro-aggregatory thromboxane. However, it increases gastrointestinal bleeding, can promote fluid retention and is nephrotoxic, all of which may lead to adverse cardiovascular outcomes. Patients at especially high risk of cardiovascular events from analgesic use include the elderly, and those with heart failure, hypertension, rheumatoid arthritis, chronic renal disease, chronic obstructive airway disease and previous myocardial infarction, cerebrovascular disease or peripheral vascular disease. Adverse cardiovascular events can occur within a week of initiation of analgesic treatment.

INTRODUCTION

The classical non-steroidal anti-inflammatory drugs (NSAID) and the newer specific cyclooxygenase-2 (COX-2) inhibitors are commonly used analgesics, widely prescribed for a range of aches and pains. Patients using these drugs are often elderly and have a range of co-existing medical conditions which increases their risk of experiencing an adverse cardiovascular event such as myocardial infarction (MI), stroke or even cardiovascular mortality. It is thus vitally important that doctors prescribing these drugs are aware of the cardiovascular consequences of the NSAID, coxibs and other analgesics.

PROSTAGLANDINS AND PAIN

Prostaglandins are lipid-compounds derived by the enzymatic oxidation of polyunsaturated fatty acids [1]. They contain 20 carbon atoms, are locally acting messenger molecules and have a variety effects in many places throughout the human body. Clinically they have numerous patho-physiological effects, and are involved in inflammation, pain, platelet aggregation, smooth muscle function and gastric mucosal ulceration [2]. Fatty acid in the cell is changed to arachidonic acid by phospholipase; subsequently, clyclooxygenase (COX) produces prostaglandin and tromboxane from arachidonic acid (Figure 1). Although prostaglandins are involved in inflammation, they also protect gastric mucosa thus reducing peptic ulceration and produce an anti-thrombotic effect by promoting endothelial dilatation while preventing platelet aggregation. Thromboxane, another product of arachidonic acid from the COX enzyme, promotes vasoconstriction, platelet aggregation and thrombosis. Thus COX inhibition while reducing inflammation may also increase gastric ulceration and have an effect on platelet thrombosis depending on whether COX inhibition affects more prostaglandin or thromboxane formation [3,4,5].

THE COXIB STORY

The classical NSAIDs are well known to have a detrimental effect on the gastric mucosa, increasing peptic ulceration and bleeding [6,7]. While it is the COX-2 isoenzyme that produces the prostaclyclin involved in inflammation, the COX-1 isoenzyme produces those prostaglandins involved in gastric mucosal protection. Thus, it is hoped that with selective COX-2 inhibitors (coxibs), the production of inflammation producing prostaglandins will be interrupted while leaving the favorable COX-1 pathway intact, ensuring the continued production of the gastric protecting prostaglandins. In the CLASS trial, amongst 8,059 arthritis patients, compared to those on the nonselective NSAIDs, patients on the COX-2 inhibitor celecoxib had significantly lower symptomatic peptic ulceration, an effect more pronounced in patients not on concomitant aspirin therapy [8]. In the VIGOR trial, amongst 8076 patients with rheumatoid arthritis followed-up for 9 months, those on the selective COX-2 inhibitor, refecoxib, had significantly less clinical gastrointestinal events, as well as less complicated gastrointestinal events, when compared to patients on the nonselective NSAID naproxen [9]. Numerous other trials and reviews similarly showed that selective COX-2 inhibitors had better gastrointestinal safety profile compared to classical NSAIDs [10-12]. Worldwide sales for these drugs escalated exceeding $5 billion in 2003 with rofecoxib alone accounting for about half total sales value [13,14].

Yet even the initial publications hinted at the adverse cardiovascular effect they produce. The VIGOR study provided a hint that all was not well since the rate of

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Table I: Association of valdecoxib and NSAID use with cardiovascular outcomes in a meta-analysis of 8000 patients with rheumatoid arthritis

	Valdecoxib (mg)					
	Placebo	10	20	40	80	NSAID
All Patients (n)	1142	1543	1519	1066	403	2261
CVS events (n)	2	5	5	6	1	13
(%)	0.175	0.324	0.324	0.562	0.248	0.575
Non-aspirin Users (n)	1001	1327	1337	926	342	1950
CVS events (n)	0	2	3	3	0	7
(%)	0.000	0.151	0.224	0.324	0.000	0.359

NSAID = non-steroidal anti-inflammatory drugs;
CVS = cardiovascular
n= number patients

myocardial infarction was significantly lower on naproxen compared to rofecoxib (0.1% vs 0.4%, RR 0.2, 95%CI 0.1-0.7). The annualized myocardial infarction rates of trial patients on rofecoxib (0.74%) and celecoxib (0.8%) were significantly higher than those in the placebo group of other similar trials (0.52%) [15]. It is also difficult to understand how some can reach a conclusion so very different from what the data reveals. A review of about 8,000 patients recruited into 10 trials concluded that therapeutic, and even supratherapeutic, doses of valdecoxib were not associated with any increase in cardiovascular thrombotic events when compared to placebo or to nonselective NSAIDs [16]. In fact, as shown in Table I, the data clearly reveals that for overall patients and those not on aspirin, the cardiovascular event rate on valdecoxib is higher than placebo, and appears to be higher at higher valdecoxib doses from 10mg to 40 mg daily. Data for valdecoxib 80mg is not reliable in view of the small numbers in this group. The increased risk of cardiovascular events with valdecoxib may not be apparent in patients on aspirin treatment, presumably because aspirin modifies the thrombotic process by blocking the production of the pro-thrombotic thromboxane. The data also suggest that even classical NSAIDs can increase cardiovascular events compared to those on placebo, a fact presently no longer in dispute.

It was the trials of colorectal adenoma prevention with the selective COX-2 inhibitors that conclusively proved their cardiovascular adverse effects. In APPROVE, 2,586 patients with a history of colorectal ademona were randomized to either 25 mg rofecoxib or placebo (17). After 3 years follow up, the cardiovascular thrombotic event rate per 100 patient-year on rofecoxib was 1.5, while the rate on placebo was 0.78 (RR 1.92, 95%CI 1.19-3.11, p=0.008). In APC, 2,035 patients with prior adenoma were randomized to celecoxib 200 mg bd, 400 mg bd or placebo (18). Cardiovascular event rate was 1% for placebo, 2.3% on celecoxib 200 mg bd (RR 2.3, 95% CI 0.9 to 5.5) and 3.4% on celecoxib 400 mg bd (RR 3.4, 95% CI 1.4 to 7.8). In September 2004, rofecoxib was withdrawn on advice from the FDA, and in April 2005, valdecoxib was similarly withdrawn [19]. Celecoxib was also noted to cause an excess of cardiovascular events similar to the nonspecific NSAIDs, and allowed to continue in the market.

There are good patho-physiological reasons for the elevated risk of cardiovascular thrombosis from coxib use [20,21]. There are two classes of COX enzymes and their action in different parts of the body produces prostaglandins of differing physiological functions (Figure 1). COX-1 is involved in the production of prostaglandins responsible for gastric mucosal protection, and in platelets causes thromboxane formation which promotes platelet aggregation, vasoconstriction and vascular smooth muscle cell proliferation. COX-2 at the joints produces prostaglandins responsible for inflammation while at the vascular endothelium produces prostaglandins promoting vasodilatation with inhibitory effect on platelet aggregation and smooth muscle proliferation. The inhibition of COX-2 by the coxibs thus reduces inflammatory mediator production, but also reduces the anti-thrombotic prostaglandins while leaving the pro-thrombotic thromboxane production intact. Hence cardiovascular thrombotic events will be increased, an effect clearly proven by the clinical trials [22].

Table II: Risk of adverse cardiovascular outcomes associated with different non-selective NSAID and the COX-2 specific inhibitors (coxibs)

Classical Non-Steroidal Anti-inflammatory Drugs (NSAID)		
	RR	95% CI
diclofenac	1.40	(1.27 - 1.55)
indometacin	1.30	(1.19 - 1.41)
meloxicam	1.20	(1.07 - 1.33)
ibuprofen	1.18	(1.11 - 1.25)
naproxen	1.09	(1.02 - 1.16)
**piroxicam	1.08	(0.91 - 1.30)

Specific Cyclo-oxygenase-2 (COX-2) inhibitors		
	RR	95% CI
etoricoxib	2.05	(1.45 – 2.88)
etodolac	1.55	(1.28 – 1.87)
rofecoxib	1.45	(1.33 – 1.59)
celecoxib	1.17	(1.08 – 1.27)

NSAID = non-steroidal anti-inflammatory drugs; RR = relative risk;
CI = confidence interval
** Piroxicam has highest likelihood to induce significant gastrointestinal bleed.

The cardiovascular impact of the classical NSAIDs, which are non-specific COX inhibitors, depends on the balance between inhibition of the COX-1 mediated pro-thrombotic thromboxane and of the COX-2 mediated anti-thrombotic endothelial prostaglandin. We need to establish which NSAIDs are safest and which have the worst effect on clinical cardiovascular events. We also need to know which patients are most susceptible to the adverse effects of NSAIDs. Fortunately, several studies have answered these important practical questions.

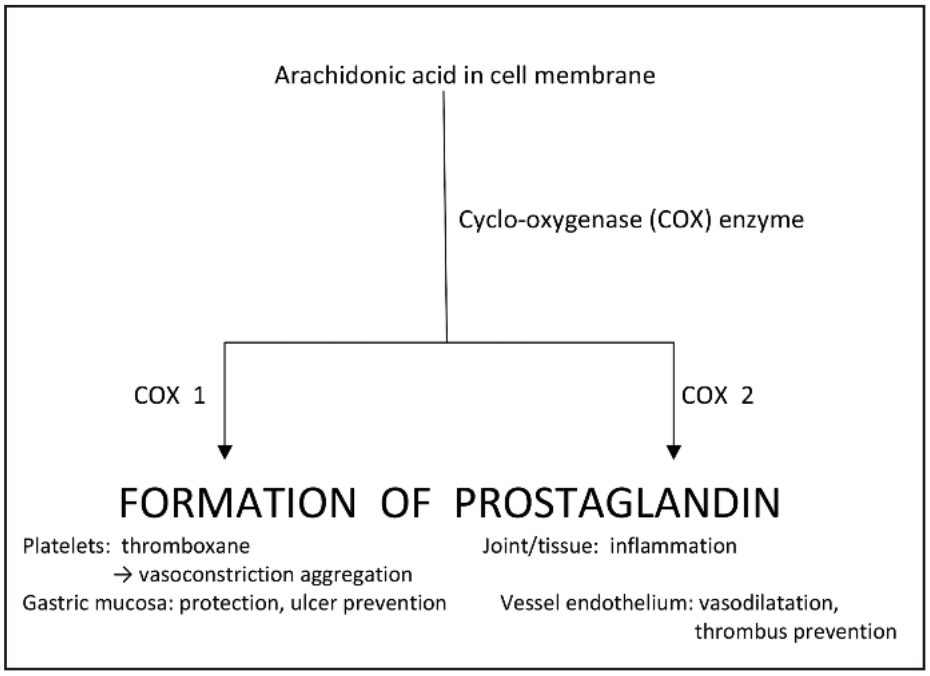

Fig. 1: COX enzymes acting on cellular arachidonic acid leads to prostaglandin formation. At different tissue site, different prostaglandins are formed with differing patho-physiological effects.

WHICH NSAID, WHICH PATIENT GROUP, FARES WORST FOR CARDIOVASCULAR OUTCOMES?

A review of 51 population-based controlled observational studies (30 case-controlled, 21 cohort) reported on over 2.7 million exposed patients and involved over 180,000 cardiovascular events [23]. Highest risk for cardiovascular events occurred in patients on etoricoxib (RR 2.05, 95%CI 1.45-2.88), etodolac (RR 1.55, 95%CI 1.28-1.87) and diclofenac (RR1.40, 95%CI 1.27-1.55). Lowest risk occurred in patients on celecoxib (RR 1.17, 95%CI 1.08-1.27), ibuprofen (RR1.18, 95%CI 1.11-1.25) and naproxen (RR1.09, 95%CI 1.02-1.16). Cardiovascular risk can come on within a week of treatment initiation, and generally increases with higher dose.

In matching 10,280 myocardial infarction (MI) patients with 102,797 non-MI sex- and age-matched controls, current users of rofecoxib (ARR 1.80; 95% CI, 1.47-2.21), other COX-2 inhibitors (ARR 1.45; 95% CI, 1.09-1.93) and other conventional NSAIDs (ARR 1.68; 95% CI, 1.52-1.85) all had elevated risk for MI [24]. Amongst 107,092 patients discharged from their first hospitalization after heart failure, 36,354 patients (33.9%) were found to have subsequently received least 1 prescription of an NSAID [25]. The subsequent relative risk for death was increased for patients on analgesics, with diclofenac at 2.08 (95% CI 1.95-2.21), celecoxib 1.75 (95% CI 1.63-1.88), rofecoxib 1.70 (95% CI 1.58-1.82), ibuprofen 1.31 (95% CI 1.25-1.37), naproxen 1.22 (95% CI 1.07-1.39), and other NSAIDs 1.28 (95% CI 1.21-1.35).

From the above studies, it is reasonable to conclude that amongst the coxibs, etoricoxib has a highest cardiovascular and celecoxib the lowest. Amongst the nonspecific NSAIDs, diclofenac has the highest cardiovascular risk profile, and naproxen the lowest. The two analgesics with the highest cardiovascular risk, etoricoxib and diclofenac, are comparable and equivalent in the cardiovascular events they are associated with [26].

Patients with prior MI and heart failure will of course be at higher risk for future cardiovascular events, and so require special caution when given analgesics. A retrospective comparative study compared 76,082 new patients on coxibs, 53,014 on nonselective NSAIDs with 46,558 nonusers [27]. Compared to nonusers, patients on rofecoxib had increased cardiovascular events (RR 1.22, 95% CI 1.14-1.30) while those on naproxen had decreased events (RR 0.79, 95% CI 0.67-0.93). Patient characteristic found to increase risk of cardiovascular events in analgesic users are the elderly (above 80 years), hypertension, prior MI or cerebrovascular disease, rheumatoid arthritis, chronic renal disease and chronic obstructive lung disease. Clinicians must be aware of the need for extra caution in these high risk groups, prescribing analgesics at lowest dose for the briefest of duration possible.

An important group of patients to consider are those on low-dose aspirin for its anti-platelet effect in preventing cardiovascular or cerebrovascular events [28]. A review of the subject suggests that low dose aspirin is able to reduce the increased cardiac risk from most NSAID and coxib, with the exception of ibuprofen. This finding is compatible with the data on valdecoxib compiled by White which showed that the higher cardiovascular event rate induced by valdecoxib was not apparent in the aspirin users [16]. Thus, patients on low dose aspirin may represent a group in which NSAID and even the coxib can be given with the knowledge that their adverse cardiovascular effects may be ameliorated.

OTHER ANALGESIC AND ANTI-INFLAMMATORY DRUGS

The opiates are excellent analgesic drugs, although they have no anti-inflammatory effect. Because of the potential for addiction, their use in non-terminally ill patients should never be over a prolonged duration and so their adverse cardiovascular impact differs from that caused by chronic use of NSAIDs. Intravenous morphine actually provides excellent relief from the pain of MI, and because of its venodilatory and hypotensive action is valuable in the treatment pulmonary edema. However, morphine depresses respiration, and so the dose used has to be minimised and ventilator support should be available in case the need arises [29]. Morphine also causes nausea, vomiting and constipation, all of which can induce tachycardia and hypertension which further strains the cardiac patient. Thus, morphine use in patients with cardiovascular disease must be thoughtful and cautious, balancing its therapeutic potential with the adverse effects it induces.

Paracetamol has a unique mechanism of action, blocking prostaglandins both peripherally at the inflamed tissue and also in the central nervous system. Initial confidence that paracetamol produces no adverse cardiovascular impact has now been replaced by growing realisation that paracetamol may not be benign for the cardiovascular system [30,31]. In a prospective cohort study of 5123 initially normotensive women enrolled in the Nurses' Health Study, those reporting usage of paracetamol and NSAID were at higher risk of subsequently developing hypertension compared to nonusers[32]. Amongst younger women aged 34-53 years, the relative risk of developing hypertension on NSAID was 1.60 (95% CI 1.10-2.32) and on paracetamol was 1.99 (95%CI 1.39-2.85). Amongst older women aged 51-77 years, the risk of hypertension on NSAID was 1.78 (95%CI 1.21-2.61) and on paracetamol was 1.93 (95%CI 1.39-2.85). Since hypertensive patients are be at higher cardiovascular risk, long term paracetamol use will adversely affect the cardiovascular system.

Corticosteroids have no analgesic effect but being potent anti-inflammatory drugs, they produce good pain relief since it is the metabolic products of inflammation that causes symptomatic pain. Corticosteroids induce hypertension, hyperglycemia and dyslipidemia which over the long term will result in a higher cardiovascular event rate [33,34]. Sodium and water retention induced by corticosteroid can be associated with hyokalemia and can lead to heart failure as well as cardiac arrhythmias [35]. Thus in a patient with inflammatory pain, corticosteroid use should be of the lowest dose possible, and over the shortest duration of time.

Low dose aspirin less than 300 mg a day has been shown in clinical trials to be definitely useful for the secondary prevention of cardiovascular disease, although its role in primary prevention is more debatable given the evidence for increased bleeding episodes [36,37,38]. Its cardiovascular protective effect is likely derived from its COX-1 inhibition which thus prevents pro-aggregatory thromboxane synthesis in platelets. Anti-pyretic and anti-inflammatory effects only come on at high doses, above 1 G a day. However, aspirin's inhibition of the COX-1 enzyme means that it reduces production of prostaglandins protecting the gastric mucosa making it prone to ulceration and bleeding. This limits its value as an anti-inflammaory analgesic drug. Even low-dose aspirin may have nephrotoxic effects and increase heart failure hospitalisation by promoting fluid retention [39,40,41]. Thus patients on anti-inflammatory doses of aspirin should be careful monitored to ensure that they do not develop gastrointestinal bleeding with anaemia or nephrotoxicity with fluid retention.

CONCLUSION

The COX enzymes form prostaglandins that produce inflammation in joints and tissue (COX-2), prevent thrombosis at vascular endothelium (COX-2) and protect the gastric mucosa from ulceration and bleeding (COX-1). Classical NSAIDs inhibit both the COX-1 and COX-2 enzymes and so prevent the formation of prostaglandins which mediate inflammation, prevent vascular thrombosis and protect the gastric mucosa. The coxibs specifically inhibit COX-2 thus reduce inflammation and anti-thrombotic potential but leave gastric mucosal protection intact. Rofecoxib and valdecoxib have both been withdrawn because of the increase in cardiovascular events associated with their use. As shown in Table II, amongst available coxibs cardiovascular risk is highest with enterocoxib and lowest with celecoxib [23]. Amongst NSAID, the risk is highest with diclofenac and lowest with naproxen. Although piroxicam appears to produce no significant increase in cardiovascular risk, it has the highest risk of serious gastrointestinal bleeding and its usage is presently declining [23, 42]. Paracetamol and corticosteroids induce hypertension, while steroids also adversely affect the heart from metabolic change as well as fluid retention. Aspirin is an anti-thrombotic agent because of its ability to inhibit the COX-1 enzyme that produces the pro-aggregatory thromboxane. However, it increases gastrointestinal bleeding, can promote fluid retention and is nephrotoxic, all of which may lead to adverse cardiovascular outcomes. Patients at especially high risk of cardiovascular events from analgesic use include the elderly, and those with heart failure, hypertension, rheumatoid arthritis, chronic renal disease, chronic obstructive airway disease and previous myocardial infarction, cerebrovascular disease or peripheral vascular disease. Adverse cardiovascular events can occur within a week of initiation of analgesic treatment[43]. Since patients requiring analgesics are often those most vulnerable to their cardiac complications, clinicians prescribing analgesics must do so cautiously and judiciously.

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Multiple Choice Questions

1. Prostaglandins are
A. produced from arachidonic acid by action of cyclo-oxygenase (COX) enzymes.
B. formed by cyclo-oxegenase 1 (COX 1) enzymes leads to joint inflammation.
C. formed by cyclo-oxegenase 2 (COX 2) enzymes leads to thrombus prevention.
D. formed by COX 2 enzymes leads to platelet aggregation.
E. formed by COX 1 enzymes leads to gastric mucosal protection.

2.
A. Classical NSAIDs do not cause to gastric ulceration.
B. Classical NSAIDs can increase coronary thrombosis.
C. Naproxen is amongst the NSAID least likely to lead to adverse cardiovascular events.
D. Diclofenac is amongst the NSAID with the highest risk of cardiovascular events.
E. Classical NSAIDs increase mortality rate in patients with prior heart failure.

3.
A. Roficoxib and valdecoxib have been withdrawn because of their adverse cardiovascular side -effects.
B. Celecoxib does not increase cardiovascular events.
C. Etoricoxib has a higher cardiovascular risk than celecoxib.
D. Risk of adverse cardiovascular events from COX-2 inhibitor (coxib) is usually dose-related.
E. Coxibs reduce the risk of subsequent myocardial infarction.

4.
A. Paracetamol increases incidence of hypertension.
B. Corticosteroids promote salt and water retention and can lead to heart failure.
C. Corticosteroids induce hypoglycaemia.
D. Low dose aspirin promotes coronary thrombosis.
E. Aspirin use can lead to nephro-toxicity and fluid retention.

5. The following patients are at increased risk of cardiovascular effects from analgesic use.
A. Patients above 80 years.
B. Patients with prior MI.
C. Patients with peptic ulcer.
D. Patients with rheumatoid arthritis.
E. Patients with chronic renal disease.