Review Article

Clinical implications of cyclooxygenase-2 inhibitors

Yutaka Kawahito

Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

The mechanism underlying the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) is suppression of the activity of cyclooxygenase (COX). It has been surmised that selective COX-2 inhibitors can inhibit only the production of prostaglandin (PG) related to inflammation but not PG related to physiological functions. However, COX-2 is present in some tissues with physiological function. It has been established that selective COX-2 inhibitors are safer with respect to upper gastrointestinal tract complications than traditional non-selective NSAIDs. Furthermore, selective COX-2 inhibitors are effective in suppressing familial adenomatous polyposis. In contrast, recent studies have shown that selective COX-2 inhibitors and non-selective NSAIDs increase the cardiovascular risk. In Japan, celecoxib, a selective COX-2 inhibitor, was approved for clinical use in 2007. In this review, we outline the benefits and advantages of selective COX-2 inhibitors and suggest how best to use NSAIDs in daily clinical practice.

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Correspondence should be addressed to:
Yutaka Kawahito, MD, PhD. Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan. Phone: +81-75-251-5505, FAX: +81-75-252-3721, e-mail: kawahity@koto.kpu-m.ac.jp

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory, antipyretic, and analgesic activity, and are widely used for the treatment of inflammatory diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA). Their mechanism of action is to prevent the generation of proinflammatory eicosanoid though the inhibition of activity of cyclooxygenase (COX). The development of NSAIDs has been proceeding since the introduction of aspirin for clinical use in 1899. In 1991, COX2, an inducible enzyme by various stimuli, was found as another isoform of COX and is related to the production of prostaglandin (PG) at inflammatory sites. Traditional NSAIDs inhibit both COX-1 and COX-2 to different degrees. These drugs have many deleterious effects such as NSAID-induced gastropathy, because eicosanoid products derived from COX-1 have cytoprotective roles within an organism. Selective COX-2 inhibitors were developed to target COX-2 in the 1990s. In 1998, celecoxib, one of coxib series of selective COX-2 inhibitors, was developed based on the stereoisomerically-different structure between COX-1 and COX-2. Selective COX-2 inhibitors have the same anti-inflammatory, antipyretic, and analgesic activities as traditional NSAIDs and are safer with respect to gastrointestinal (GI) tract side effects. However, COX-2 also exists and has physiological functions in various normal tissues such as kidney, pancreas, brain and female genital organs. Therefore there are some concerns that selective COX-2 inhibitors as well as non-selective NSAIDs may have deleterious effects on the cardiovascular and renal systems.

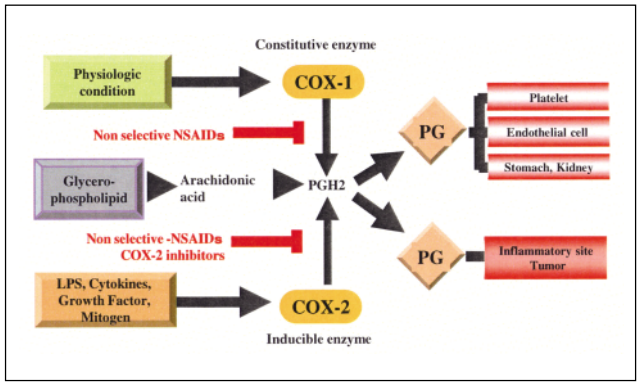

Fig.1 Action of nonsteroidal anti-inflammatory drugs

The biology and efficacy of COX-2 inhibitors (Fig.1)

Arachidonic acid is released from phospholipids by the enzyme phospholipase A2. Unesterified intracellular arachidonic acid is immediately metabolized by cyclooxygenase (COX), lipoxygenase, or epoxygenase enzyme. COX is an integral membrane protein found predominantly in the endoplasmic reticulum and produces the intermediate PGH_2 from which prostaglandins, prostacyclin, and thromboxanes are derived. Two COX isoforms, COX-1 and COX-2, are found in human. COX-1 and COX-2 share 60% sequence homology at the amino acid level[1]. Constitutively expressed COX-1 is found in many tissues and organ systems and is believed to play a role in various physiological functions including vascular homeostasis, maintenance of renal and GI blood function, renal function, intestinal mucosal proliferation, platelet function and anti-thrombogenesis. In contrast, COX-2 is an inducible enzyme in inflamed and activated tissues by various stimuli such as growth factors, cytokines and various mitogens. Its function is mainly implicated in inflammation, fever, pain, mitogenesis and carcinogensis. But constitutive COX-2 is detected in pancreas, kidney and brain. It is also associated with some types of physiological functional expression such as ovulation, placentation, uterine contractions of labor and renal adaptation to stress. Its function in brain remains to be elucidated.

NSAIDs exert their effects by inhibition of PG production. Traditional NSAIDs inhibit both COX-1 and COX-2 to different degrees. Because of COX-1 inhibition, these NSAIDs have many serious adverse effects, in particular, GI ulceration, perforation and bleeding. Recently, selective COX-2 inhibitors, new drugs that selectively inhibit COX-2, have been developed. Both COX-1 and COX-2 share hydrophobic tunnels that afford access of the lipid substrate to its active site. The COX-2 tunnel is more accommodating and the amino acid residues Val434, Arg513, and Val523 form a side pocket not present in COX-1. This structural difference has allowed the development of drugs that bind with higher affinity to COX-2 than to COX-1. Selective COX-2 inhibitors, celecoxib, rofecoxib, valdecoxib, are sulfonic derivatives that have 100-fold selectivity for COX-2 compared to COX-1[1]. These drugs have the same anti-inflammatory and analgesic effects as traditional non-selective NSAIDs. For example, in the Successive Celecoxib Efficacy and Safety Studies (SUCCESS)-1 examining a total of 13 274 osteoarthritis patients from 39 countries, celecoxib 100 or 200 mg bid was as effective as the nonspecific NSAIDs, diclofenac 50 mg bid and naproxen 500 mg bid, in treating the signs and symptoms of osteoarthritis[2]. Furthermore, rofecoxib and celecoxib are similarly analgesic to non-selective NSAIDs with regard to postdental surgery pain[3]. In this way selective COX-2 inhibitors have anti-inflammatory and analgesic effects similar to those of traditional non-selective NSAIDs.

Benefit of selective COX-2 inhibitors in upper gastrointestinal tract

In 1991 the Japanese Rheumatic Foundation reported an epidemiological survey of upper GI diseases in patients with arthritis who had taken NSAIDs. Endoscopic examinations were performed in 1008 patients who had taken NSAIDs for more than 3 months. Some kind of upper GI injury was present in 62.2%, gastric ulcer in 16% and duodenal ulcer in 2%. Upper GI symptoms of duodenal and gastric ulcer induced by NSAIDs were present in about 40% of patients. Because more than 50% had no symptoms, these ulcers may become serious[4]. Traditional NSAIDs inhibit COX-1 as well as COX-2, resulting in numerous upper GI events. Recently very effective anti-rheumatoid drugs have appeared for the treatment of rheumatoid arthritis, but the frequency of use of NSAIDs is still high and they are usually used for long periods. Development of drugs that reduce or abolish these GI side effects is important. Selective COX-2 inhibitors might reduce this burden. It is known that meloxicom and etodorac, which exert the highest selective COX-2 inhibition among traditional non-selective NSAIDs, are associated with a lower incidence of GI side effects than other non-selective NSAIDs[5,6]. Large-scale clinical trials have demonstrated that the incidence of upper GI injuries with selective COX-2 inhibitors was consistently about half of that with traditional non-selective NSAIDs. In randomized trials, selective COX-2 inhibitors showed significantly lower rates of upper GI bleeding, ulcers, and withdrawal due to GI symptoms[7-9](Table.1). However, if

Table1 Serious GI events of selective COX-2 inhibitors from large clinical trials

	Patient's disease	Observation period	Participant total No	Drug	control (NS-NSAIDs)	RR compared with control*
CLASS trial[7]	OA, RA	6 mo	7,982	celecoxib (400mg bid)	Ibuprofen (800mg tid) Diclofenac (5mg tid)	0.35(0.14-0.98)
VIGOR trial[8]	RA	9 mo	8,076	rofecoxib (50mg/day)	naproxen (1000mg bid)	0.5 (0.3–0.6)
TARGET trial[9]	OA	54 wk	18,375	lumiracoxib 400 mg /day	ibuprofen (800 mg tid) naproxen (1000mg bid)	0·21 (0·12–0·37)

*Relative risk of serious GI injuries for non aspirin users (95% confidence interval)
OA: osteoarthritis, RA: rheumatoid arthritis, NS-NSAIDs: non-selective anti-inflammatory NSAIDs

we use a low dose of aspirin with selective COX-2 inhibitors for the prevention of cardiovascular (CV) events, no advantage regarding side effects of the upper GI tract for selective COX-2 inhibitors is obtained[7,9]. In addition, it is reported that the infection of Helicobacter pylori increases 20-50 fold of the incidence of NSAIDs induced ulcer in upper GI tract[10]. The eradiation of Helicobacter pylori can decrease its incidence, but the use of proton pump inhibitors (PPI) is more effective for the prevention of NSAID induced ulcer than the eradiation of Helicobacter pylori[11]. Furthermore, the treatment of celecoxib plus PPI for patients with a past history of GI bleeding can reduce the incidence of recurrent GI bleeding and the rate of GI hospitalization compared with celecoxib alone[12]. It is also reported that celecoxib or celecoxib plus PPI would be clearly safer than traditional non-selective NSAID plus PPI for the GI tract in the population aged 65 years or older[13] Thus, COX-2 selective inhibitors are safer for the upper GI tract compared with traditional non-selective NSAIDs. In addition, a COX-2 selective inhibitor plus PPI is the safest option for patients at high risk for upper GI disease.

Benefit of selective COX-2 inhibitors in lower gastrointestinal tract

With recent improved technology such as capsule endoscopy and colonoscopy, there is emerging evidence that traditional non-selective NSAIDs cause lower GI injuries. In western countries, 60% of patients prescribed with NSAIDs for a long term develop injuries of the small intestine[14] with 75 % of these patients manifesting mucosal ulcers of the lower GI tract including colon[15,16]. NSAIDs induced colitis is often detected in the terminal ileum and reveals various types of mucosal damage such as redness, erosion, small ulcer, ring ulcer and hemorrhagic ulcer. These lesions appear even in the absence of upper GI injury. In a multicenter, double-blind, placebo-controlled trial with video capsule endoscopy, the percentage of subjects with these mucosal breaks was 55% for naproxen/omeprazole compared to16% for celecoxib and 7% for placebo. Celecoxib was associated with significantly fewer small bowel mucosal breaks than naproxen plus omeprazole. This means that PPI do not inhibit the development of small bowel mucosal breaks induced by NSAIDs[17]. Laine et al. reported that nearly 40% of the serious GI events developed in rheumatoid arthritis patients taking the non-selective NSAID naproxen with the incidence of serious lower GI events 54% lower with the use of the selective COX-2 inhibitor rofecoxib[14]. Thus selective COX-2 inhibitors may have some benefits in decreasing the frequency of lower GI tract injuries.

The efficacy of selective COX-2 inhibitors on tumor prevention

COX-2 gene is up-regulated in various cancers such as breast[18] and gastric cancer[19]. COX-2 activity is very low in the normal state, but is induced by several stimuli such as cytokines and mitogens, and participates in the processes of cancer cell proliferation and differentiation[20,21]. In colorectal cancer, immunoreactive COX-2 is found to be elevated in cancer cells, inflammatory cells, vascular endothelial cells, and fibroblasts in tumor surrounding tissues[22,23]. Epidemiologic studies have demonstrated that NSAIDs and aspirin reduce the incidence of colorectal carcinoma[24,25]. PGs and COX enzymes may be involved in the initiation and/or the promotion of carcinogenesis and metastasis because the major action of NSAIDs is the inhibition of COX. Aspirin also inhibits COX, but has other effects including inhibition of nuclear factor-κB and induction of apoptosis by activation of p38 kinase[26]. A key question is whether the inhibitory effect of NSAIDs on colon carcinogenesis is mediated by inhibition of either COX-1 or COX-2, or both. There has been some debate as to whether COX-2 is a key enzyme for the promotion of colon cancer. A recent study with 2,446,431 person-years of follow-up of 82,911 women and 47,363 men suggested that regular use of aspirin reduces the risk of colorectal cancers that overexpress COX-2 but not the risk of colorectal cancers with weak or absent expression of COX-2[27]. COX-2 may thus be an important target molecule for the prevention and therapy of colon cancer. A high level of expression of COX-2 is also detected in adenomas and may be related to potential cancer promotion. Familial adenomatous polyposis (FAP) is inherited in a dominant manner and is associated with malignant transformation at

a high rate. In patients with FAP, six months of twice-daily treatment with 400 mg of celecoxib leads to a significant reduction in the number of colorectal polyps[28]. At present, the cost of the use of celecoxib for FAP is still covered by insurance in the USA, even if the CV event risk is recognized. Moreover, treatment with celecoxib as compared with placebo in the adenoma prevention with celecoxib (APC) study and the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trials was associated with a pronounced reduction in the risk of metachronous adenomas and advanced adenomas[29,30]. In conclusion, for colon metachronous adenomas at this time, the use of celecoxib for up to three years can reduce the risk, but is not indicated for either patients with nonfamilial colonic adenomas or in the general population because of the associated increase in the frequency of CV events.

Cardiovascular events of selective COX-2 inhibitors

Thromboxane A_2, the major COX-1 product in platelet, causes irreversible platelet aggregation. In contrast, prostacyclin, COX-1 and COX-2 product in endothelial cells, inhibit platelet aggregation and induce vasodilatation. In theory, aspirin produces irreversible COX-1 suppression in platelets at low doses. Unlike low dose aspirin, selective COX-2 inhibitors suppress the production of prostacyclin but not thromboxane A_2. Thus, selective COX-2 inhibitors may tend to induce thromboembolism. Against this background, the cardiovascular safety of selective COX-2 inhibitors has recently been questioned. A subanalysis of the VIGOR trial[8] demonstrated a 5-fold increase in thromboembolic CV events in rofecoxib users as compared with naproxen users. Though there was a low event rate and no placebo group in the subanalysis, these data suggest an increased risk of acute myocardial infarction (AMI) associated with rofecoxib and a cardioprotective effect of naproxen as a control. After these results, the Adenomatous Polyp Prevention on Vioxx (APPROVe) study[31] including almost 2600 patients was performed. In 36 months, the incidence of severe thromboembolic events was 1.92 times higher in those treated with rofecoxib than in the placebo group. The risk increased only after 18 months of continuous use. In addition, high dose naproxen inhibits platelet aggregation but the clinical cardioprotective effect is not sufficiently strong to explain the results of the APPROVe study. In 2004, the manufacturer finally withdrew rofecoxib from the market after this result. Furthermore, in the placebo controlled Coronary Artery Bypass Graft (CABG)-1 study[32], the incidence of severe CV events in the parecoxib/valdecoxib group was significantly higher than in the parecoxib/valdecoxib group. In 2005 the manufacturer similarly withdrew valdecoxib from the market.

Table2 Cardiovascular events of celecoxib from long-term clinical trials

	Patient's disease	Observation period	Participant total No	Drug	Relative CV risk compared with placebo(95% CI)
APC trial[29]	Colon polyp	About 3 yr	2035	celecoxib (200mg bid)	2.3 (0.9-5.5)
				celecoxib (400mg bid)	3.4 (1.4-7.8)
PreSAP trial[30]	Colon polyp	About 3 yr	1561	celecoxib (400mg bid)	1.3 (0.65-2.62)
ADAPT trial[33]	Alzheimer's disease	About 2 yr	2528	celecoxib (200mg bid)	1.10 (0.67-1.79)
				naproxen (220mg bid)	1.63 (1.04 -2.55)

*Relative risk of serious GI injuries for non aspirin users (95% confidence interval)

It remains to be clarified whether the CV adverse effect of COX-2 specific inhibitors is a class effect. The Celecoxib Long term Arthritis Safety Study (CLASS) showed that the incidence of MI and CV events in the celecoxib group (400 mg bid) did not differ from that in the NSAID group during the 6-month treatment period[7], with the CV risk of celecoxib possibly having been masked by the use of aspirin and the shortness of the observation period. The analysis of the adenoma prevention with celecoxib (APC) study showed at least a tripling of risk for the celecoxib group (400 mg bid) compared with the placebo group during an about 3-year observation period. CV events occurred in patients treated with celecoxib dose and time dependently[29]. However, a second placebo controlled (PreSAP) study with a comparable study design did not show any increased CV risk with celecoxib (400 mg bid) after a similar mean treatment period[30]. The placebo controlled, Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) in 2400 elderly people for about 2 years also showed that the naproxen group (220 mg bid) had a significant increase in CV risk compared with the placebo but not celecoxib group (220 mg bid)[33](Table 2). Several recent epidemiologic studies and a meta-analysis of randomized trials demonstrated that the CV risk of celecoxib is generally similar to that in patients receiving conventional non-selective NSAIDs and is not as high as that of rofecoxib[34]. Rofecoxib is more COX-2 selective and has a longer half-life than celecoxib. The increase in blood pressure with celecoxib is not greater than that with rofecoxib. But, in the VIGOR study high blood pressure due to rofecoxib cannot explain the increase in CV risk compared with naproxen. As other reasons, selective COX-2 inhibitor increases the susceptibility of biological lipids to oxidative modification

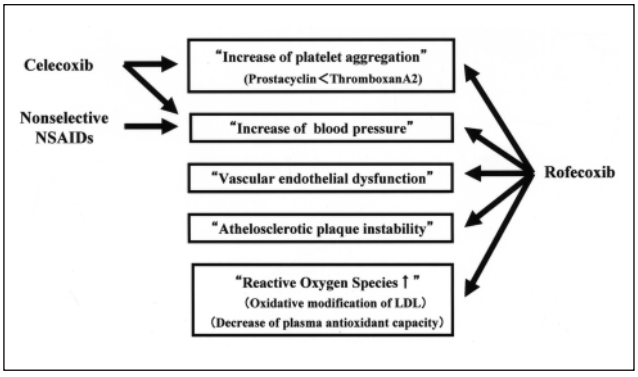

Fig.2 The presumed mechanism of cardiovascular risk by NSAIDs

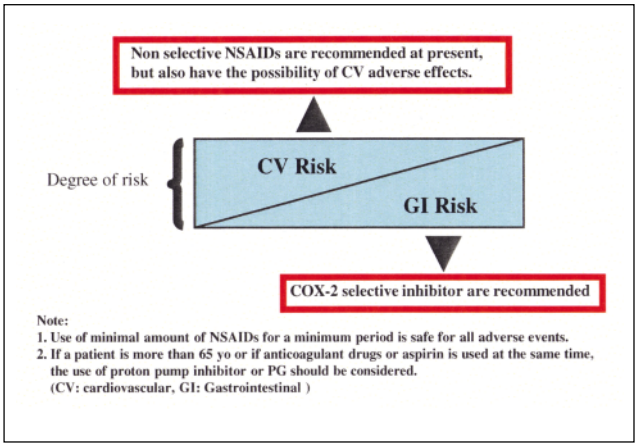

Fig.3 Direction for recommended use of NSAIDs on the basis of risk

through a non-enzymatic process and adverse effect on endothelial function. Celecoxib, but not rofecoxib, produced a marked improvement in endothelial-dependent vasodilatation and reduced markers of oxidative stress in human and animal studies[35-38](Fig.2). Thus each selective COX-2 inhibitor has different characteristics underlying its beneficial effect. Celecoxib is safer than rofecoxib with respect to CV risk. As stated by the Food and Drug Administration (FDA), non-selective NSAIDs as well as selective COX-2 inhibitors should be used at the lowest possible dose for the shortest possible period, and high-risk cardiac patients should be fully informed about the excess CV risks. These findings indicate that the CV risk for selective COX-2 inhibitors may be dependent on the individual drug and not reflect a class effect.

How to use selective COX-2 inhibitor in clinical practice

Use of NSAIDs requires balancing the risks and benefits for pain relief. Much thought should be given to the probability of GI and CV risk. Patients with high GI risk and no CV risk should use celecoxib. However we should pay attention to GI events even when celecoxib is used, because the GI events caused by NSAIDs remain as a significant problem. Moreover, patients with a history of GI bleeding should use PPI with celecoxib. In contrast, patients with high CV risk should be advised to use traditional non-selective NSAIDs at present. However we should pay attention to CV events even with use of non-selective NSAIDs, because non-selective NSAIDs have a similar possibility of CV events. In addition, PPI or a high dose of H2-receptor blocker or misoprostol (PG analogue) should be used for patients aged more than 65 years, or a combination of anticoagulant drugs or aspirin. In Japan it is a problem that these drugs have not yet been approved for the prophylaxis of GI tract ulcers. Therefore use of celecoxib in patients at high GI tract risk seems to be the best option. Furthermore, ibuprofen has been found to compete with low-dose aspirin in binding to the COX-1 pathway in platelets, but, in contrast to low-dose aspirin, the block is not irreversible[39]. Therefore concomitant use of NSAIDs such as ibuprofen and aspirin by patients with CV risk may decrease the protective effects of aspirin, although this phenomenon has not been detected with celecoxib. In any case, it is very important that the smallest amount of NSAIDs for the shortest period be used. I show my recommendations for the use of NSAIDs in clinical practice in Fig.3.

Conclusion

Many studies have demonstrated that treatment with non-selective NSAIDs as well as selective COX-2 inhibitors is associated with an increased risk of CV events. The relationship between COX-2 inhibitors and CV events needs to be addressed further, although ethical and safe clinical trials are difficult to implement in practice. According to data from the Organisation for Economic Co-operation and Development (OECD), the incidence of ischemic heart disease is low in Japan compared with western countries. Therefore the magnitude of the increase in CV risk induced by the use of selective COX-2 inhibitors in Japan may not be as high as that in western countries. Moreover, COX-2 inhibitors having advantages with regard to GI tract events are safer than traditional non-selective NSAIDs. Taken together, it is very important for daily clinical work to determine the best use of the advantages of NSAIDs with particular attention paid to patients with elevated CV and or GI risk.

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