

COX-2 inhibitors for endodontic pain

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The recent introduction of non-steroidal anti-inflammatory drugs (NSAIDs) that selectively inhibit cyclooxygenase-2 (COX-2), has generated considerable enthusiasm as a potential class of analgesic drugs with reduced side-effect liability. This article reviews the pharmacology of the COX-2 inhibitors from the perspective of their potential role in the management of the endodontic pain patient.

Achieving effective pain control is one of the major challenges of dentistry. Pain associated with dentistry contributes to apprehension about dental care and patients frequently report themselves as very nervous or terrified at the prospects of receiving dental therapy (1). Moreover, patients who are anxious about endodontic treatment report greater levels of postoperative pain (2).

Studies have shown that approximately 20% of patients report moderate to severe pain after endodontic procedures (3). While pain during therapy is usually controlled by local anesthesia, postoperative pain control is often inadequate either because of insufficient relief of pain or unacceptable side-effects. Side-effects such as drowsiness, nausea, and vomiting from opioids occur with greater frequency in ambulatory dental patients than in nonambulatory hospitalized patients. In addition, inadequate pain control during the immediate postoperative period may contribute to the development of hyperalgesia leading to greater pain at later time points during recovery (4, 5). These considerations indicate that optimal analgesic therapy for endodontic patients should be efficacious, with a minimum incidence of side-effects, and, ideally, lessen the prospects for pain associated with future dental therapy.

Dentists largely rely on non-steroidal anti-inflammatory drugs (NSAIDs) as alternatives to traditional

combinations of aspirin or acetaminophen with opioid analgesics (e.g. codeine) to treat patients. Although NSAIDs are remarkably effective in the management of pain and inflammation, their chronic use is limited by a number of adverse effects including gastrointestinal bleeding and ulceration, impaired renal function, and inhibition of platelet aggregation. The mortality rate associated with NSAID administration is one of the highest attributable to any drug class (6). Gastrointestinal toxicity associated with chronic NSAID use is estimated to result in more than 100 000 hospitalizations and 16 000 deaths per year in the US alone (7). However, this estimate regards all NSAIDs as one homogeneous group and thus may not be truly reflective of the adverse events associated with a particular NSAID. For example, the use of ibuprofen instead of other standard NSAIDs would lead to a dramatic reduction in the incidence of adverse effects.

The new generation of selective cyclooxygenase-2 (COX-2) inhibitors holds promise for achieving the therapeutic effects of the traditional NSAIDs without the adverse effects associated with non-selective COX-1/COX-2 inhibitors. Moreover, recent identification of COX-3 has elucidated a central mechanism of action of NSAIDs and acetaminophen and raises the possibility of a new class of NSAIDs designed to selectively inhibit COX-3 (8). This chapter reviews

the therapeutic use of selective COX-2 inhibitors with emphasis on the potential safety associated with their use.

Role of cyclooxygenase in pain and inflammation

Tissue injury and other proinflammatory stimuli activate phospholipases that, in turn, release arachidonic acid from cell membranes. The arachidonic acid in turn forms the substrate for the enzymes cyclooxygenase (COX) and lipoxygenase leading to the synthesis of the various eicosanoids. COX constitutes the rate-limiting step in the synthesis of prostaglandins. It is commonly believed that NSAIDs exert their therapeutic effect by inhibiting the enzyme COX, thereby inhibiting the synthesis of prostaglandins. As prostaglandins are also involved in maintaining a broad spectrum of homeostatic functions such as cytoprotection of the gastric mucosa and control of renal function, inhibition of prostaglandin synthesis results in a number of adverse effects.

Elucidation of the two COX isoforms gave rise to the concept that the constitutive enzyme COX-1 is responsible for the production of the prostaglandins with homeostatic functions in tissues such as the stomach, kidney, and platelets, while COX-2, the inducible enzyme, is responsible for the production of the prostaglandins involved in inflammation (9). Figure 1 illustrates the high level of expression of COX-2 in samples of human dental pulp with a diagnosis of irreversible pulpitis (10).

Based on these findings, it was postulated that the therapeutic effects of NSAIDs are attributable to inhibition of COX-2, while inhibition of COX-1 accounts for the adverse effects associated with NSAIDs. This led to the development of selective COX-2 inhibitors as a class of NSAIDs designed to selectively inhibit COX-2 without effects on COX-1 at therapeutic doses.

Recent studies have challenged the hypothesis that COX-1 plays no role in inflammation and that COX-2 is the only isoform responsible for the synthesis of pro-inflammatory PGs (11–13). It is now believed that COX-1 is responsible for the immediate prostanoid response to inflammatory stimuli and COX-2 becomes the primary contributor to prostanoid synthesis as inflammation progresses. This finding may have considerable significance for treating endodontic

pain patients since the inflammatory response is often chronic in nature.

Selective COX-2 inhibitors

As described earlier, development of the selective COX-2 inhibitors was based on the concept that the constitutive enzyme COX-1 is responsible for the production of prostaglandins with homeostatic functions in tissues such as the stomach, kidney, and platelets, while COX-2, the inducible enzyme, is responsible for the production of the prostaglandins involved in inflammation. One of the differences between the structures of the two COX isoforms is the substitution of valine by isoleucine in COX-2 at amino acid 523 that lines the surface of the cyclooxygenase active site. This change permits access to a pocket near the central channel of the enzyme. Thus, the volume of the NSAID binding site in COX-2 is larger than that in COX-1. A second valine substi-

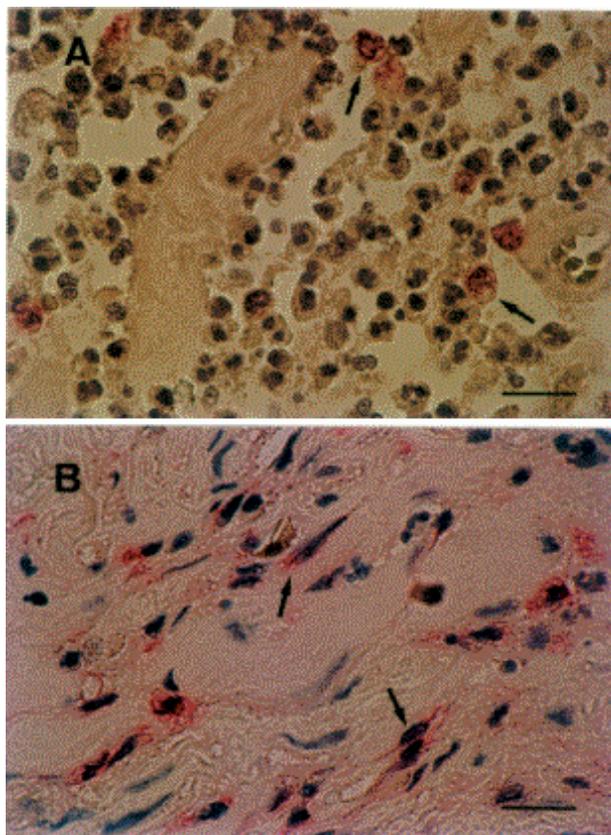


Fig. 1. Tissue levels of COX-2 are detectable in samples of human dental pulp collected from teeth with a diagnosis of irreversible pulpitis. From: Nakanishi T, Shimizu H, Matsuo T. *J Endod* 2001; 27:385–388 (10).

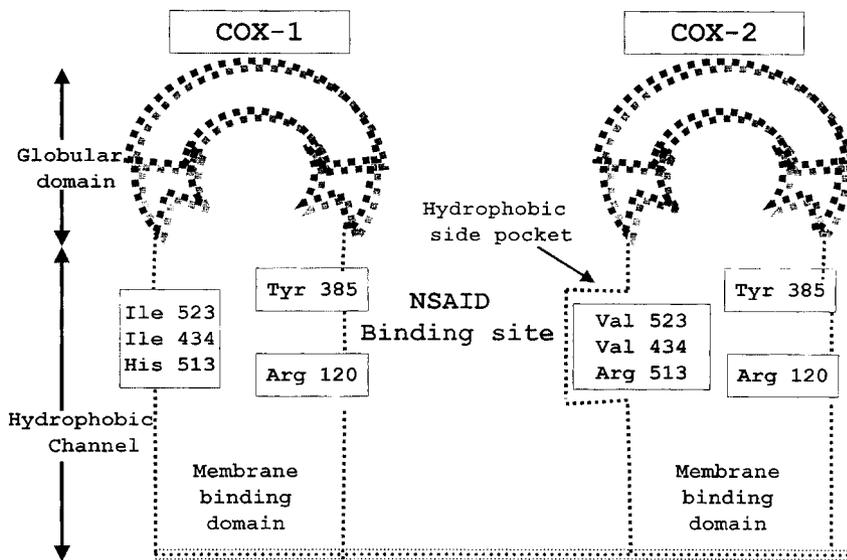


Fig. 2. Schematic illustration of the structures of COX-1 and COX-2. The cyclooxygenase active site of COX-2 is larger than that of COX-1 and contains a side pocket. Thus selective COX-2 inhibitors are larger than the non-selective NSAIDs and can be accommodated only in COX-2 but not in COX-1.

tution in COX-2 further increases the access to this pocket. As a result, the NSAID binding channel in COX-2 is about 25% larger than that in COX-1 (14). These differences have been exploited in the design of the selective COX-2 inhibitors, also known as coxibs (Fig. 2). Celecoxib and rofecoxib are the first generation of selective COX-2 inhibitors approved by the Food and Drug Administration (FDA) for pain indications. Valdecoxib belongs to the second generation of selective COX-2 inhibitors more recently approved by the FDA.

Analgesic efficacy and anti-inflammatory effect

Celecoxib, the first selective COX-2 inhibitor to be approved by the FDA, accounts for almost 25% of the anti-inflammatory drug market in the US based on costs. Its indications include the management of rheumatoid arthritis, osteoarthritis, acute pain, and primary dysmenorrhea in adults (Table 1). Celecoxib has demonstrated a COX-1 sparing effect *in vitro* and *ex vivo* studies (15, 16). A study examining the *in vivo* selectivity of celecoxib demonstrated that administration of celecoxib 200 mg PO prior to the extraction of impacted third molars had no effect on thromboxane B₂ (a product of COX-1) and inhibited PGE₂ only at time points which are consistent with induction of COX-2 (Fig. 3) (17). However, time-action curve for celecoxib analgesia and its peak analgesic effect are lower than that of ibuprofen 600 mg PO.

Another study using the oral surgery model, demonstrated celecoxib to be superior to placebo, comparable to 650 mg of aspirin, but generally less effective than standard doses of naproxen (18).

Rofecoxib has been reported to be more selective for COX-2 than celecoxib using *in vitro* assays (19). It is approved for the management of osteoarthritis, acute pain, and treatment of primary dysmenorrhea. Rofecoxib appears to have greater analgesic efficacy than celecoxib based on the results of studies in the oral surgery model. Rofecoxib 50 mg was compared to ibu-

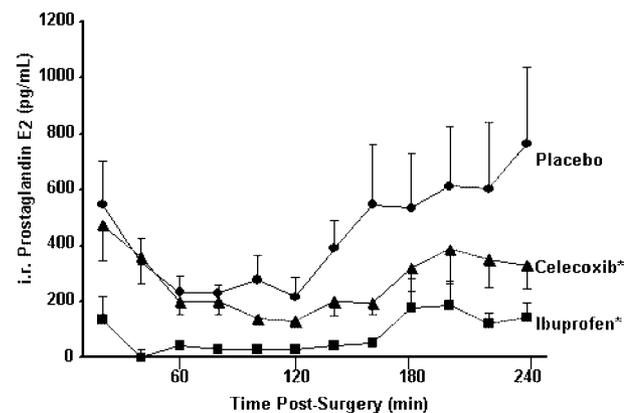


Fig. 3. Time course of immunoreactive PGE₂ (a product of COX-1 and COX-2) and TxB₂ (a product of COX-1) collected from the surgical site by microdialysis in the 4 hour postoperative period following oral surgery. Ibuprofen suppressed both PGE₂ and TxB₂ while celecoxib only suppressed PGE₂ at time points consistent with COX-2 activity, thus demonstrating a COX-1 sparing effect. Adapted from: Khan et al. *Clin Pharmacol Therap* 2002; 72: 44–49 (17).

Table 1. Pharmacokinetics and drug interactions of coxibs.

	Celecoxib	Rofecoxib	Valdecoxib
Onset of analgesia	60 minutes	30 minutes	60 minutes
Drug intercation			
ACE enzyme converting inhibitors	Y	Y	Y
Antacids	Y	Y	N
Codeine and Oxycodone	Y	N	N
Frusemide and Thiazides	Y	Y	Y
Inhibitors of CYP2D9	Y	N	?
Lithium	Y	Y	Y
Methotrexate	N	Y	N
Substrates of CYP2D6	Y	N	Y
Warfarin	Y	Y	Y
Approved doses (mg/day)			
For acute pain	400 mg first dose 200 mg/day	50 mg	20 mg q12h (primary dysmenorrhoea)
For osteoarthritis	200 mg/day	12.5–25 mg	10 mg/day
For rheumatoid arthritis	100–200 mg q12h	not approved	10 mg/day

profen 400 mg and placebo in a single dose study in the oral surgery model of acute pain using traditional analgesic endpoints as well as the two-stopwatch method for estimating analgesic onset (Fig. 4). The total pain relief and sum of the pain intensity difference score over 8 h following a single 50 mg dose of rofecoxib was superior to placebo but not distinguishable from ibuprofen 400 mg (20). The median time to onset of pain relief was indistinguishable for rofecoxib (0.7 h) and ibuprofen (0.8 h) but significantly fewer subjects in the rofecoxib group required additional analgesic within 24 h of study drug than in the placebo or ibuprofen groups. In a second study comparing rofecoxib in doses of 12.5, 25, and 50 mg to naproxen 550 mg, and placebo, a clear analgesic dose-response was demonstrated (21). The 25 and 50 mg doses of rofecoxib were statistically indistinguishable from naproxen for both pain relief and pain intensity difference. In both studies, the incidences of clinical and laboratory adverse experience were similar. A single-dose study using the oral surgery model demonstrated that the analgesic effect of rofecoxib 50 mg lasts up to 24 h, ibuprofen 400 mg lasts approximately 9 h, and celecoxib 200 mg has an estimated duration of 5 h (22).

Valdecoxib, a second generation coxib, has been approved for the management of osteoarthritis, rheumatoid arthritis and primary dysmenorrhea in the United States. It is highly selective for COX-2 and has no effect on platelet function (23). Using the oral surgery model the efficacy of valdecoxib 40 mg was compared to rofecoxib 50 mg (21). The results of this clinical trial demonstrated that valdecoxib 40 mg has

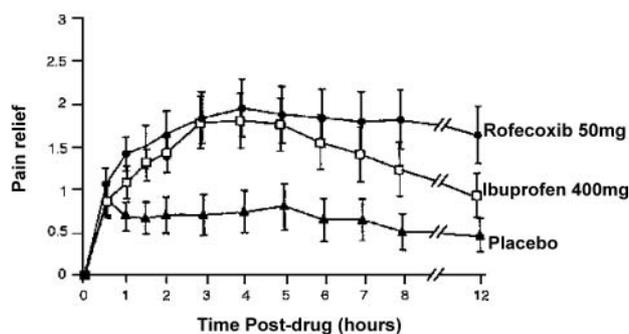


Fig. 4. Comparison of the analgesic effects of a single dose of rofecoxib 50 mg to ibuprofen 400 mg and placebo. The total pain relief and sum of the pain intensity of rofecoxib 50 mg was superior to placebo but not distinguishable from ibuprofen 400 mg. From: Khan A & Dionne RA. *Dent Clin North Am* 2002; 46(4): 679–90.

a quicker onset of action than that of rofecoxib 50 mg. The administration of valdecoxib resulted in better pain relief as compared to rofecoxib. However, valdecoxib was not approved for the management of acute pain at the initial FDA review.

Central vs. peripheral effects of coxibs

Early observations supported the hypothesis that NSAIDs acted primarily by inhibiting PG synthesis in the peripheral tissues (24, 25). The anti-inflammatory potency of some NSAIDs has been, in part, attributed to their high concentration in inflamed tissues. The appreciation of a dissociation between the anti-inflammatory and the analgesic actions of these drugs, however, suggested a central site of action (26). It is well established that peripheral inflammation leads to the up-regulation of COX-2 and PG synthesis in the central nervous system (27, 28). Intrathecal (i.e. injection into the space around the spinal cord) administration of NSAIDs has been shown to prevent hyperalgesia (29, 30). Orally administered celecoxib markedly attenuates PGE₂ content in the rat brain after kainate treatment, at doses below those needed for anti-inflammatory activity (31). This finding suggests that celecoxib and potentially also other NSAIDs can inhibit central COX-2 independent of any peripheral action.

Management of acute orofacial pain with selective COX-2 inhibitors

A number of studies have examined the analgesic efficacy of coxibs using the oral surgery model of acute inflammation (22, 32–34). However there are no published reports examining the efficacy of COX-2 inhibitors in orofacial pain of other etiologies such as endodontic pain, pain resulting from orthodontic treatment, and pain following periodontal surgery.

Limitations of orally administered selective COX-2 inhibitors, as well as the non-selective NSAIDs for dental pain, include delayed onset when compared to an injectable opioid and the inability to consistently relieve severe pain. The analgesic dose of rofecoxib, 50 mg as a single dose over 24 h, is greater than the recommended dose for rheumatoid and osteoarthritis (12.5–25 mg), due to concern about a greater incidence of side-effects with repeated doses, such as extremity edema. This could present a problem if pain

occurs prior to the recommended remedication time, i.e. a second dose of rofecoxib should not be administered until 24 h after the initial dose. In such a situation it would be safer to administer acetaminophen with or without an opioid.

The best strategy for minimizing pain onset is administration of an NSAID or coxib prior to the postoperative induction of COX-2. Preemptive analgesia is based on the principle that therapeutic intervention prior to pain onset, rather than in response to it, attenuates the development of changes that manifest as hyperalgesia at later time points. This strategy reduces pain during the immediate postoperative period as well as at later time points. As a result, fewer analgesics are consumed, resulting in fewer adverse drug reactions and enhanced recovery (35). It is reasonable to assume that administration of an NSAID or coxib prior to induction of COX-2 will not only suppress pain in the immediate postoperative period but will also prevent peripheral and central sensitization, thus preventing hyperalgesia. The administration of 20, 40 or 80 mg of valdecoxib prior to the surgical extraction of two impacted third molars significantly increased the time to rescue medication and attenuated pain intensity during the postsurgical period (33). A dose-dependent effect was observed up to 40 mg valdecoxib and the 80 mg dose did not provide any additional analgesic benefit.

The use of COX-2 inhibitors in preemptive analgesia has been evaluated in patients undergoing spinal fusion surgery (36). The preoperative oral administration of rofecoxib 50 mg or celecoxib 200 mg resulted in lower pain scores and decreased use of morphine during the postoperative period as compared to placebo.

Preoperative administration of rofecoxib provided a more sustained analgesic effect compared to preoperative treatment with celecoxib. The administration of rofecoxib 50 mg 1 h before arthroscopic knee surgery resulted in lower incidental pain score and less opioid use in the 24 h post surgical period as compared to rofecoxib 50 mg administered after surgery (37). To our knowledge there are no published reports evaluating the efficacy of preemptive analgesia in endodontic therapy. As the most severe postoperative pain often occurs within the first 24 h following endodontic therapy, it can safely be assumed that administration of an NSAID prior to postoperative pain onset is an effective strategy in pain management.

Multimodal analgesia is another way of achieving

effective postoperative pain control. The combined use of NSAIDs with an opioid is effective in relieving moderate to severe postoperative pain as compared to single-drug regimens. Premedication with celecoxib 200 mg and acetaminophen 2000 mg was highly effective in reducing postoperative pain as compared to celecoxib 200 mg or acetaminophen 2000 mg alone after ambulatory ENT surgery (38). An effective approach in managing moderate to severe postoperative endodontic pain is to coprescribe an alternating schedule of an NSAID with an acetaminophen–opioid combination (39). An advantage of using a multimodal approach is that the combination of these three drugs can have additive analgesic effects.

Adverse effects associated with selective COX-2 inhibitors

Gastrointestinal effects

A number of studies have examined the gastrointestinal complications following the use of coxibs. Predominant among these are the Celecoxib Long-Term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR). The CLASS trial lasted 13 months and consisted of two studies: one study compared celecoxib 400 mg BID with diclofenac 75 mg BID and the other study compared celecoxib with ibuprofen 800 mg TID (40). The primary endpoints were ulcer, perforation, gastric-outlet obstruction, and upper gastrointestinal bleeding. The published data from only the first 6 months demonstrated that the incidence of GI effects in the celecoxib group (0.8%) was numerically lower than the NSAID group (1.5%). No comparison was made with placebo due to the duration of the study. On reviewing the entire study data, the FDA's Arthritis Advisory Committee concluded that celebrex offered no proven safety advantage over the other two drugs (diclofenac and ibuprofen) in reducing the risk of ulcer complications (*Washington Post*, August 5, 2001).

The VIGOR trial compared rofecoxib 50 mg QD to naproxen 500 mg BID in patients with rheumatoid arthritis ($N=8076$) (41), over a median period of 9 months. The incidence of GI perforation, GI hemorrhage or symptomatic peptic ulcer was 4.5 per 100 patient-years in the naproxen group and 2.1 per 100 patient-years in the rofecoxib group – a difference of 54% ($P<0.001$) between the two groups. A similar study comparing rofecoxib 12.5, 25, or 50 mg/day to ibuprofen

800 mg/3 times daily, diclofenac 50 mg/3 times daily, and nabumetone 1500 mg/day in osteoarthritic patients ($N=5435$) over a 12-month period demonstrated that the incidence of GI effects following the use of rofecoxib (1.3%) was slightly lower than with the conventional NSAIDs (1.8%) (42). These data indicate that rofecoxib is associated with fewer gastrointestinal events than non-selective NSAIDs.

However, subjects who have preexisting risk factors such as history of peptic ulcers and gastrointestinal bleeding are likely to be at a higher risk of developing GI events following the use of selective COX-2 inhibitors. Other risk factors for the development of ulcers include the concurrent use of anticoagulants and life style factors such as the use of alcohol and smoking.

Cardiovascular effects

The current clinical data on the cardiovascular effects of coxibs is limited. Thromboxane A₂ (TxA₂) and prostacyclin I₂ (PGI₂), products of the cyclooxygenase pathway, are involved in platelet–vascular homeostasis. PGI₂, a vasodilator, inhibits platelet aggregation and leukocyte adherence, whereas TxA₂, a vasoconstrictor, promotes platelet aggregation. Selective COX-2 inhibitors suppress the synthesis of PGI₂ and have no effect on TxA₂, shifting the hemostatic balance towards a prothrombotic state with greater potential to initiate adverse occlusive vascular events (43).

The CLASS trial demonstrated that there was no significant difference in the rates of major cardiovascular events between the treatment groups. However, the VIGOR trial showed that administration of rofecoxib was associated a greater risk of developing a thrombotic cardiovascular event as compared with naproxen ($P<0.005$). It is yet to be elucidated whether these results reflect a beneficial effect of naproxen to decrease platelet aggregation or a prothrombotic effect of rofecoxib.

As the CLASS and VIGOR trials had distinctly different patient populations and used different NSAIDs as comparators, it is difficult to compare the results of the two trials. The CLASS study comprised patients with rheumatoid arthritis or osteoarthritis, while the VIGOR study consisted entirely of patients with rheumatoid arthritis, a risk factor for myocardial infarction (44). Furthermore, 21% of the subjects in the CLASS trial were permitted to use aspirin <325 mg/day while those in the VIGOR trial were not.

This may in part account for the lower incidence of cardiovascular event in the CLASS trial.

Renal effects

Both COX isoforms are constitutively expressed in the kidneys and the effects of selective COX-2 inhibitors on renal function are currently being evaluated. Inhibition of COX-2 can potentially cause hypertension and renal failure. Post hoc analysis of the marketing data for celecoxib and rofecoxib reveal that the incidence of hypertension and edema does not differ from that of the non-selective NSAIDs (45). The effect of celecoxib 200mg and rofecoxib 25mg on renal function as measured by urinary sodium secretion, systolic and diastolic blood pressure and creatinine clearance did not differ from that of naproxen 500mg in a study using elderly subjects (16).

The effect of coxibs on healing

An important issue to be addressed is the potential role of COX-2 in the resolution of inflammation. It has been suggested that while COX-2 is pro-inflammatory in the early stages of inflammation, which is dominated by polymorphonuclear leukocytes, it may actually aid in the resolution of inflammation in the later stages (which are dominated by mononuclear cells) (11). As the various PG synthases exhibit different cell- and tissue-specific distributions, this effect of COX-2 may be via the generation of anti-inflammatory PGs such as those of the cyclopentone family (46). Studies using selective COX-2 inhibitors have been inconclusive. Elliot et al. demonstrated that the COX-2 inhibitors L745 337 and nabumetone had no effect on the healing of gastric ulcers (47). In contrast, NS-398, a selective COX-2 inhibitor, delayed the healing of ulcers (48).

Cyclooxygenase is also known to play an important role in bone metabolism. COX-2 regulates mesenchymal cell differentiation and plays a pivotal role in bone repair (49). Thus, both coxibs and the non-selective NSAIDs can impair the healing of bone as well as soft tissues.

Drugs in the pipeline

Etoricoxib, a highly selective COX-2 inhibitor, is currently being reviewed by the FDA. It is a potent

COX-2 inhibitor in various animal models including carrageenan-induced paw-edema and hyperalgesia, and adjuvant-induced arthritis. Parecoxib, an injectable prodrug of valdecoxib, holds the promise of an effective means of managing severe acute pain including postoperative pain. Desjardins et al. demonstrated that the preoperative administration of parecoxib 40 and 80mg is effective and safe for treating postoperative pain (33). Parecoxib 40mg IV and IM provides effective analgesia in the oral surgery model with the analgesic relief provided by parecoxib being comparable to 60mg of ketorolac (32). JTE-522 is also being developed for the management of pain. It has been demonstrated to selectively inhibit the synthesis of PGE₂ in the inflammatory tissue at doses having no effect on PGE₂ production in the gastric mucosa (50).

Dual-acting anti-inflammatory drugs that inhibit both COX and lipoxygenase constitute another therapeutic option in the management of inflammation. Leukotrienes, products of lipoxygenase, are potent mediators of inflammation. The effects of leukotrienes include chemotaxis, neutrophil degranulation and lysosomal enzyme release, induction of neutrophil-endothelial cell adhesion and the modulation of pain induced by inflammatory responses. Thus, a drug which inhibits both COX and lipoxygenase would have a potent anti-inflammatory effect. Examples of these drugs include tepoxalin and tebufelone (51, 52).

Other therapeutic uses of coxibs

While coxibs were first developed as analgesics, future clinical use of these drugs is likely to extend beyond their use as analgesics. Epidemiological studies report reduced prevalence of Alzheimer's disease (AD) in chronic users of NSAIDs (53). The chronic use of NSAIDs is associated with delayed expression of AD among twins (54) as well as among siblings (55). A subset of NSAIDs including ibuprofen and indomethacin lower amyloidogenic A β 42, which is believed to be the main culprit in the pathogenesis of AD. This effect is independent of cyclooxygenase activity (56). There is a growing consensus supporting the hypothesis that neuronal COX-2 plays an important role in the development of AD (57). These and other findings have led to the initiation of several trials evaluating whether selective COX-2 inhibitors or

low doses of non-selective NSAIDs can delay the onset of AD.

Another potential clinical use of coxibs is the prevention or management of benign and malignant tumors (tumorigenesis). NSAIDs restore normal apoptosis and inhibit angiogenesis and thus help to suppress malignant transformation and tumor growth. Controlled clinical trials have demonstrated that both the dual-acting NSAID sulindac and the selective COX-2 inhibitor celecoxib inhibit the growth of adenomatous polyps and cause regression of existing polyps in patients with Familial Adenomatous Polyposis (58–60). Studies are currently in progress evaluating the utility of coxibs as chemopreventive agents in colorectal adenomas. Coxibs may potentially be used to induce regression of oral premalignant lesions such as leukoplakia and dysplastic Barrett's esophagus (61). Second, both non-selective and selective NSAIDs effectively inhibit the early stages of tumor development, whereas only selective COX-2 inhibitors are effective when treatment is delayed. For example, celecoxib (1500 ppm in food) reduced tumor incidence and multiplicity by approximately half, even when treatment was delayed until the tumor promotion/progression stage (62). Third, NSAID treatment must be continued without interruption to prevent resumption of tumor growth. The potential use of coxibs in the management of cancer pain is also being explored (63). These drugs offer the advantage of providing pain relief as well as having a chemopreventive effect.

Identification of COX-3

A recent development in pain research is the identification of a variant of COX-1, which has been named COX-3 (8). COX-3 was first identified in the canine brain and its activity is inhibited by acetaminophen as well as NSAIDs such as ibuprofen. The identification of COX-3 may explain the mechanism of action of acetaminophen, which has long eluded researchers. Acetaminophen is a centrally acting drug with a potent antipyretic and analgesic effect and a weak anti-inflammatory effect (64). It is now clear that acetaminophen acts by inhibiting COX-3 activity in the brain. COX-3 differs in its pharmacological activities from both COX-1 and COX-2 and is a potential target for analgesic and antipyretic drugs.

The identification of a partial COX-1 protein

(PCOX-1a) was also reported in the same paper. Like COX-3, PCOX-1a is a variant of COX-1. It lacks cyclooxygenase activity and thus does not contribute to PG synthesis.

Conclusion

While achieving effective pain control represents an ongoing challenge in endodontics, selective COX-2 inhibitors offer a therapeutic alternative to the conventional non-selective NSAIDs. These drugs are also indicated in patients who are likely to undergo surgery or invasive procedures in the near future because they do not prolong the bleeding time. The pharmacoeconomic impact of COX-2 inhibitors must also be considered, as the cost of selective COX-2 inhibitors is considerably higher than that of the other commonly used NSAIDs.

While it is clear that COX-2 inhibitors offer some advantages over the non-selective NSAIDs in terms of a lower risk of GI toxicity with long-term use, the effects following short-term use are still unclear. Until more data are available, COX-2 inhibitors should be avoided or used with the same caution as conventional NSAIDs in patients with compromised renal and cardiac function.

Acknowledgments

This work was supported by Division of Intramural Research, NIDCR, and Training grant T-32DE14318.

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