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The COX-2 inhibitors: new analgesic and anti-inflammatory drugs

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One of the major challenges in dentistry is the management of pain. Pain not only signals tissue injury, but it also acts as an impediment to most dental procedures, delays the resumption of normal activities following dental surgical procedures, and lessens the likelihood of patients seeking dental procedures in the future. Although pain during therapy usually is 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 later during recovery [1]. Pain associated with dentistry also is recognized as contributing to apprehension about future dental care such that patients frequently report themselves as nervous or terrified at the prospects of dental care [2]. These considerations indicate that optimal analgesic therapy for ambulatory dental patients should be efficacious, with a minimum incidence of side effects, and, ideally, should lessen the prospects for pain associated with future dental therapy.

Dentists largely rely on nonsteroidal anti-inflammatory drugs (NSAIDs) as alternatives to traditional combinations of aspirin or acetaminophen

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with opioid analgesics such as codeine to treat pain in ambulatory patients. Although NSAIDs are remarkably effective in the management of pain and inflammation, their use is limited by several 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 [3]. 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 United States alone [4]. It has been reported that geriatric patients are at an even greater risk for toxicity with chronic use of NSAIDs [5,6].

The new generation of selective cyclooxygenase-2 (COX-2) inhibitors holds promise for achieving the therapeutic effects of the traditional NSAIDs without the deleterious side effects associated with nonselective COX-1/COX-2 inhibitors. This article reviews the therapeutic use of selective COX-2 inhibitors with emphasis on the potential safety associated with their use.

Role of cyclooxygenase in pain

Numerous endogenous mediators are involved in nociception and in the inflammatory response. Among these are proinflammatory prostaglandins such as prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2). Cyclooxygenase (COX) constitutes the rate-limiting step in the synthesis of these prostaglandins. It is commonly believed that NSAIDs exert their therapeutic effect by inhibiting the enzyme COX, which in turn inhibits 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 many 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, whereas COX-2, the inducible enzyme, is responsible for the production of the prostaglandins involved in inflammation [7]. Accordingly, it was postulated that the therapeutic effects of NSAIDs are attributable to inhibition of COX-2, whereas 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 and to have no effect on COX-1 at therapeutic doses. 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 and was recently approved by the FDA.

Selective COX-2 inhibitors

Analgesic efficacy and anti-inflammatory effect

Celecoxib was the first selective COX-2 inhibitor to be approved by the FDA and accounts for almost 25% of the anti-inflammatory drug market. 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 both in vitro and ex vivo studies [8,9]. A study examining the in vivo selectivity of celecoxib demonstrated that administration of celecoxib 200 mg orally (PO) before the extraction of impacted third molars had no effect on thromboxane B_2 (a product of COX-1) and inhibited PGE_2 only at time points that are consistent with induction of COX-2 (Fig. 1) [10]. The time-action and peak analgesic effect of celecoxib is approximately half (much 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 [11].

Rofecoxib has been reported to be more selective for COX-2 than celecoxib using in vitro assays [12]. It is approved for the management of osteoarthritis, acute pain, and treatment of primary dysmenorrhea. Rofecoxib seems to have greater analgesic efficacy than celecoxib based on the results of studies in the oral surgery model. Rofecoxib 50 mg was compared with ibuprofen 400 mg and placebo in a single dose study in the oral surgery model of acute pain using traditional analgesic endpoints and the two-stopwatch method for estimating analgesic onset (Fig. 2). The total pain relief and sum of the pain intensity difference score over 8 hours following a single 50 mg

Table 1
Pharmacokinetics and drug interactions of celecoxib and rofecoxib

	Celecoxib	Rofecoxib
Onset of analgesia	60 min	30 min
Drug interaction		
ACE enzyme converting inhibitors	Y	Y
Antacids	Y	?
Codeine and oxycodone	Y	N
Frusemide and thiazides	Y	Y
Inhibitors of CYP2D9	Y	N
Lithium	Y	Y
Methotrexate	N	Y
Substrates of CYP2D6	Y	N
Warfarin	Y	Y
Approved doses (mg/day)		
For acute pain	200–400	Up to 50
For osteoarthritis	100–200	Not approved
For rheumatoid arthritis	200–400	12.5–25

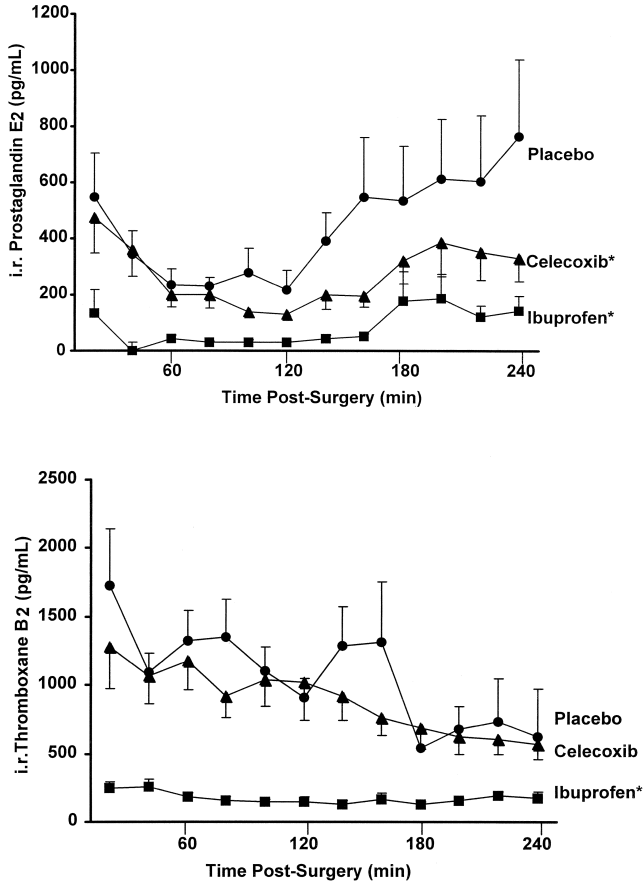

Fig. 1. Comparison of immunoreactive levels of (A) prostaglandin E_2 (i.r.PGE_2) and (B) thromboxane B_2 (i.r.TxB_2) at the surgical site after extraction of impacted third molars. Ibuprofen suppressed levels of PGE_2 and TxB_2, whereas celecoxib suppressed only PGE_2 ($P < 0.001$), thus demonstrating a COX-1 sparing effect. (*Adapted from* Khan AA, Dionne RA, Capra NF. In vivo selectivity of a selective cyclooxygenase-2 inhibitor in the oral surgery model. Clin Pharmacol Therap 2002;72:44–9; with permission.)

dose of rofecoxib was superior to placebo but not distinguishable from ibuprofen 400 mg [13]. The median time to onset of pain relief was indistinguishable for rofecoxib (0.7 hour) and ibuprofen (0.8 hour), but significantly fewer subjects in the rofecoxib group required additional analgesic within 24 hours 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 dose analgesic response was demonstrated [14]. The 25- and 50-mg doses of rofecoxib were statistically indistinguishable from naproxen for pain relief and pain intensity difference. In both studies, the incidence of clinical and laboratory adverse experience were similar. A single-dose study

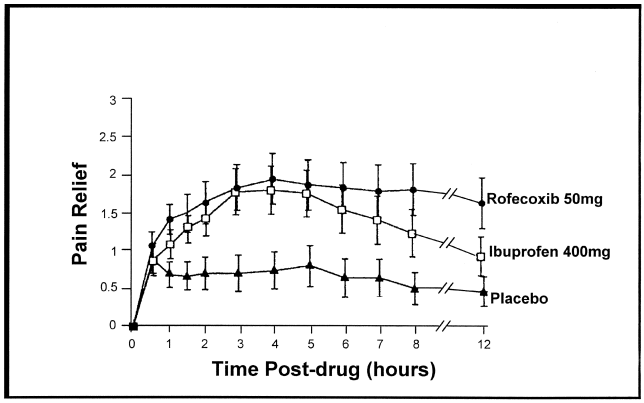

Fig. 2. Comparison of the analgesic effects of a single dose of rofecoxib 50 mg to ibuprofen 400 mg and placebo.

using the oral surgery model demonstrated that the analgesic effect of rofecoxib 50 mg lasts up to 24 hours, ibuprofen 400 mg lasts approximately 9 hours, and celecoxib 200 mg has an estimated duration of 5 hours [15].

Valdecoxib has been approved for the treatment of osteoarthritis, rheumatoid arthritis, and for the management of primary dysmenorrhea. Using the oral surgery model, the efficacy of valdecoxib 400 mg was compared with that of rofecoxib 50 mg [16]. The results of this clinical trial demonstrated that valdecoxib 40 mg has a quicker onset of action than that of rofecoxib 50 mg. The administration of valdecoxib resulted in better pain relief and lower pain intensity as compared with rofecoxib. Valdecoxib was not approved for the management of acute pain at this initial FDA review.

Management of acute orofacial pain with selective COX-2 inhibitors

Several studies have examined the analgesic efficacy of rofecoxib and celecoxib using the oral surgery model of acute inflammation [10,15,17]. There are, however, no published reports examining the efficacy of rofecoxib in acute 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 and the nonselective NSAIDs for dental pain include delayed onset when compared with an injectable opioid and the inability to consistently relieve severe pain. The analgesic dose of rofecoxib 50 mg as a single dose over 24 hours is greater than the recommended dose for rheumatoid and osteoarthritis 12.5–25 mg, owing to concern for a greater incidence of side effects with repeated doses, such as extremity edema. This could present a problem if pain occurs before the recommended remedication time, (ie, a second dose of rofecoxib should not be administered until 24 hours 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 before the postoperative induction of COX-2. The use of COX-2 inhibitors in preemptive analgesia has been evaluated in patients undergoing spinal fusion surgery [18]. 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 with placebo. Preoperative administration of rofecoxib provided a more sustained analgesic effect compared with preoperative treatment with celecoxib. The administration of rofecoxib 50 mg 1 hour before arthroscopic knee surgery resulted in lower incidental pain score and less opioid use in the 24-hour post surgical period [19]. It is reasonable to assume that administration of a COX-2 inhibitor before 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.

Management of chronic orofacial pain with selective COX-2 inhibitors

A review of the primary literature reveals little scientific support that the daily use of NSAIDs offers benefit for chronic orofacial pain [20]. The results of two placebo-controlled studies suggest that NSAIDs are ineffective for chronic orofacial pain. The analgesic effects of ibuprofen, 2400 mg per day for 4 weeks, could not be separated from placebo in a group of patients with chronic myogenous orofacial pain [21]. A similar comparison of piroxicam, 20 mg daily for 12 days, to placebo for pain associated with temporomandibular disorders (TMD) also failed to demonstrate any therapeutic advantage for the NSAID [22]. Although little evidence from randomized clinical trials exists regarding the efficacy of NSAIDS in chronic orofacial pain, standard texts and summaries of expert opinion often provide recommendations for specific drugs and doses but either do not provide support for these recommendations or extrapolate from chronic inflammatory conditions such as arthritis [23,24]. A short trial of an NSAID may be considered for patients with an inflammatory component to their TMD. The development of selective COX-2 inhibitors offers an alternative for use of NSAIDs without the adverse effects associated with dual COX-1/COX-2 inhibitors.

Clinical and animal studies suggest that tolerance to NSAIDs can develop with repeated administration. In a group of subjects with chronic lower back pain, the mean reduction in chronic lower back pain intensity following an initial dose of 1200 mg per day ibuprofen was 23% [25]. After 2 weeks of 2400 mg per day of ibuprofen or placebo, the mean reduction in pain intensity for the last dose was fourfold lower in the drug group. The initial low level of response suggests that lower back pain is not particularly sensitive to ibuprofen and may explain, in part, the poor response seen for chronic musculoskeletal pain in the orofacial area. The development of tolerance over 2 weeks would suggest a similar process for TMD pain that

could make the analgesic response negligible over the course of a chronic condition. Tolerance to diflunisal with repeated administration has been demonstrated in animals without a reduction in the amount of drug in the blood over time following administration of the first dose in comparison with a dose given following 3 days of diflunisal [26]. This suggests a functional change in the pharmacologic response rather than enhanced pharmacokinetic disposition such that the same amount of drug elicits less analgesia. Long-term administration of selective COX-2 inhibitors for chronic orofacial pain should be evaluated for initial analgesic efficacy, the development of tolerance, and safety with repeated dosing.

Adverse effects

Numerous recent studies have suggested that the original paradigm regarding the roles of COX-1 and COX-2 was overly simplistic. Findings from animal studies have demonstrated constitutive expression of COX-2 in specialized cell types or tissues including the kidney, brain, ovary, and uterus [27–29]. There is also evidence that COX-1 can be induced by stressful stimuli such as radiation injury to the intestine, and may play a protective role in this circumstance [30].

It has been suggested that although COX-2 is proinflammatory in the early stages of inflammation, it may aid in the resolution of inflammation in the later stages [31]. This effect of COX-2 may be by way of the generation of anti-inflammatory prostaglandins of the cyclopentone family. Studies on the gastric mucosa in mice have demonstrated that inhibition of COX-2 delays the healing of ulcers [32]. It has also been demonstrated that COX-2 inhibition exacerbates the inflammation associated with colonic injury [33]. Newberry et al [34] reported that COX-2 dependent metabolites are essential in the development and maintenance of intestinal immune homeostasis. This emerging information clearly demonstrates that COX-1 and COX-2 have more complex physiologic and pathophysiologic roles than originally thought.

Gastrointestinal effects

Two large, randomized clinical trials have examined the risk for gastrointestinal complications following the use of these drugs, the Celecoxib Long-Term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR). The CLASS trial consisted of two studies: Celecoxib 400 mg twice daily (BID) was compared with diclofenac 75 mg BID in one study and with ibuprofen 800 mg three times daily (TID) [35]. The primary end points were ulcer, perforation, gastric-outlet obstruction, and upper gastrointestinal bleeding. The duration of the study was 13 months. 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 to placebo because of the duration of the study. A subsequent report [36] indicates that after 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 for ulcer complications.

In the VIGOR trial, rofecoxib 50 mg once daily (QD) was compared with naproxen 500 mg BID in patients with rheumatoid arthritis ($N = 8076$) [37]. The median of the total treatment time was 9 months. The incidence of gastrointestinal (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 conducted over a 12 month period comparing rofecoxib 12.5, 25, or 50 mg/day to ibuprofen 800 mg/3 times daily, diclofenac 50 mg/3 times daily, and nabutmatone 1500 mg/day in osteoarthritic patients ($N = 5435$) demonstrated that the incidence of GI effects following the use of rofecoxib (1.3%) was slightly lower than with the conventional NSAIDs (1.8%) [38]. These data indicate that selective rofecoxib seems to be associated with fewer gastrointestinal events than the nonselective NSAIDs. Subjects who have preexisting risk factors such as history of peptic ulcers and gastrointestinal bleeding, however, are likely to be at a higher risk for developing GI events following the use of selective COX-2 inhibitors.

Cardiovascular effects

Thromboxane A_2 (TxA_2) and prostacyclin I_2 (PGI_2) are products of the cyclooxygenase pathway that are involved in platelet-vascular homeostasis. PGI_2 is a vasodilator and inhibits platelet aggregation and leukocyte adherence, whereas TxA_2 is a vasoconstrictor and promotes platelet aggregation. Selective COX-2 inhibitors suppress the synthesis of PGI_2 and have no effect on TxA_2, shifting the hemostatic balance toward a prothrombotic state [39] with greater potential to initiate adverse occlusive vascular events.

The results of the CLASS trial demonstrated that there was no significant difference in the rates of major cardiovascular events between the treatment groups. The results of the VIGOR trial showed that the risk for developing a thrombotic cardiovascular event following treatment with rofecoxib as compared with naproxen was 2.38 ($P = 0.002$). It is not clear at this point whether these results reflect a beneficial effect of naproxen to decrease platelet aggregation or a prothrombotic effect of rofecoxib.

A comparison of the cardiovascular effects of celecoxib and rofecoxib using the data from the two trials is difficult because they had distinctly different patient populations and the NSAIDs used as controls were different. It is likely that the CLASS trial failed to reveal the increased risk for cardiovascular events following celecoxib administration, as 21% of the subjects in this trial were permitted to take aspirin <325 mg/day, whereas its use was not permitted in the VIGOR study. All the subjects in the VIGOR trial had

rheumatoid arthritis, whereas only 11% of the subjects in the CLASS trial had rheumatoid arthritis, a risk factor for myocardial infarction [40].

Renal effects

Although both COX isoforms are constitutively expressed in the kidneys, the effect of COX-2 inhibition on renal function remains unknown. As COX-2 is involved in the regulation of the renin-angiotensin system, inhibition of COX-2 has the potential to cause hypertension and renal failure [28]. The results of a study by Rossat et al [41] using healthy salt-depleted male volunteers demonstrated that selective COX-2 inhibition causes water and salt retention with a transient decrease in glomerular filtration rate. Analyses of the post marketing data for celecoxib and rofecoxib reveal that the incidence of hypertension and edema is similar to that of the nonselective NSAIDs [42].

Drugs in the pipeline

Parecoxib, an injectable prodrug of valdecoxib, holds the promise of an effective means of managing severe acute pain, including postoperative pain. Desjardins et al [43] demonstrated that the preoperative administration of parecoxib 40 and 80 mg is effective and safe for treating postoperative pain. It has been demonstrated that parecoxib 40 mg IV and IM provides effective analgesia in a postoral surgery model with the analgesic relief provided by parecoxib being comparable to 60 mg of ketorolac [44]. Etoricoxib is yet another selective COX-2 inhibitor that is currently being reviewed by the FDA. It has been demonstrated to be highly selective for COX-2 (Table 2). It has also been reported to be a potent COX-2 inhibitor in various animal models including carrageenan-induced paw-edema and hyperalgesia, and adjuvant-induced arthritis. JTE-522, a selective COX-2 inhibitor also being developed for the management of pain, has been demonstrated to selectively inhibit the synthesis of PGE_2 in the inflammatory tissue at doses having no effect on PGE_2 production in the gastric mucosa [45].

Table 2
Ratios of COX-1 IC_{50}/COX-2 IC_{50} values of NSAIDs in human whole blood assays

Drug	IC_{50} ratios
Etoricoxib	106
Rofecoxib	35
Valdecoxib	30
Celecoxib	7.6
Diclofenac	3.0
Ibuprofen	0.2

A high ratio of Cox-1 IC_{50}/Cox-2 IC_{50} implies that the agent is relatively selective for COX-2. *Data from* Riendeau D, Percival MD, Bridean C, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J Pharmacol Exp Ther 2001;296(2):558–66.

Summary

Selective COX-2 inhibitors offer a therapeutic alternative to the conventional nonselective NSAIDs. Rofecoxib has been demonstrated to be a valuable therapeutic agent in the management of acute orofacial pain. Selective COX-2 inhibitors are also indicated in patients who are likely to undergo surgery or invasive procedures in the near future because these drugs do not prolong the bleeding time. The efficacy of these drugs in the management of chronic orofacial pain is yet to be evaluated. The pharmacoeconomic impact of COX-2 inhibitors must also be considered, as the cost of selective COX-2 inhibitors is considerably higher than the other commonly used NSAIDs.

Although it is clear that COX-2 inhibitors offer some advantages over the nonselective 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 for conventional NSAIDs in patients with compromised renal and cardiac function.

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