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Cox-2 selective inhibitors: A literature review of analgesic efficacy and safety in oral-maxillofacial surgery

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Background. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed analgesic agents in surgical outpatients. Major limitations of NSAIDs are their gastrointestinal (GI) adverse events (perforation, ulceration, and bleeding), impairment of hemostatic function, and renal failure (with long-term therapy). A new class of NSAIDs, the COX-2 selective inhibitors (CSIs or Coxibs), have been developed with the aim of reducing the GI adverse events of traditional NSAIDs while maintaining their effective anti-inflammatory and analgesic properties.
Objective. This is a narrative review of the literature aimed to discuss analgesic efficacy, clinical safety and cost-benefit ratio of CSIs in the treatment of post–oral surgery pain.
Methods. Relevant drug and clinical studies of analgesic efficacy and safety of CSIs in the management of postoperative dental pain were identified through searches of MEDLINE/PubMed, in peer-reviewed journals of medicine and dentistry. The Food and Drug Administration Web site was searched for data of tolerability. Hand-searching included several dental journals and bibliographies of relevant studies. The last electronic search was conducted in April 2003.
Results. Data from well-designed, randomized, controlled trials of CSIs on the management of post–oral surgery pain indicate that these drugs are as well-effective analgesic agents as traditional NSAIDs and offer clinical advantages in terms of GI safety and unimpaired platelet function. CSIs do not offer advantages of renal safety over traditional NSAIDs.
Conclusion. Although CSIs display analgesic efficacy similar to that of traditional NSAIDs in the treatment of acute, post–oral surgery pain, there is reasonable evidence that these new drugs are preferable in patients who are at an increased risk of developing serious upper-GI complications, in patients who take aspirin for cardiovascular comorbid conditions, and in those allergic to aspirin. Furthermore, CSIs may be given more safely than NSAIDs in perioperative settings, because of their lack of impairment of the blood-clotting. However, the high costs of CSIs available at present limit their routine use in the short period of postoperative dental pain—in most cases 2 to 4 days after surgery—because there is not an increased risk of developing serious GI complications with the use of cost-saving NSAIDs. The GI safety advantages of CSIs may improve the tolerability of long-duration analgesic therapies, such as cases of painful temporomandibular joint disorders and chronic orofacial pain. Further studies are needed to determine the cost-benefit ratio of using CSIs for the management of acute pain.
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Effective pain control in dentistry including oral-maxillofacial surgery is essential for the delivery of optimal therapies and for the quality of life of patients and their compliance with dental cares.

ENZYME CYCLOOXYGENASE

The enzyme cyclooxygenase (COX) catalyzes the first step of the synthesis of prostanoids implicated in the pathogenesis of inflammatory pain. In 1990, the enzyme cyclooxygenase was demonstrated to exist in 2 distinct isoforms, COX-1 and COX-2.[1] COX-l has been found to be constitutively expressed in most tissues of the human body and provides prostaglandins with a role in the homeostatic functions, including affecting gastric mucosa, renal blood flow, hemostasis, wound healing, and ovulation.[2] By contrast, COX-2 maintains a low

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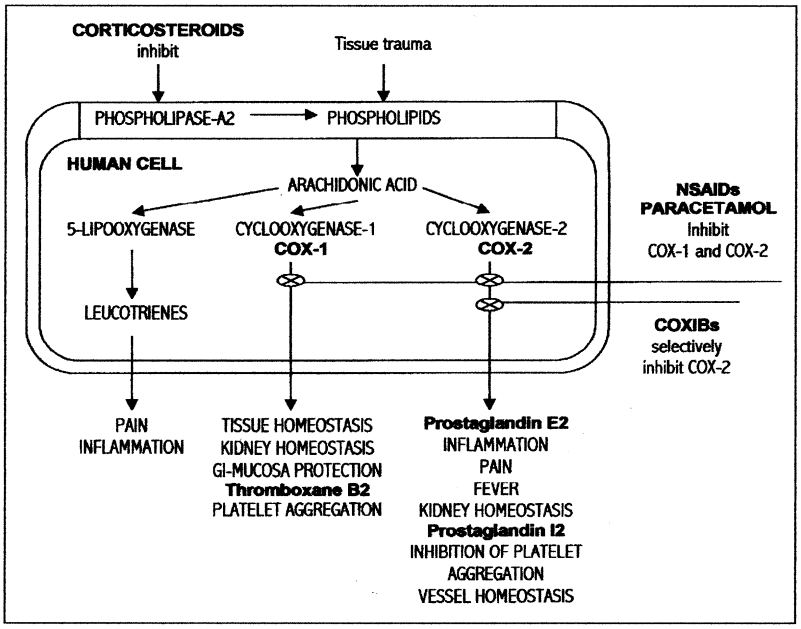

Fig 1. Drug interaction with the arachidonic acid cascade and pain-related prostanoid biosynthesis.

level of basal constitutive expression only in the brain neurons, kidneys, female reproductive system, and bone where it may be up-regulated, whereas in most tissues it may be inductively expressed by inflammatory cytokines and growth factors in response to inflammation and tissue injury (such as a surgical trauma).[3-5] In animal studies, COX-2 has been inductively expressed within 2-4 hours after a trauma, and within 1-2 hours from surgery in the oral cavity–mucosa, thus leading to a rapid onset of the postoperative pain.[6]

NSAIDS AND INHIBITION OF COX-1

As a result of the ubiquitous expression of COX-1, gastrointestinal (GI) toxicity is the major clinical limitation of traditional NSAIDs (especially with long-term therapy), thus resulting in upper-GI adverse events, such as perforation, ulceration, and bleeding in up to 4% of patients per year, and up to 20% of those taking long-term NSAID medications. Furthermore, up to 4% of NSAID users develop GI complications serious enough to require hospitalization, thus discouraging clinicians from prescribing nonselective NSAIDs in patients who are at an increased risk of developing serious GI adverse events.[7,8]

COX-2 SELECTIVE INHIBITORS

A new class of NSAIDs, the COX-2 selective inhibitors (CSIs or Coxibs), were developed and approved in 1999 by the US Food and Drug Administration (FDA) with the aim of reducing the GI adverse effects of NSAIDs, deriving from the inhibition of COX-1. The specific roles and localizations of the 2 COX isoforms may explain the GI safety advantages of CSIs and their selective inhibition of the biosynthesis of inflammatory mediators, as shown in Fig 1.

The aim of this article is to review and critically discuss data selected from well-designed studies of the analgesic efficacy and clinical safety of CSIs in the treatment of acute, post–oral surgery pain, and to describe a cost-benefit ratio for the use of these drugs in oral-maxillofacial surgery.

METHODS

Search strategy

Relevant drug and clinical studies of the use of CSIs in the treatment of acute, post–oral surgery pain were retrieved on MEDLINE/Pubmed, from peer-reviewed journals in medicine and dentistry. Hand-searching included several dental journals and bibliographies of relevant studies. Data of tolerability of CSIs were searched on the FDA Web site. The last electronic search was conducted in April 2003.

Selection criteria

Relevant randomized, controlled clinical trials of the use of CSIs in the management of acute pain were selected by authors through a quality assessment of the study-design and conduct, according to the CONSORT guidelines (Consolidated Standard of Reporting Trials; http://www.consort-statement.org/).

Table I. Pharmacological and clinical properties of COX-2-selective inhibitors

Drug	*Brand names*	*Dosage for moderate to severe post oral surgery acute pain*	*Route of admin.*	*Adverse events*
Celecoxib[47]	Celebrex, Solexa, Artilog	100 or 200 mg up to 3 times a day	Oral	Nausea, headache, somnolence, vomiting, dizziness, dyspepsia
Rofecoxib[55]	Vioxx, Coxxil, Arofexx	50 mg/day loading dose, followed by 25 or 50 mg once daily	Oral	Diarrhea, headache, nausea, upper respiratory tract infection
Valdecoxib[32]	Bextra	40 mg/day	Oral	Nausea, abdominal pain, headache, abdominal fullness, dizziness, vomiting
Parecoxib[34]	Dynastat, Rayzon, Xapit	20-40 mg/day	Intravenous or intramuscular	

No additional statistical analysis has been applied to data retrieved.

CLINICAL EXPERIENCES IN RELIEVING POST–ORAL SURGERY PAIN

Data of efficacy and tolerability of CSIs as analgesic medications in the treatment of post–oral surgery pain have been retrieved from clinical trials in which CSIs are compared to traditional NSAIDs or placebo. Most of the studies included are based on the postoperative dental impaction pain model, which is an accepted, sensitive, and validated model for assessing the efficacy of new analgesic drugs in humans.[9-11]

CSIs include celecoxib (Celebrex, Solexa, Artilog) and rofecoxib (Vioxx, Coxxil, Arofexx), which are both currently available in the United States and Europe, and second-generation agents, such as valdecoxib (Bextra), parecoxib (Dynasta, Rayzon, Xapit), etoricoxib (Arcoxia), and lumiracoxib (Prexige), which still are under investigation. Pharmacological and clinical properties of CSIs used in the treatment of acute pain are shown in Table I.

Celecoxib and rofecoxib

Celecoxib (the first Coxib developed) and rofecoxib have been licensed by the FDA for the management of inflammatory chronic pain of osteoarthritis, rheumatoid arthritis, and acute pain of primary dysmenorrhea. A number of trials of high quality have been performed in adults for the treatment of moderate to severe postoperative dental pain.[12]

In studies of postoperative dental pain, a single dose of celecoxib (200 mg) provided analgesic efficacy similar to that of aspirin (650 mg), and inferior to those of ibuprofen (400 mg) and naproxen (550 mg), as measured by time to onset of pain relief and peak pain relief; even at doses up to 400 mg, celecoxib was still inferior to naproxen (550 mg).[13-16] Five studies of postoperative dental pain compared the analgesic efficacy of single doses of rofecoxib, celecoxib, ibuprofen, and naproxen.[17-21] Those results demonstrated that rofecoxib (50 mg) was superior to celecoxib (200 mg) and similar to ibuprofen (400 mg) and naproxen (550 mg), as measured by total pain relief at 8 hours (TOPAR8) and time to onset of pain relief; the duration of analgesia provided by a single dose of rofecoxib (>24 hours) was longer than that provided by celecoxib (~5 hours) or ibuprofen (~9 hours). In one study of postoperative dental pain, a single dose of rofecoxib (50 mg) was superior to 3 doses of enteric-coated diclofenac (50 mg every 8 hours), as measured by TOPAR24 (assessment at 24 hours).[22] In a study of moderate to severe postoperative dental pain, the analgesic efficacy of rofecoxib (50 mg) was greater than that of a fixed formulation of codeine (60 mg)/acetaminophen (paracetamol) (600 mg), as measured by TOPAR6.[23] Findings from 6 placebo-controlled studies evaluating the single-dose analgesic efficacy of rofecoxib in the treatment of post–oral surgery pain support the recommended dose regimen of 50 mg of rofecoxib once daily, as compared to maximal analgesic daily-doses of naproxen (550 mg every 12 hours) and ibuprofen (400 mg every 4-6 hours).[24] Rofecoxib was recently approved in Europe for the treatment of acute pain (on PubMed: MMW Fortschr Med 2002 Mar 7;144(10):62 [no authors listed]).

Research has demonstrated that administering NSAIDs preoperatively can significantly reduce the intensity and duration of postoperative pain for up to 8 hours.[25] Since rofecoxib has been demonstrated to enter the central nervous system, where it may inhibit the constitutive COX-2 enzyme,[26] this drug is now under investigation in a phase II trial of preemptive analgesia for the treatment of postoperative dental pain (extraction of impacted third molars), with the aim of inhibiting the development of central and peripheral sensi-

Table II. COX-2/COX-1 ratios of Coxibs and traditional NSAIDs*

Coxibs	*COX-2/COX-1 ratio*
Lumiracoxib[39]	700
Etoricoxib[38]	106
Rofecoxib[55]	35
Valdecoxib[32]	30
Parecoxib[34]	30
Celecoxib[47]	7
NSAIDs[28,29]	
Meloxicam	4
Aspirin	3.12
Indomethacin	1.78
Ibuprofen	1.78
Naproxen	0.88
Ketorolac	0.68

*A ratio of >1 indicates a greater inhibition of COX-2 than COX-1.

tization to pain rising after a tissue injury and manifesting later as hyperalgesia.[27]

Second-generation CSIs

Second-generation CSIs are characterized by an improved COX-2/COX-1-selectivity ratio, compared with rofecoxib and celecoxib (Table II).[28,29]

Valdecoxib. In one trial of postoperative dental pain, a single oral dose of valdecoxib (40 mg) was superior to rofecoxib (50 mg) with respect to the onset of pain relief, duration of analgesia, and percentage of patients requiring rescue medication.[30] In a similar study, valdecoxib (40 mg) showed an overall analgesic efficacy similar to that of a fixed formulation of oxycodone (10 mg)/acetaminophen (paracetamol) (1000 mg); valdecoxib was better tolerated and resulted in a duration of analgesia significantly longer than that of oxycodone/acetaminophen.[31] In a meta-analysis of 8 randomized, controlled trials, the safety profile of valdecoxib was better than that of traditional NSAIDs, as displayed by a reduced incidence of adverse events.[32] Valdecoxib has been shown to be effective in a study of preemptive analgesia for the treatment of post–oral surgery pain, thus demonstrating an inhibitory action of the constitutive COX-2 enzyme of the central nervous system.[33]

Parecoxib. Parecoxib is the prodrug of valdecoxib and is the only Coxib available for intravenous or intramuscular injection. In trials of acute pain after orthopedic or oral surgery, parecoxib (20-40 mg) showed similar analgesic efficacy to that of ketorolac (30-60 mg), and superior efficacy to that of morphine (4 mg).[34,35] When administered preoperatively, parecoxib (40 mg) has been demonstrated to be an effective analgesic agent compared with placebo.[36] In cases of postoperative nausea and vomiting, or where the oral route for administration is inaccessible (eg, after oral-maxillofacial surgery), parecoxib may be an option to the few parenteral NSAIDs (eg, ketorolac [Toradol]) available for the treatment of moderate to severe postoperative pain.

Etoricoxib. Etoricoxib has a higher COX-2/COX-1 selectivity ratio than those of celecoxib, rofecoxib, valdecoxib, and parecoxib (Table I).[37] In 2 studies of postoperative dental pain, etoricoxib showed analgesic efficacy (TOPAR8) similar to naproxen or ibuprofen, with duration of analgesic effect longer than that of comparative NSAIDs, and displayed higher analgesic efficacy (TOPAR8) than the combination codeine/acetaminophen.[38] Etoricoxib has been related to fewer upper-GI complications than comparative NSAIDs.[38]

Lumiracoxib. COX-189 is the last molecule of the CSIs family, characterized by the highest COX-2/COX-1 selectivity ratio (Table I). It is still under investigation, but in one study of dental pain, it has already shown analgesic efficacy superior to that of ibuprofen.[39]

CLINICAL SAFETY AND IMPLICATIONS OF CSIs

Although NSAIDs can achieve high concentrations in inflamed tissues, which accounts for their anti-inflammatory and analgesic efficacy, they also can reach high concentrations in the stomach wall, kidney cortex, and blood, resulting in the well-known GI, renal, and platelet side effects.[40] Like traditional NSAIDs, CSIs distribute homogeneously throughout the body, which is a cause for concern since COX-2 has been found to be constitutive in the brain, female reproductive system, kidneys, and bone. Apart from the safety profile of CSIs dealing with the upper-GI tract and kidneys, dentists, including oral-maxillofacial surgeons, should be aware of the potential implications of these drugs on the hemostatic function and physiology of bone fracture and wound healing.

CSIs and the upper-GI tract

GI side-effects of NSAIDs range from nausea and dyspepsia to gastroduodenal ulcers, to potentially fatal complications, such as bleeding and perforation. Four large studies of CSIs, the VIGOR trial (Vioxx), the CLASS trial (Celecoxib), the ADVANTAGE trial (Vioxx and Naproxen), and the SUCCESS trial (Celecoxib), examined the GI safety profile of rofecoxib and celecoxib in more than 39,000 patients with chronic pain (osteoarthritis and rheumatoid arthritis) in different patient populations with an age range of 18-95 years.[41] Results of these studies show that patients taking rofecoxib or celecoxib had significantly lower

rates of gastroduodenal ulcers than those taking a traditional NSAIDs (naproxen, ibuprofen, or diclofenac).

CSIs and kidneys

Since both COX-isoforms are constitutively expressed in the human kidney, CSIs have a renal safety similar to that of traditional NSAIDs. In the renal cortex, COX-2 enzyme increases in response to a high-salt diet and water deprivation, therefore a high degree of COX-2 inhibition can alter renal blood flow, urine formation, and salt and water homeostasis, thus leading to hypertension.[42] Data from the FDA's Adverse Event Reporting System (AERS) database indicate that the renal tolerability of CSIs in patients with normal or impaired renal function is similar to that of traditional NSAIDs, even after short-term therapy.[43,44] Patients at risk for severe renal adverse events with CSIs are those with preexisting renal impairment, heart failure, liver dysfunction, those taking diuretics and/or ACE inhibitors, and the elderly.[42]

CSIs and the hemostatic/trombotic balance

Aspirin has an irreversible inhibitory effect on platelet function that persists until new platelets are produced. Traditional NSAIDs reversibly inhibit platelet aggregation and prolong bleeding time (by decreasing the platelet production of thromboxane), thus leading to an increased risk of perioperative bleeding.[45] Rofecoxib and valdecoxib do not impair platelet aggregation, and rofecoxib does not alter the antiplatelet effect of aspirin.[46-48] These findings suggest that CSIs may be given more safely than traditional NSAIDs in perioperative settings and in patients who take concomitant low-dose aspirin for the prevention of cardiovascular events. Although CSIs have not been shown to inhibit platelets, they do inhibit the production of prostacyclin (PGI2) (Fig 1), a vasodilator and inhibitor of platelet aggregation. The clinical consequence of inhibiting PGI2 does not lead to spontaneous thrombosis but may increase response to thrombotic stimuli. Therefore, it has been hypothesized that a high degree of COX-2 inhibition could be prothrombotic.[49] However, at present, there is no evidence that CSIs increase the risk of myocardial infarction.[50]

CSIs and bone

Nonselective NSAIDs, such as indomethacin, seem to delay but not stop fracture healing in experimental animal models.[51] In an experimental animal study investigating the role of COX-2 inhibitors in bone fracture healing, both rofecoxib and celecoxib stopped the normal fracture healing and induced the formation of incomplete unions, thus suggesting that COX-2 activity is required for a normal endochondral ossification during fracture healing.[3] The total amount of rofecoxib used to treat the rats (200 mg/70 kg) was approximately 4 times the maximum daily dose of 50 mg that is recommended to manage acute pain in humans, whereas the celecoxib dose used (280 mg/70 kg) was in the recommended daily dose range of this drug for humans (200 mg twice a day).

CSIs and wound healing

A clinical concern of the use of NSAIDs in surgical settings is their theoretical effect in modifying the inflammatory response in wound healing. Only anecdotal case reports describe impaired postoperative wound healing in patients receiving perioperative NSAIDs.[52] Studies of animal models are conflicting.[53,54] Controlled studies evaluating wound healing in humans receiving CSIs as analgesic anti-inflammatory medications have not yet been published.

Drug interactions with CSIs

Like nonselective NSAIDs, CSIs are metabolized in the liver: rofecoxib by reduction by cytosolic enzymes and celecoxib by the cytochrome P450 enzyme system. Since rofecoxib does not alter the metabolism of drugs metabolized via the P450 isozymes, it would have fewer potential drug interactions than celecoxib.[55,56] Because of its lack of cross-reactivity in aspirin-sensitive patients, rofecoxib may be given safely in patients allergic to aspirin.[57] A number of interactions of CSIs with oral anticoagulants leading to an increased risk of hemorrhage have been documented.[58]

COST/BENEFIT RATIO

Since a number of clinical trials have demonstrated that CSIs have analgesic efficacy similar to that of traditional NSAIDs, the clinical advantage of these drugs is founded primarily on their lack of significant GI side-effects. Even if the costs of currently available CSIs, rofecoxib and celecoxib, are considerably higher than generic and over-the-counter NSAIDs, pharmacoeconomic analysis suggests that the use of CSIs may be cost-saving. Indeed, because of their reduced GI complications compared with NSAIDs, CSIs should lower indirect costs of diagnostic and therapeutic procedures required for managing possible GI disability (resulting from long-term NSAID therapy).[59] Patients of the VIGOR trial treated with rofecoxib required fewer upper-GI diagnostic procedures (biopses or endoscopy) and comedications (antacids, histamine 2-receptor antagonists, proton pump inhibitors, sucralfate, or prostaglandins) and fewer hospitalizations than those treated with naproxen.[60] These findings suggest that for individuals who are at an increased risk of developing serious GI adverse events attributable to NSAIDs, CSIs

are a cost-effective treatment option and have the potential to result in savings to health care resources and improve the quality of life of patients undergoing chronic analgesic and anti-inflammatory medications.[61] Neverthless, the short-term use of CSIs needed for the treatment of acute post–oral surgery pain is unlikely to result in a significantly better patient tolerance and a cost-savings advantage than that seen with traditional NSAIDs.

CONCLUSIONS

The ideal CSI would demonstrate efficacy comparable or superior to that of the best NSAID and would be less gastrotoxic than the safest traditional NSAID; in addition, it would have no effect on the hemostatic function and limited or no cardiovascular or renal toxicity.[40]

There is reasonable evidence that CSIs available for prescribing (celecoxib and rofecoxib) display analgesic efficacy similar to that of traditional NSAIDs (eg, ibuprofen or naproxen) in the treatment of acute, post–oral surgery pain. These new drugs are preferable in patients who are at an increased risk of developing serious upper-GI complications (with long-term medications), in patients who take aspirin for cardiovascular comorbid conditions, and in those allergic to aspirin, as confirmed by the Australian COX-2-Specific Inhibitor Prescribing Group, which recently aimed to develop evidence-based clinical practice guidelines.[62] Furthermore, CSIs may be given more safely than NSAIDs in perioperative settings, because of their lack of impairment of the platelet aggregation. At present, the limited number of well-designed clinical trials available on the second-generation agents do not carry strong evidence of superior analgesic efficacy from that of nonselective NSAIDs. Nevertheless, taken together, the trials provide evidence that the second-generation CSIs are more efficacious than traditional NSAIDs in the short-term management of acute, postoperative pain; however, the tolerability profile of these newest molecules is still to be fully investigated, both in long- and short-term use. Although it appears that CSIs would be preferable to conventional NSAIDs for dental pain control, because they are expected to produce fewer GI adverse events, oral-maxillofacial surgeons and other dentists must consider the length of time patients are treated with analgesic drugs, which in most cases amounts to 2 to 4 days after a surgical procedure. It is reasonable to state that in this short period, the risk of developing serious upper-GI complications with nonselective NSAIDs is low. Therefore, CSIs would be more appropriate for patients with chronic pain who require long-term medication, such as cases of painful temporomandibular joint disorders and chronic orofacial pain (a phase II clinical trial using celecoxib is ongoing[63]). Although the clinical utility of CSIs is evident because of their analgesic efficacy and relative GI safety advantage, their high price, at present, limits their routine use in most oral surgery settings. Further studies are needed to determine the cost-benefit ratio of using CSIs for the management of acute, postoperative dental pain.

To summarize, there are some important advantages and disadvantages to consider before prescribing a CSI to patients undergoing oral-maxillofacial surgery: (1) CSIs are equivalent to traditional NSAIDs (eg, ibuprofen or naproxen) as analgesic agents in the short-term treatment of acute, postoperative dental pain; (2) CSIs display a longer duration of analgesic effect than aspirin, acetaminophen, and ibuprofen; (3) CSIs are associated with reduced incidence of upper-GI complications, especially bleeding (with long-term administration); (4) CSIs do not inhibit platelet aggregation, but could adversely affect the hemostatic balance and favor thrombosis, thus the cardiovascular safety of CSIs remains subject to debate; (5) CSIs have similar effects to NSAIDs on renal function and blood pressure (risk of developing hypertension).

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