
Analgesia and COX-2 inhibition

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ABSTRACT

While non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy for the management of acute pain and rheumatoid arthritis, toxicity associated with chronic administration limits their benefit-to-risk relationship in many patients.

A series of studies is reviewed that assesses the relationship between cytokines released at the site of tissue injury and NSAID analgesia, and the in vivo selectivity of a selective cyclooxygenase (COX)-2 inhibitor (celecoxib) in comparison to a dual COX-1/COX-2 inhibitor (ketorolac). Three replicate studies in the oral surgery model of acute pain used submucosal microdialysis sample collection for the measurement of prostaglandin E₂ (PGE₂; a product of both COX-1 and COX-2) and thromboxane B₂ (as a biomarker for COX-1 activity) with parallel assessments of pain.

The time course of PGE₂ production was consistent with early release due to COX-1 activity followed by increased production 2-3 hours after surgery, consistent with COX-2 expression. Ketorolac 30 mg at pain onset suppressed both pain and peripheral PGE₂ levels. Ketorolac 1 mg either at the site of injury or intramuscularly also produced analgesia but without any effect on peripheral PGE₂ levels. Celecoxib selectively suppressed PGE₂ but not TxB₂ at time points consistent with COX-2 activity, while producing analgesia.

These studies demonstrate the ability to assess the time course and selective effects of COX-2 inhibitors in vivo and suggest that suppression of COX-2 mediated PGE₂ is temporally related to NSAID analgesia.

Introduction

Pain not only signals tissue injury but also acts as an impediment to most clinical procedures, delays the resumption of normal activities after surgical

procedures and may contribute to the development of plastic changes within the central nervous system that contribute to pain chronicity. Acute 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 more often in ambulatory patients than in non-ambulatory hospitalized patients. In addition, inadequate pain control during the immediate postoperative period may contribute to the development of hyperalgesia (1), leading to greater pain later during recovery. These considerations indicate that optimal analgesic therapy should be efficacious, with a minimal incidence of side effects and, ideally, should lessen the prospects for development of chronic pain.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy for the management of acute pain and rheumatoid arthritis. They have also been evaluated for a wide variety of chronic pain conditions and to minimize inflammation after surgery. Gastrointestinal toxicity associated with chronic NSAID administration is well documented and is estimated to result in more than 100,000 hospitalizations and 16,000 deaths per year in the US alone (2), suggesting the need to weigh carefully the benefit-to-risk relationship for each therapeutic indication. The new generation of selective cyclooxygenase (COX)-2 inhibitors promises to achieve the therapeutic effects of traditional NSAIDs without the toxic gastrointestinal effects associated with traditional dual COX-1/COX-2 inhibitors (3, 4). Their renal safety and possible interactions with adjuvant therapies, such as low-dose aspirin, needs to be further elucidated (5).

Knowledge of the clinical pharmacology of NSAID drugs is largely based on studies performed in the oral surgery model (6). Ibuprofen, the prototype of

the NSAID class, has demonstrated analgesic activity over a dose range from 200 to 800 mg with a duration of activity of 4-6 hours (7). Given before pain onset, it suppresses the onset of pain and lessens its severity (8, 9). Ibuprofen suppresses swelling over the initial 2-3 day postoperative course, when edema associated with the inflammatory process is most prominent. Interactions with the release of β -endorphin have been demonstrated both intraoperatively during surgical stress and during postoperative pain, suggesting that NSAIDs can modify the neurohumoral responses to pain (10, 11). The wealth of data from clinical trials using NSAIDs (12) supports these generalizations and makes NSAIDs one of the most well-studied drug classes for acute inflammatory pain in ambulatory patients.

Role of COX in acute pain

Acute pain and the inflammatory process are modulated in response to tissue injury by locally released mediators acting synergistically to produce plasma extravasation and sensitization of peripheral nociceptors. Inflammatory mediators also act locally to sensitize peripheral nerve endings, resulting in hyperalgesia. The essential role of prostaglandins (PG) derived from COX during acute inflammation is supported by elevated PG levels and hyperalgesia in carrageenan-inflamed rat paws, both of which are rapidly reversed by dosing with ketorolac, the COX-2 selective inhibitor celecoxib, and within 2-3 hours after administration of an antibody against prostaglandin E₂ (PGE₂) (13). These data suggest that maintenance of a hyperalgesic state after tissue injury requires continuous production of PGE₂ by COX-2. The complex biochemical interactions of short-lived inflammatory mediators after tissue injury, combined with the neural release of substance P and the process of plasma extravasation, result in a positive feedback loop continually refueling the inflammatory process. The continued synthesis or release of these mediators explains the prolonged duration of inflammation, which far exceeds the initial stimulation.

Tissue injury and ischemia act on vascular endothelium to release arachidonic acid from phospholipid stores which are acted upon by COX and other enzymes of the prostanoid pathway, resulting in the local formation of one or two major products, depending on the enzymes that are constitutively present. PGE₂ is the predominant eicosanoid released from endothelial cells of small blood vessels (14), producing vasodilatation (15) and hyperalgesia (16). Thromboxane A₂ (TxA₂) is the predominant eicosanoid product of platelets (17) - producing platelet aggregation (18) and vasoconstriction (18) - and of monocytes, which participate in the cellular response to inflammation.

Oral surgery as a model for evaluating COX-2 inhibitors *in vivo*

Third molar extraction is a useful and reproducible model for acute pain, widely used in analgesic research. Adapting microdialysis to the oral surgery model of acute pain has facilitated examination of the relationship between inflammatory mediators and clinical pain. The use of microdialysis in a well-characterized model of acute pain and inflammation permits concurrent assessment of analgesic activity, surrogate endpoints for COX-1 and COX-2 activity, and other measures of inflammation, such as edema. The experimental design and postoperative observations can be controlled up to 48 hours so that the development of hyperalgesia later, investigational strategies for preventive analgesia and the side effect liabilities of multiple doses can also be assessed. Bilateral extractions permit measurement of more than one inflammatory mediator in the same patient. Crossover designs can be used to minimize the influence of comparisons between groups and to enhance assay sensitivity.

Hargreaves and colleagues demonstrated the presence of bradykinin in perfusate collected by microdialysis after third molar extraction and its suppression by both glucocorticoids (19) and the NSAID flurbiprofen (20). More recently, they have reported that pretreatment with flurbiprofen suppresses PG levels in comparison to placebo

with concomitant pain suppression (21). Although these studies have shown suppression of synthesis of inflammatory mediators when given before tissue injury, the dynamic relationship between prostanoid release and the development of acute pain and subsequent suppression of inflammatory mediators in relation to clinical analgesia has not been described.

The oral surgery model with submucosally implanted microdialysis probes was used to evaluate the *in vivo* selectivity of COX-2 inhibitors. A series of three studies evaluated the time course of the peripheral release of the inflammatory mediators, PGE₂ and TxA₂, their temporal relationship to clinical pain and NSAID analgesia, and the *in vivo* selectivity of the selective COX-2 inhibitor celecoxib. PGE₂ levels are interpreted as indicative of both constitutive COX-1 and inducible COX-2 activity. Thromboxane B₂ (TxB₂) is measured as a stable marker for TxA₂ produced by COX-1.

Synopsis of experimental design and methods

Subjects were dental outpatients undergoing the surgical removal of impacted mandibular third molars with intravenous midazolam and 2% lidocaine (with epinephrine 1:100,000). After each extraction, we placed a microdialysis along the buccal aspect of the mandible, beneath the mucogingival flap that is elevated for the surgical procedure. We secured the probe and polyethylene tubing (PE 50) to an adjacent tooth and closed the flap in the usual fashion. Sterile lactated Ringer's solution was pumped at 10 μ L per minute and samples collected at 15-30 minute intervals after completion of surgery but before pain onset. At the end of each sample collection interval, patients provided pain ratings using a 100 mm visual analog scale and a four-point category scale; they also reported signs of inferior alveolar nerve anesthesia ("numb", "tingling" or "normal") and any adverse effects.

In the first study (22), a single impacted third molar was removed and samples collected every 30 minutes with concurrent reports of pain and anesthesia

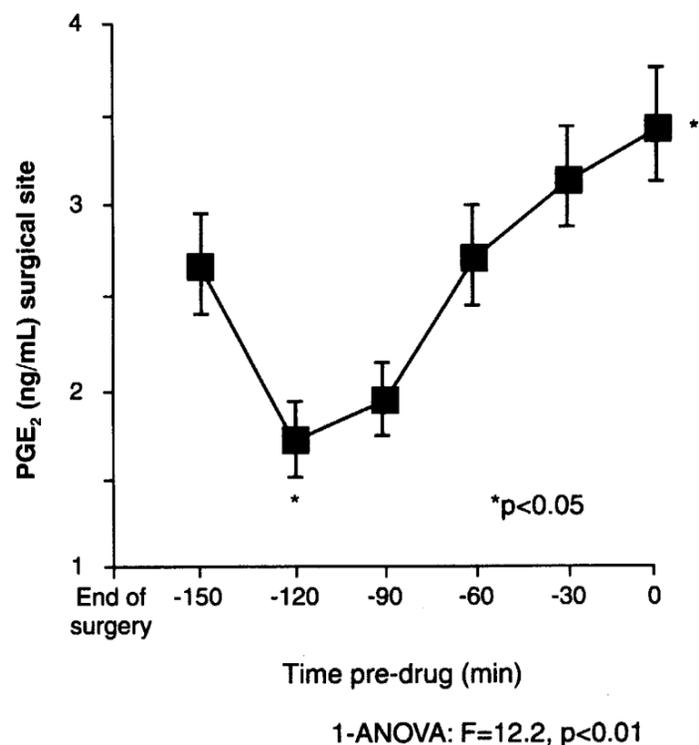


Fig. 1. Time course of immunoreactive prostaglandin E₂ (i.r. PGE₂) collected by microdialysis at the surgical site from the end of surgery to the onset of postoperative pain with local anesthetic offset (time 0).

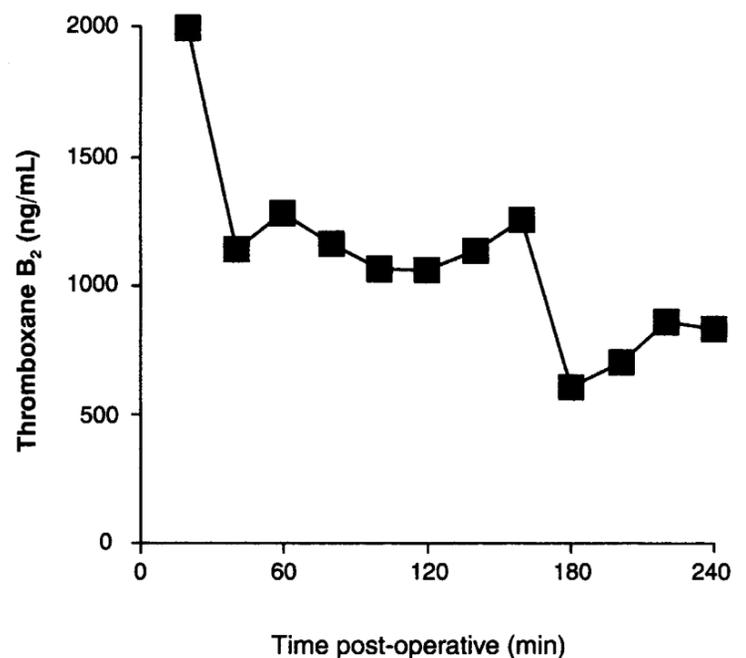


Fig. 2. Time course of immunoreactive thromboxane B₂ collected by microdialysis at the surgical site over the first 240 min following oral surgery.

of the inferior alveolar nerve. At the report of moderate pain, usually consistent with loss of the subjective signs of anesthesia, subjects received one of the four interventions by intramuscular or submucosal administration and remained in the clinic for an additional 180 minutes for continued sample collection and pain assessment every 15 minutes.

In the second study (23), both lower third molars were removed and microdialysis probes placed bilaterally; samples were collected every 20 minutes with concurrent monitoring for the loss of anesthesia and the onset of postoperative pain. Dexamethasone or placebo was administered 12 hours and 1 hour before surgery with postoperative intravenous administration of ketorolac at the onset of moderate pain. We collected microdialysis samples for an additional 180 minutes at 15 minute intervals with concurrent pain scales at 5, 10, 15, 20, 25 and 30 minutes and every 15 minutes thereafter.

The third study (24) evaluated the *in vivo* selectivity of a selective COX-2 inhibitor in subjects administered with either celecoxib 200 mg, ibuprofen 600 mg or placebo 8 hours before surgery and a second dose 1 hour before surgery. Samples were collected in vials that were changed every 20 minutes, with concurrent measurement of pain for up to 4 hours postoperatively.

Time course of prostanoid levels after tissue injury

PGE₂ was detectable in the initial postoperative samples, decreased in samples collected over the next hour and then significantly increased over time coincident with pain report (Fig. 1). TxB₂ was also detectable in the initial samples collected after surgery in the placebo group but did not change over time or with the onset of postoperative pain (Fig. 2). The time course of PGE₂ and TxB₂ observed following tissue injury is suggestive of COX-1 activity immediately after injury, with additional PGE₂ production due to induction of COX-2 coincident with pain onset.

Effect of ketorolac on pain and PGE₂ levels at the site of injury

Intramuscular administration of ketorolac 30 mg resulted in a significant analgesic effect by the first observation 15 minutes afterwards; this reached near-maximum levels by 60 minutes. PGE₂ levels in the microdialysate decreased more gradually, reaching significantly lower levels in the ketorolac group in comparison to placebo by 60 minutes (Fig. 3). Administration of ketorolac 1 mg, both at the extraction site or intramuscularly, resulted in a slower onset of action than intramuscular ketorolac 30 mg, but produced significant pain relief in comparison to

placebo by the 45 and 60 minute observations. Parallel assessment of PGE₂ levels in the dialysate did not demonstrate any changes from the initial sample at pain onset over the 60 minutes after drug administration. These data show that administration of the dual COX-1/COX-2 inhibitor ketorolac at a therapeutic dose results in analgesia and reduces peripheral PGE₂ levels at the site of injury. Administration of low-dose ketorolac results in analgesia without effects on peripheral levels of PGE₂ or TxB₂, suggestive of an action at another site. These observations in a sensitive clinical model of acute pain are supportive of both a peripheral and a central site of NSAID analgesia.

Effect of dexamethasone pretreatment on pain and prostanoid levels

Administration of dexamethasone 12 hours and 1 hour before surgery does not attenuate the time to onset of postoperative pain in comparison to placebo pretreatment or its severity when patients request postoperative medication as the local anesthetic dissipates. PGE₂ levels in the microdialysate were comparable between dexamethasone pretreatment and placebo over the first 60 minutes from the end of surgery, but were significantly lower in the dexamethasone pretreatment group over the last 3 observations coincident with pain onset (Fig. 4, upper panel). TxB₂

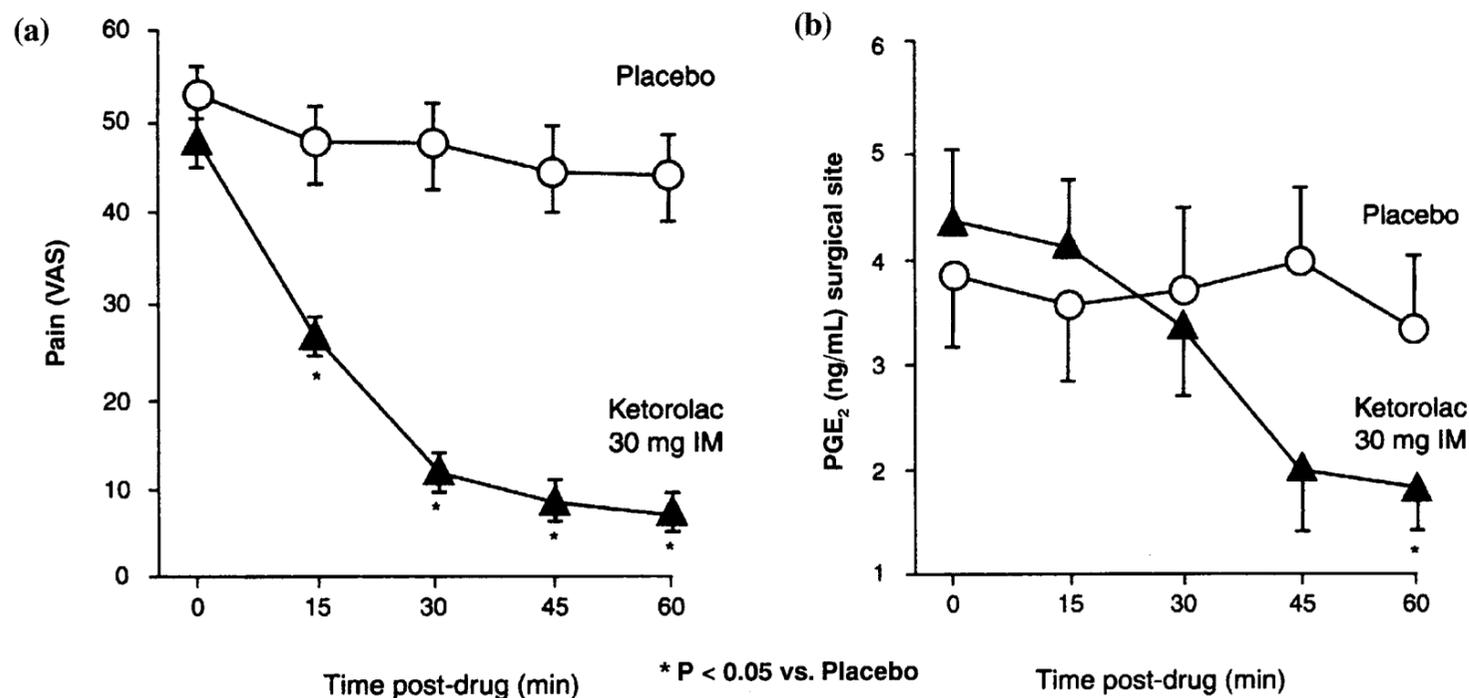


Fig. 3. Comparison of the (a) analgesic effect and (b) levels of immunoreactive prostaglandin E₂ (i.r. PGE₂) levels collected by microdialysis at the surgical site. The analgesic effect was detected at 15 min post-drug but did not result in detectable changes in peripheral PGE₂ levels until the sample collected from 45 to 60 min. *p < 0.05 vs placebo.

levels, by contrast, were significantly suppressed in all samples collected from the end of surgery to pain onset (Fig. 4, lower panel). The failure of dexamethasone to suppress PGE₂ levels at the early time points, presumably regulated by COX-1 activity and suppression of PGE₂ levels at later time points, is consistent with *in vitro* COX-2 selectivity in some tissues. Suppression of TxB₂ as a surrogate endpoint for COX-1 activity, at all time points, is inconsistent with this hypothesis. Subjects randomly received either intravenous ketorolac 30 mg or placebo at pain onset based on the factorial design to result in four sub-groups: dexamethasone preoperatively, ketorolac at pain onset, both dexamethasone preoperatively and ketorolac at pain onset, or placebo. Ketorolac resulted in a significant, near-maximal analgesia

over time with mean levels by 60 minutes post-drug, equivalent to "slight" pain on the category scale. No additive analgesic effect was detectable for the combination of dexamethasone and ketorolac in comparison to ketorolac alone. In addition, dexamethasone pretreatment did not have any effect on pain reported after the loss of anesthesia in comparison to placebo. PGE₂ levels in the microdialysate were significantly decreased from levels at pain onset by ketorolac in comparison to placebo over the first 60 minutes post-drug, and eventually also decreased in the placebo groups after 60 minutes as patients requested rescue analgesic. Thromboxane levels were also decreased at the extraction site over the first 60 minutes by ketorolac in comparison to placebo, and decreased eventually in the placebo groups after

60 minutes and administration of rescue analgesic. The effects of ketorolac on both PGE₂ and TxB₂ levels are consistent with its dual COX-1/COX-2 inhibitory effects but do not rule out additional effects at other sites in the central nervous system.

Selectivity *in vivo* of the COX-2 inhibitor celecoxib

Both celecoxib and ibuprofen had a significant analgesic effect compared with placebo. Pain intensity in the placebo group, as measured by both category and visual analog scale, increased to reach a mean value equivalent to "moderate" about 160 minutes after surgery. Analysis of the area under the curve revealed that the time-action and peak analgesic effect of celecoxib was about half that of ibuprofen. Administration of ibuprofen suppressed PGE₂ levels

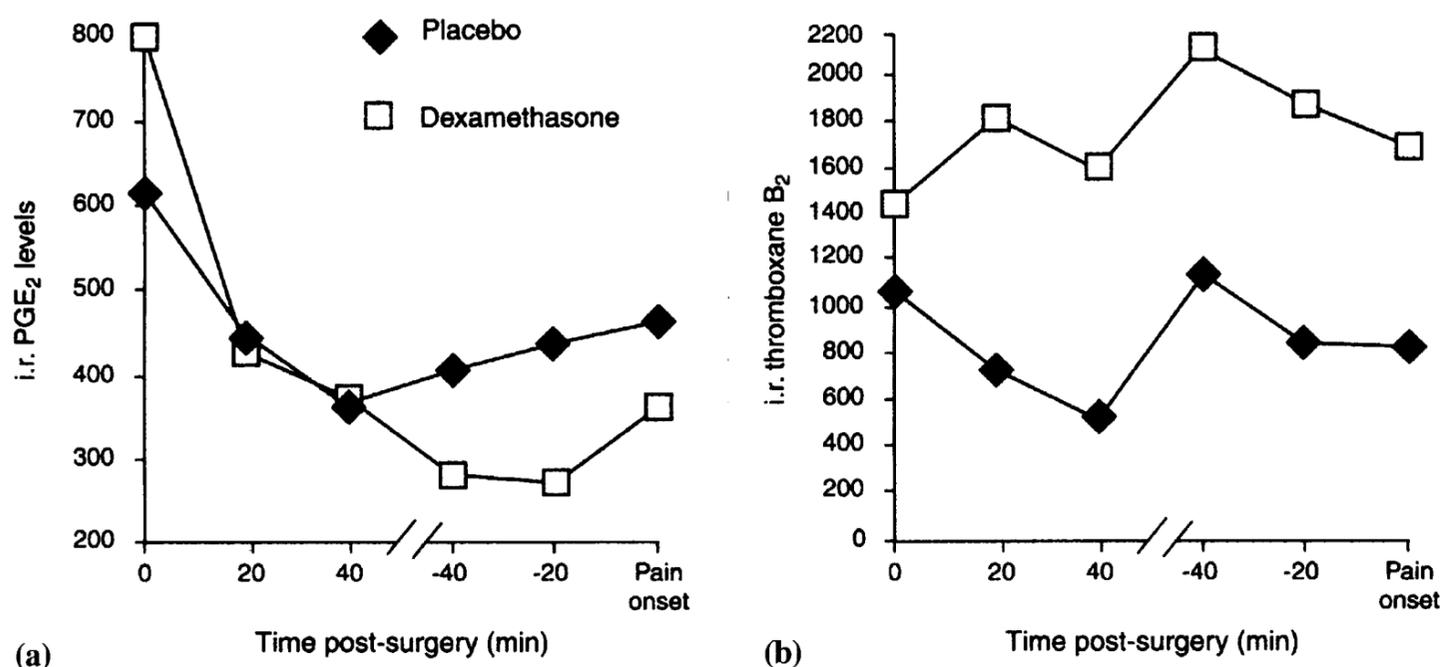


Fig. 4. Comparison of the effects of dexamethasone on (a) immunoreactive prostaglandin E₂ (i.r. PGE₂) levels and (b) immunoreactive thromboxane B₂ levels in the first three samples collected postoperatively and prior to pain onset. No significant effect was seen for i.r. PGE₂ levels but levels of thromboxane were significantly suppressed over the entire postoperative period in the dexamethasone group.

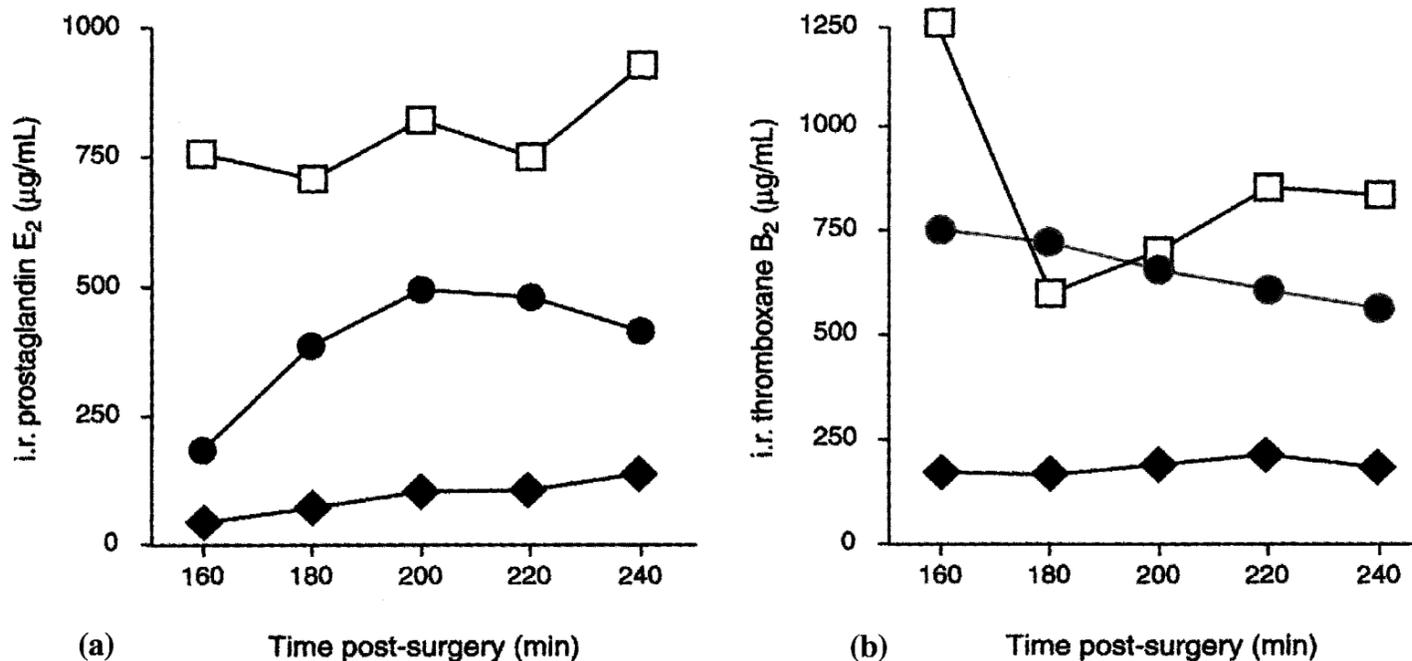


Figure 5. Comparison of (a) immunoreactive prostaglandin E₂ (i.r. PGE₂) levels and (b) immunoreactive thromboxane B₂ levels collected by microdialysis at the surgical site following the loss of local anesthesia at a mean time of 150 min post-surgery. Ibuprofen resulted in a significant suppression of both cytokines over this time course, while celecoxib only resulted in a significant suppression of PGE₂. □ placebo; ● celecoxib; ◆ ibuprofen.

consistently. Administration of celecoxib suppressed PGE₂ levels at later time points but had no effect on PGE₂ levels at the earlier time points (Fig. 5). Administration of ibuprofen consistently suppressed TxB₂ after surgery. The effect of celecoxib on TxB₂ levels did not differ from placebo (Fig. 5). These results indicate that celecoxib has a COX-1 sparing effect *in vivo* and suggest that *in vitro* and *ex vivo* analyses are reliable predictors of *in vivo* selectivity (see Patrono and FitzGerald, this volume).

Selective COX-2 inhibitors

Single doses of celecoxib have been shown in the oral surgery model of acute pain to be superior to placebo (at all doses reported in published abstracts) comparable to aspirin 650 mg but generally less effective than standard doses of naproxen (25). In multiple-dose studies conducted in patients after orthopedic and general surgery, celecoxib's analgesic efficacy is inconclusive. As celecoxib failed to satisfy the criterion of demonstrating analgesic efficacy in at least two different pain models, it did not receive approval in the USA for the management of acute pain. Celecoxib is more effective than placebo for the treatment of osteoarthritis and was approved and marketed for that indication.

Rofecoxib appears to have greater analgesic efficacy than celecoxib based on the results of studies in the oral surgery model and patients with painful dysmenorrhea (26-29). Rofecoxib 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 as well as the two-stopwatch method for estimating analgesic onset. The total pain relief and sum of the pain intensity difference score over 8 hours after a single dose of rofecoxib 50 mg was superior to placebo but not distinguishable from ibuprofen 400 mg (26), arguably the maximal ibuprofen dose for acute pain. The median time to onset of pain relief was indistinguishable for rofecoxib (0.7 hours) and ibuprofen (0.8 hours), but significantly fewer subjects in the rofecoxib group needed additional analgesic within 24 hours of the study drug than in the placebo or ibuprofen groups. In a second study comparing rofecoxib in doses of 12.5, 25 and 50 mg with naproxen 550 mg and placebo, a clear dose-response relationship was demonstrated for analgesia (27). The 25 and 50 mg doses of rofecoxib were numerically superior but statistically indistinguishable from naproxen for both pain relief and pain intensity difference. In both studies, the incidence of clinical and laboratory adverse experiences was similar.

Rofecoxib's analgesic efficacy was also evaluated in replicate studies for primary dysmenorrhea, generally accepted as a sensitive model of acute pain. Subjects with a self-reported history of moderate to severe dysmenorrhea received rofecoxib 50 mg, naproxen 550 mg or placebo in a crossover study over three menstrual cycles (28). Both

rofecoxib and naproxen produced greater analgesia over 8 hours as assessed by pain relief and pain intensity difference scores, time to onset of pain relief and the percentage of patients needing more analgesia over the first 12 hours. In a similar study, rofecoxib 25 and 50 mg and naproxen 550 mg were superior to placebo but indistinguishable from each other on all measures of efficacy (29). In both dysmenorrhea studies, the incidence of clinical and laboratory experiences was reported as similar across groups.

The published data for rofecoxib provide clear evidence of an acute analgesic effect in replicate studies in two models of acute pain and selectivity for COX-2 inhibition. The drug is well tolerated following single doses and does not appear to inhibit COX-1 mediated platelet aggregation. These data provided a basis for approval of rofecoxib as the first selective COX-2 inhibitor indicated in the USA for the management of acute pain (up to a maximum of 5 days) as well as for the treatment of osteoarthritis. The analgesic activity of rofecoxib 50 mg should be comparable to that of ibuprofen 400 mg; the expected gastrointestinal toxicity is predicted to be less than dual COX-1/COX-2 inhibitors such as ibuprofen. Rofecoxib's effects on the kidney with widespread administration are yet to be determined.

Pre-emptive COX-2 to suppress postoperative pain

Most studies in which an NSAID is

given orally after pain onset demonstrate activity within 30 minutes and peak analgesic activity at 2-3 hours. An early attempt to optimize ibuprofen analgesia immediately after surgery following local anesthesia offset involved giving the drug before oral surgery. That allowed enough time for drug absorption during surgery and the 1-2 hour duration of standard local anesthetics postoperatively. Preoperative ibuprofen 400 mg was shown to increase the time to the first postoperative dose of analgesic by about 2 hours in comparison to placebo before treatment (8). A subsequent study showed that preoperative ibuprofen 800 mg significantly lowered pain intensity over the first 3 hours postoperatively as the residual effects of the local anesthetic dissipated (9). A second dose of ibuprofen 4 hours after the initial dose extended this preventive analgesic effect, resulting in less pain than placebo, acetaminophen (given both pre- and postoperatively) or acetaminophen plus 60 mg codeine (given postoperatively). The ability to suppress the onset and lower the intensity of postoperative pain for up to 8 hours is replicable (30-32) and extends to the use of other NSAIDs, such as flurbiprofen (33). Compared with placebo, ibuprofen both before and immediately after periodontal surgery significantly delayed pain onset (34). A similar study in the oral surgery model using naproxen did not differentiate between pre- and postoperative administration (35), suggesting that preoperative administration is not essential for suppressing pain onset. Recognition of the induction of COX-2 in the postoperative period suggests that blockade of the formation of prostanoids released during surgery by constitutive COX-1 is less important than suppression of COX-2 and prostanoid release during the postoperative period. This is supported by the data shown in Figure 1, where PGE₂ levels (presumably mediated by constitutive COX-1) are detectable in the first immediate postoperative sample (see also Fig. 4, upper panel), subsequently decrease over the first 60 minutes postoperatively and then start to increase over the next 60-120 minutes coincident

with COX-2 induction and the onset of pain (22). These observations support the administration of NSAIDs before the induction of COX-2 and subsequent release of prostanoids as a preventive analgesic strategy for suppressing pain in the immediate postoperative period as well as for inhibiting peripheral and central sensitization leading to hyperalgesia.

Central versus peripheral analgesic action

The analgesic effects of ketorolac 1 mg administered directly into the extraction site or intramuscularly without altering peripheral PGE₂ levels is suggestive of analgesic activity at a site other than in the periphery – presumably the central nervous system. The peripheral effects of NSAIDs have also been evaluated by administration of ketoprofen locally into the site of injury as a strategy for reducing systemic exposure to NSAIDs. A gel formulation was placed directly into the extraction site 1 hour after oral surgery and pain intensity was evaluated for 6 hours. There was significantly less pain than with placebo after peripheral administration of ketoprofen 10 and 30 mg. Peripheral administration of the 10 mg dose also resulted in greater analgesia than the same dose given orally or placebo (36). These data indicate that administration of an NSAID to a peripheral site of tissue injury results in a greater analgesia than oral administration and suggest potential for less drug toxicity through lower circulating drug levels.

An open-label comparison of ketorolac 10 mg administered orally or injected in the buccal vestibule of an endodontically treated tooth failed to differentiate between the two formulations. The lack of a placebo group, however, limits interpretation of therapeutic equivalency (37). Another study also evaluated the local administration of injectable ketorolac in 52 endodontic emergency patients after pulpotomy. Maxillary or mandibular infiltration of ketorolac 30 mg produced significant analgesic effects (38). An interesting observation was the demonstration of analgesic effects for the mandibular infiltration,

contrary to the poor efficacy usually reported for local anesthetic infiltration in the mandible. It also appears that the presence of inflammation did not hinder the analgesic effect of ketorolac infiltration and injection of ketorolac did not result in any tissue irritation. These data, albeit from a limited number of studies, are supportive of direct NSAID actions when administered into a site of injury and may lower the potential for systemic toxicity by lowering circulating drug levels associated with traditional routes of administration.

Pain relief versus anti-inflammatory actions

The acute postoperative sequelae of surgical procedures include other signs of inflammation due to tissue injury, edema being the most prominent. While synthetic analogs of endogenous corticosteroids are used extensively to control the sequelae of both acute and chronic inflammation, their use postoperatively is tempered by their ability to suppress the immune system, thereby increasing the risk of infection. NSAIDs have a more selective mechanism of action than glucocorticoids and a more favorable side-effect profile, suggesting that drugs of this class may inhibit inflammation without the risks of corticosteroid administration. Ibuprofen 400 mg three times daily for 3 days produced a trend for reduced swelling in comparison to placebo (39). Ibuprofen 600 mg four times daily for 2 days also showed a trend towards suppressed edema formation at 48 hours after oral surgery (32). A retrospective analysis of the data from two studies performed in series, evaluating the effects of two NSAIDs (ibuprofen and flurbiprofen), indicated that NSAIDs significantly suppress edema formation following oral surgery in comparison to placebo (32). A more recent study concluded that the combination of ibuprofen 400 mg three times daily and methylprednisolone 32 mg (given 12 hours before and after surgery) reduced swelling 50% more than placebo (40). The lack of separate groups receiving either ibuprofen alone or methylprednisolone does not permit any conclusion about

the reported contribution of ibuprofen to the total effect on swelling.

While somewhat inconclusive, the observations from the two studies in which an NSAID was given alone demonstrated less swelling than with placebo; side effects were minimal and there was no evidence of interference with healing or perioperative bleeding.

Tolerance to NSAID analgesia

Both clinical and animal studies suggest that tolerance to NSAIDs can develop with repeated administration. The mean reduction in chronic lower back pain intensity after an initial dose of ibuprofen 1200 mg was 23% (41). After 2 weeks of ibuprofen 2400 mg daily or placebo, the mean reduction in pain intensity for the last dose was four times lower in the drug group. The initial low level of response (23%) suggests that low back pain is not particularly sensitive to ibuprofen - this may partly explain 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 chronic orofacial pain, which could make the analgesic response negligible by the end of 4 weeks. Tolerance to diflunisal with repeated administration has been demonstrated in animals without a reduction in the amount of drug in the blood over time after the first dose in comparison to a dose given after 3 days of diflunisal (42). That suggests a functional change in the pharmacological response rather than enhanced pharmacokinetic disposition: the same amount of drug elicits less analgesia. This hypothesis could be evaluated in the oral surgery model using microdialysis, by comparing the acute effects of an NSAID administered perioperatively to groups of subjects chronically administered the drug before surgery with a placebo group. Concurrent measurements of prostanoid levels, analgesia and drug levels (collected in the microdialysate) would permit comparison of the acute analgesic effects across groups with changes in the surrogate markers for COX-2 activity.

References

- GORDON SM, DIONNE RA, BRAHIM J, JABIR F, DUBNER R: Blockade of peripheral neuronal barrage reduces postoperative pain. *Pain* 1997; 70: 209-15.
- SINGH G, TRIADAFILOPOULOS G: Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol* 1999; 26 (Suppl. 56): 18-24.
- HAWKEY C, LAINE L, SIMON T *et al.*: Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis. *Arthritis Rheum* 2000; 43: 370-7.
- SIMON LS, WEAVER AL, GRAHAM DY: Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. *JAMA* 1999; 282: 1921-8.
- FITZGERALD GA, PATRONO C: The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; 433-42.
- COOPER SA, BEAVER WT: A model to evaluate mild analgesics in oral surgery outpatients. *Clin Pharmacol Ther* 1976; 20: 241-50.
- COOPER SA: Five studies on ibuprofen for postsurgical dental pain. *Am J Med* 1984; 77A: 70-7.
- DIONNE R, COOPER SA: Evaluation of preoperative ibuprofen on postoperative pain after impaction surgery. *Oral Surg Oral Med Oral Pathol* 1978; 45: 851-6.
- DIONNE RA, CAMPBELL RL, COOPER SA, HALL DL, BUCKINGHAM B: Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen and acetaminophen plus codeine. *J Clin Pharmacol* 1983; 23: 37-43.
- TROULLOS E, HARGREAVES KM, DIONNE RA: Ibuprofen elevates β -endorphin levels in humans during surgical stress. *Clin Pharmacol Ther* 1997; 62: 74-81.
- DIONNE RA, MCCULLAGH L: Enhanced analgesia and suppression of plasma beta-endorphin by the S(+)-isomer of ibuprofen. *Clin Pharmacol Ther* 1998; 63: 694-701.
- DIONNE RA, BERTHOLD CB: Critical review of the use of NSAIDs in dentistry. *Crit Rev Oral Biol Med* 2001; in press.
- ZHANG Y, SHAFFER A, PORTANOVA J, SEIBERT K, ISAKSON PC: Inhibition of cyclooxygenase-2 rapidly reverses inflammatory hyperalgesia and prostaglandin E₂ production. *J Pharmacol Exp Ther* 1997; 283: 1069-75.
- CARLEY WW, NEIDBALA MJ, GERRITSEN ME: Isolation, cultivation and partial characterization of microvascular endothelium derived from human lung. *Amer J Resp Cell Mol Biol* 1992; 7: 620-30.
- CHATZIANTONIOU C, PAPANIKOLAOU N: The role of prostaglandin and thromboxane synthesis by the glomeruli in the development of acute renal failure. *Eicosanoids* 1989; 2: 157-61.
- FERREIRA S, NAKAMURA M, ABREAU-CASTRO M: The hyperalgesic effects of prostacyclin and PGE. *Prostaglandins* 1978; 16: 31-7.
- HAMBERG M, SVENNENSON J, SAMUELSSON B: Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc Natl Acad Sci USA* 1975; 72: 2994-8.
- DAVIES P, MACINTYRE DE: Prostaglandins and inflammation. In GALLIN JI, GOLDSTEIN IM, SYNDERMAN R (Eds): *Inflammation: Basic Principles and Clinical Correlates*. New York, Raven Press 1992: 123-38.
- HARGREAVES KM, COSTELLO A: Glucocorticoids suppress release of immunoreactive bradykinin from inflamed tissue as evaluated by microdialysis probes. *Clin Pharm Ther* 1990; 48: 168.
- SWIFT JQ, GARRY MG, ROSZKOWSKI MT, HARGREAVES KM: Effect of flurbiprofen on tissue levels of immunoreactive bradykinin and acute postoperative pain. *J Oral Maxillofac Surg* 1993; 51: 112.
- ROSZKOWSKI MT, SWIFT JQ, HARGREAVES KM: Effect of NSAID administration on tissue levels of immunoreactive prostaglandin E-2, leukotriene B-4 and (S)-flurbiprofen following extraction of impacted third molars. *Pain* 1997; 73: 339-45.
- DIONNE RA, GORDON SM, BRAHIM JS, ROWAN J, KENT AA: Peripheral PGE₂ levels following tissue injury and NSAID analgesia (abstract). *Clin Pharmacol Ther* 1998; 63: 240.
- KHAN AA, DIONNE RA, CAPRA NF: *In vivo* selectivity of cyclooxygenase inhibitors in the oral surgery model (abstract). *Society for Neurosciences* 2000, p. 1675.
- KENT AA, BRAHIM JS, GILRON I, ROWAN JS, DIONNE RA: Effect of dexamethasone on PGE₂ and thromboxane B₂ levels following tissue injury (abstract). *Clin Pharmacol Therap* 2000; 67: 143.
- CLEMETT D, GOA KL: Celecoxib. A review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; 957-80.
- BROWN J, MORRISON BW, CHRISTENSEN S *et al.*: MK-0966 50 mg versus ibuprofen 400 mg in post-surgical dental pain (Abstract). *Clin Pharmacol Ther* 1999; 65: 118.
- FRICKE JF, MORRISON BW, FITE S *et al.*: MK-966 versus naproxen sodium 550 mg in postsurgical dental pain (Abstract). *Clin Pharmacol Ther* 1999; 645: 119.
- BROWN J, MORRISON BW, BITNER M *et al.*: The COX-2 specific inhibitor, MK-0966, is effective in the treatment of primary dysmenorrhea (Abstract). *Clin Pharmacol Ther* 1999; 65: 118.
- DANIELS S, MORRISON BW, CANTU N *et al.*: Dose ranging trial of the effect of MK-966 in primary dysmenorrhea (Abstract). *Clin Pharmacol Ther* 1999; 65: 118.
- BERTHOLD CW, DIONNE RA: Clinical evaluation of H1 receptor and H2 receptor antagonists for acute postoperative pain. *J Clin Pharmacol* 1993; 33: 944-8.
- HILL CM, CARROLL MJ, GILES AD, PICKVANCE N: Ibuprofen given pre- and postoperatively for the relief of pain. *Int J Oral Maxillofac Surg* 1987; 16: 420-4.
- TROULLOS ES, HARGREAVES KM, BUTLER DP, DIONNE RA: Comparison of non-steroidal anti-inflammatory drugs, ibuprofen and flurbiprofen, to methylprednisolone and

- placebo for acute pain, swelling and trismus. *J Oral Maxillofac Surg* 1990; 48: 945-52.
33. DIONNE RA: Suppression of dental pain by the preoperative administration of flurbiprofen. *Am J Med* 1986; 80: 41-9.
34. VOGEL RI, DESJARDINS PJ, MAJOR KVO: Comparison of presurgical and immediate postsurgical ibuprofen on postoperative periodontal pain. *J Periodontol* 1992; 63: 914-18.
35. SISK AL, GROVER BJ: A comparison of preoperative and postoperative naproxen sodium for suppression of postoperative pain. *J Oral Maxillofac Surg* 1990; 48: 674-8.
36. DIONNE RA, GORDON S, TAHARA M, ROWAN J, TROULLOS E: Analgesic efficacy and pharmacokinetics of ketoprofen administered into a surgical site. *J Clin Pharmacol* 1999; 139: 131-8.
37. BATTRUM D, GUTMANN J: Efficacy of ketorolac in the management of pain associated with root canal treatment. *J Can Dent Assoc* 1996; 62: 36-42.
38. PENNISTON SG, HARGREAVES KM: Evaluation of periapical injection of ketorolac for management of endodontic pain. *J Endod* 1996; 22: 55-9.
39. LOKKEN P, OLSEN I, BRUASET I, NORMAN-PEDERSEN K: Bilateral surgical removal of impacted third molar teeth as a model for drug evaluation: a test with ibuprofen. *Eur J Clin Pharmacol* 1975; 8: 209-16.
40. SCHULTZE-MOSGAU S, SCHMELZEISEN R, FROLICH JC, SCHMELE H: Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. *J Oral Maxillofac Surg* 1995; 53: 2-7.
41. WALKER JS, LOCKTON AI, NGUYEN TV, DAY RO: Analgesic effect of ibuprofen after single and multiple doses in chronic spinal pain patients. *Analgesia* 1996; 2: 93-101.
42. WALKER JS, LEVY G: Effect of multiple dosing on the analgesic action of diflunisal in rats. *Life Sci* 1990; 46: 737-42.