An evidence-based update of the use of analgesics in dentistry

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The management of pain is a critical and challenging component in dentistry. Pain is a major postoperative symptom in many dental surgical procedures. Surveys show consistently that pain, including dental pain, is not adequately treated (8, 25). Improvement depends on knowing which treatments are the most effective. There are a variety of analgesics and techniques to treat dental pain. Patients want to be given the best analgesic and technique for managing their pain and dentists need to know them. Knowing how well an analgesic and technique works and its associated adverse effects is fundamental to clinical decision-making. The recent focus and publicity on the adverse effects of analgesics, in particular, non-steroidal anti-inflammatory drugs, makes selection of analgesics for pain management important both clinically and legally (90).

This review provides a critical analysis of the evidence on the use of analgesics in dentistry with the aim of helping dentists select the most appropriate analgesic and technique for their patients. It is composed deliberately to be a classic, pragmatic review and draws on the results of published systematic reviews and randomized controlled trials regarding the topic. It aims to answer the following questions. (i) Are there clinically important differences in the efficacy and safety between different analgesics and techniques? (ii) If there are differences, which are the ones that are more effective and associated with fewer adverse effects? (iii) Which are the effective therapeutic approaches that could reduce the adverse effects? Finally, an algorithm is proposed that delineates a general decision-making tree to select the most appropriate analgesic and technique for individual patients.

Pain mechanisms underlying analgesic efficacy

Oral tissue injury activates the inflammatory process, which releases a large series of pain mediators. Mediators such as prostaglandins and bradykinins cause increased sensitivity and excitation of peripheral nociceptors, which usually have little spontaneous activity under normal conditions (peripheral sensitization). With repetitive C-fiber nociceptor stimulation from the periphery, excitatory amino acids such as glutamate and aspartate, as well as several peptides (including substance P) increase and cause activation of N-methyl-D-aspartate receptors of the postsynaptic second-order neuron in the dorsal horn. This leads to increased responsiveness of neurons in the central nervous system and to central sensitization, which is responsible for the prolonged pain after dental surgery (93, 126). Some of these mediators may be usefully inhibited or blocked by analgesics (Table 1). For example, the analgesic effect of non-steroidal anti-inflammatory drugs is primarily the result of their inhibition of the synthesis of prostaglandins and bradykinins through the inactivation of cyclooxygenase (29, 38). Opioids exert at least part of their effect by inhibiting substance P release in the peripheral and the central nervous systems (129). Once central sensitization is established, larger doses of analgesics are required to suppress it. The concept of pre-emptive analgesia (analgesic intervention before nociception) is particularly useful because it can potentially prevent the induction of central sensitization by blocking the arrival of nociceptive input to the central nervous system and can prevent peripheral sensitization by

Table 1. Chemical mediators for dental pain

Pain mediators	Source	Drug antagonist
Bradykinin	Plasma kininogen	Non-steroidal anti-inflammatory drugs
Serotonin	Platelets	Non-steroidal anti-inflammatory drugs
Histamine	Mast cells	Anti-histamine
Prostaglandins	Arachidonic acid	Non-steroidal anti-inflammatory drugs
Leukotriene	Arachidonic acid	Non-steroidal anti-inflammatory drugs
Substance P	Primary afferent nerve	Opioids
Glutamate, aspartate	Primary afferent nerve	*N*-methyl-D-aspartate receptor antagonist

preventing the formation of pain mediators in the injured tissues (93).

In impacted third molar surgery, moderate to severe pain usually occurs during the first 12 hours after surgery, with maximum intensity after about 6 hours when a conventional local anesthetic is used (116). This peak pain during the early postoperative period coincides with the increased release of pain mediators (123). Similarly, it has been shown in periodontal surgery that the peak release of pain mediators and pain compares well with that in third molar surgery (87). For periodontal scaling and root planing, maximum pain occurs between 2 and 8 hours after the procedure (105). A series of studies by Hargreaves were designed to measure the level of pain mediators continuously over time in dental surgery to provide the basis for evaluating peripheral biochemical mechanisms of analgesics clinically (50, 87, 112, 123). A microdialysis technique was developed, which permits the collection of pain mediators in conscious dental surgical patients who can report pain scores simultaneously. The studies used microdialysis probes to collect tissue levels of immunoreactive bradykinin, prostaglandin E_2, leukotriene B_4, substance P, and other pain mediators at various time-points. They indicated that all the above mediators are detectable in the tissue dialysates collected from the surgical wounds after both third molar and periodontal surgery (50, 87, 112, 123). Pharmacological studies using non-steroidal anti-inflammatory drugs have shown that they significantly reduce both tissue levels of all these pain mediators and also the clinical pain scores simultaneously. In addition, it was also shown that preoperative administration of non-steroidal anti-inflammatory drugs significantly reduced patients' reports of pain after surgery and blocked the peak increase in tissue levels of pain

mediators (123). This finding further supports the usefulness of pre-emptive analgesia.

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage' (76). It has both a sensory–discriminative and an affective–motivational component. The nature and severity of pain is a consequence of both the sensory events arising from tissue damage, and the affective / cognitive mechanisms. A recent study has shown that anxiety and stress correlated with the reported level of pain, the use of pain medication, and wound healing after periodontal surgery (63). Interventions to decrease anxiety or stress before surgery are equally important as analgesic treatment postoperatively. Anxiolytic agents like midazolam has been shown to be effective in reducing postoperative dental pain (95).

Efficacy of analgesics for dental pain

There are hundreds of proprietary analgesics on the market with manufacturers' claims of efficacy. Many dentists and patients are confused as to which analgesic is most efficacious for the pain that needs to be treated. Frequently, the choice of analgesic is based on personal preference rather than evidence-based information (92). Many of the analgesics tested for pain management were tested using the dental model and hence there is a wealth of information available for the efficacy of analgesics for dental pain. A literature search shows many systematic reviews of analgesic efficacy for dental pain (Table 2). The Oxford League Table (Table 3) is an example that will be used in this review to discuss the relative efficacy of analgesics (100).

Table 2. Summary of systematic reviews of analgesics for dental pain

Reference	Design and no. of patients analyzed	Drug, dose, route	Outcome measures	Results
Desjardins et al. (27)	SR of 13 RCTs in dental surgery with 1900 patients.	Oral rofecoxib 50 mg compared with placebo and comparator non-steroidal anti-inflammatory drugs.	Onset of analgesia and duration of analgesia.	Median time to onset of analgesia was 34 minutes. Duration of analgesia for rofecoxib 50 mg was > 24 hours.
Mason et al. (71)	SR of 10 dental and general surgical RCTs with 996 patients.	Oral naproxen sodium 550 mg compared with placebo.	NNT over 4–6 hour and mean time to remediation	NNT was 2.6 for naproxen sodium 550 mg. Weighted mean time to remediation for naproxen sodium 550 mg was 7.6 hours compared with 2.6 hours for placebo.
Barden et al. (7)	SR of dental and general surgical RCTs with 945 patients.	Oral diclofenac 25 mg, 50 mg and 100 mg compared with placebo.	NNT over 4–6 hour and proportions of patients experiencing any adverse event.	NNT were 2.8, 2.3, and 1.9 for diclofenac 25 mg, 50 mg, and 100 mg respectively. No significant difference between diclofenac 50 mg and placebo in the proportion of patients experiencing adverse effects.
Chen et al. (21)	SR of RCTs in dental and orthopedic pain models. 18 RCTs with 2783 patients.	Oral rofecoxib 50 mg, valdecoxib 40 mg, celecoxib 200 mg, ibuprofen 200 mg, codeine / acetaminophen 60 / 600 mg oxycodone / acetaminophen 10 / 1000 mg	Area under the pain relief vs. time curve was used to evaluate the proportion of patients achieving at least 50% pain relief. The proportions of patients experiencing any adverse event.	Rofecoxib 50 mg was more effective than codeine / acetaminophen 60 / 600 mg, and the rate ratio (RR) was 2.11. Valdecoxib 40 mg was more effective than oxycodone / acetaminophen 10 / 1000 mg (RR 1.34). Celecoxib 200 mg was less effective than ibuprofen 400 mg (RR 0.66) and rofecoxib 50 mg (RR 0.65). No difference between rofecoxib 50 mg and valdecoxib 40 mg compared with ibuprofen 400 mg and naproxen 550 mg. The adverse effects of COX-2 inhibitors were generally less than traditional non-steroidal anti-inflammatory drugs.
Edwards et al. (34)	SR of 15 dental and one general surgical RCTs with 2063 patients.	Oral rofecoxib 50 mg compared with placebo.	NNT, time when 50% of patients had remediated (TTR_{50}) and number-needed-to-harm (NNH).	For dental pain, NNT was 1.9 for 6 hours, 2.0 at 8 hours, 2.4 at 12 hours, and 2.8 at 24 hours. The TTR_{50} was 15.5 hours. For postsurgical pain in one trial (163 patients), the NNT for 6 hours was 3.9, the TTR_{50} was 5.8 hours. Adverse effects were uncommon, though postextraction alveolitis (dry socket) occurred more often with rofecoxib 50 mg than with placebo, NNH = 24.

Table 2. Continued

Reference	Design and no. of patients analyzed	Drug, dose, route	Outcome measures	Results
Ong et al. (92)	SR of 26 dental RCTs with 5742 patients.	A variety of traditional non-steroidal anti-inflammatory drugs compared with placebo.	Number of patients reporting adverse events.	Mean number of patients reporting minor adverse effects was 9.9%. The most common were nausea, diarrhea, drowsiness, and vomiting. No single cases of serious adverse effects were reported.
Romsing and Moiniche (111)	SR of 33 dental and general surgical RCTs.	Rofecoxib 50 mg, celecoxib 200 and 400 mg, parecoxib 20, 40 and 80 mg, and valdecoxib 10, 20, 40, 80 mg compared with placebo and traditional non-steroidal anti-inflammatory drugs like ibuprofen.	Mean pain scores and total supplemental analgesics.	33 RCTs included 62 comparisons of the four COX-2 inhibitors with placebo and the COX-2 inhibitors significantly decreased postoperative pain. Rofecoxib 50 mg and parecoxib 40 mg have an equipotent analgesic efficacy relative to traditional non-steroidal anti-inflammatory drugs. Besides, rofecoxib 50 mg provides superior analgesic effect compared with celecoxib 200 mg.
Barden et al. (3)	SR of dental and general surgical RCTs for valdecoxib (four RCTs) and parecoxib (four RCTs).	Oral valdecoxib 20 mg and 40 mg (859 patients), intravenous parecoxib 20 mg and 40 mg (917 patients), compared with placebo and comparator non-steroidal anti-inflammatory drugs and opioids.	NNT over 4–6 hours and mean time to remediation	NNT was 1.7 and 1.6 for valdecoxib 20 mg and 40 mg, respectively. NNT was 3.0 and 2.3 for parecoxib 20 mg and 40 mg, respectively. Mean time to remediation was >24 hours for valdecoxib and 8.7 hours for parecoxib.
Barden et al. (4)	SR of two dental and general surgical RCTs with 418 patients.	Oral celecoxib 200 mg compared with placebo.	NNT over 4–6 hours and mean time to remediation	NNT was 4.5 and median time to remediation was 5.1 hours with celecoxib 200 mg and 1.5 hours with placebo.
Barden et al. (2)	SR of 52 dental and general surgical RCTs with 6358 patients	Oral ibuprofen in doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg and 800 mg compared with placebo.	NNT over 4–6 hours	All doses were significantly superior to placebo and the there was a lower NNT (more effect) with increasing doses. NNT was 4.7, 4.3, 2.7, 2.4, 2.4, 1.6 for 50 mg, 100 mg, 200 mg, 400 mg, 600 mg and 800 mg respectively.
Hyllested et al. (59)	SR of 41 dental and general surgical RCTs (Qualitative review).	Direct comparison of acetaminophen 1,000 mg with various non-steroidal anti-inflammatory drugs.	Mean pain scores, total supplemental analgesics.	Non-steroidal anti-inflammatory drugs were clearly more effective in dental surgery, whereas the efficacy of non-steroidal anti-inflammatory drugs and acetaminophen seemed without substantial differences in general and orthopedic surgery. Combinations of non-steroidal anti-inflammatory drugs and acetaminophen were more effective than either analgesic alone.

Table 2. Continued

Reference	Design and no. of patients analyzed	Drug, dose, route	Outcome measures	Results
Collins et al. (22)	SR of dental and general surgical RCTs for diclofenac and ibuprofen with 4561 patients.	Oral diclofenac 50 mg, 100 mg (six RCTs), and ibuprofen 200 mg, 400 mg, 600 mg (34 RCTs) compared with placebo. Two RCTs compared diclofenac 50 mg with ibuprofen 400 mg.	NNT over 4–6 hours	NNT was 2.3 and 1.8 for diclofenac 50 mg and 100 mg respectively. NNT was 3.3, 2.7, 2.4 for ibuprofen 200 mg, 400 mg, 600 mg respectively. No significant difference between diclofenac 50 mg and ibuprofen 400 mg.
Edwards et al. (31)	SR of three dental and general surgical RCTs with 141 patients	Oral piroxixam 20 mg and 40 mg with placebo.	NNT over 4–6 hours and reported adverse events.	NNT were 2.7 and 1.9 compared with placebo over 4–6 hours. The reported incidence of adverse effects was no higher with piroxicam (20 mg or 40 mg) than with placebo.
Edwards et al. (32)	SR of four dental and general surgical RCTs with 314 patients	Oral dihydrocodeine 30 mg compared with placebo and ibuprofen 400 mg.	NNT over 4–6 hours. The proportions of patients experiencing any adverse event.	NNT was 8.1 for dihydrocodeine 30 mg. When compared with ibuprofen, dihydrocodeine provides inferior analgesia and has more adverse effects.
Edwards et al. (33)	SR of seven dental and general surgical RCTs	Oral oxycodone 5 mg, 10 mg, 15 mg alone or combined with acetaminophen.	NNT over 4–6 hours. The proportions of patients experiencing any adverse event.	NNT was 2.3, 2.2, 2.6 for oxycodone 15 mg, oxycodone 5 mg plus acetaminophen 500 mg, oxycodone 5 mg plus acetaminophen 650 mg respectively. Significantly more adverse effects with active drug than with placebo were shown for all doses.
Moore et al. (81)	SR of dental and general surgical RCTs with a total of 6372 patients.	Forty RCTs of acetaminophen against placebo (4,171 patients), 22 RCTs of acetaminophen plus codeine against placebo (1,407 patients) and 12 RCTs of acetaminophen plus codeine against the same dose of acetaminophen (794 patients).	NNT over 4–6 hours and NNH.	Acetaminophen 1000 mg had an NNT of 4.6, and acetaminophen 600/650 mg had an NNT of 5.3. Acetaminophen 600/650 mg plus codeine 60 mg had an NNT of 3.6. Relative risk estimates for acetaminophen 600/650 mg plus codeine 60 mg vs. placebo showed a significant difference for 'drowsiness' (NNH 11), and 'dizziness' (NNH 27).

Oxford League Table

The information in the Oxford League Table is derived from systematic reviews of randomized, double-blind, single-dose studies in patients with moderate to se-vere acute postoperative pain, many of which were postoperative dental pain. The efficacy of analgesics is expressed as the patient number-needed-to-treat, and the number of patients who need to receive the active drug in a single dose to achieve at least 50% relief of pain compared with placebo over a 4- to 6-hour

Table 2. Continued

Reference	Design and no. of patients analyzed	Drug, dose, route	Outcome measures	Results
Moore et al. (80)	SR of 63 dental and general surgical RCTs with 4593 patients.	Thirty-one RCTs of acetaminophen against placebo (2515 patients), 19 RCTs of acetaminophen plus codeine against placebo (1204 patients) and 13 RCTs of acetaminophen plus codeine against the same dose of acetaminophen (874 patients).	NNT over 4–6 hours	NNT was 3.6 for acetaminophen 1000 mg, 5.0 for acetaminophen 600 / 650 mg, and 3.1 for acetaminophen 600 / 650 mg plus codeine 60 mg
Moore et al. (82)	SR of 18 dental and general surgical RCTs with 3453 patients.	Oral tramadol 50 mg, 100 mg, 150 mg compared with placebo.	NNT over 4–6 hours	NNT was 7.1, 4.8, 2.4 for 50 mg, 100 mg, 150 mg of tramadol respectively. With the same dose of drug dental surgical patients had less pain relief and more adverse effects compared with general surgical patients.

SR = systematic review, RCT = randomized controlled trial, NNT = number-needed-to-treat, NNH = number-needed-to-harm, NSAIDs = non-steroidal anti-inflammatory drugs, COX = cyclooxygenase.

treatment period (23). The most effective drugs would have a low number-needed-to-treat of 2. This means that for every two patients who receive the drug one patient will get at least 50% relief because of the treatment (the other patient may or may not obtain relief but it does not reach the 50% level). Information is presented in the form of a league table, which has the number of patients in the comparison, the percentage of patients with at least 50% pain relief with analgesic, the number-needed-to-treat and the 95% confidence interval (Table 3). Analgesics available for dental pain management belong to two major groups: the non-opioid analgesics (e.g. non-steroidal anti-inflammatory drugs and acetaminophen) and opioids.

Efficacy of non-steroidal anti-inflammatory drugs and acetaminophen

From the Oxford League Table, it is clear that non-steroidal anti-inflammatory drugs, including traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, do extremely well in this single-dose comparison, but they do differ in efficacy. At therapeutic doses, all non-steroidal anti-inflam-

matory drugs have number-needed-to-treat values of between 1.6 and 3, and the point estimate of the mean is below that of (i.e. better than) 10 mg intramuscular morphine (number-needed-to-treat 2.9), even though the confidence intervals overlap. Traditional non-steroidal anti-inflammatory drugs, like ibuprofen, diclofenac, and naproxen, and cyclooxygenase-2 inhibitors, like rofecoxib, valdecoxib, and lumiracoxib, top the league table. By comparison, other analgesics such as aspirin 600 mg and acetaminophen 1000 mg (numbers-needed-to-treat 4.4 and 3.8, respectively) are significantly less effective than 10 mg intramuscular morphine.

Older clinical data suggested that acetaminophen was as effective as non-steroidal anti-inflammatory drugs in many pain conditions (14, 124, 135). However, it can be seen from the Oxford League Table that overall, the non-steroidal anti-inflammatory drugs are clearly more efficacious than acetaminophen. Results from a recent meta-analysis also indicate that non-steroidal anti-inflammatory drugs are clearly more effective in dental surgery compared with acetaminophen, whereas their efficacy appeared to be without substantial differences from acetaminophen in general and orthopedic surgery (59).

Table 3. Oxford League Table (adapted with permission from http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/Leagtab.html)

Analgesic in mg	Number of patients in comparison	Percentage with at least 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Valdecoxib 40	473	73	1.6	1.4	1.8
Ibuprofen 800	76	100	1.6	1.3	2.2
Ketorolac 20	69	57	1.8	1.4	2.5
Ketorolac 60 (intramuscular)	116	56	1.8	1.5	2.3
Rofecoxib 50	1,900	63	1.9	1.8	2.1
Diclofenac 100	411	67	1.9	1.6	2.2
Piroxicam 40	30	80	1.9	1.2	4.3
Lumiracoxib 400	252	56	2.1	1.7	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Oxycodone immediate-release 5 + Paracetamol 500	150	60	2.2	1.7	3.2
Diclofenac 50	738	63	2.3	2.0	2.7
Naproxen 440	257	50	2.3	2.0	2.9
Oxycodone immediate-release 15	60	73	2.3	1.5	4.9
Ibuprofen 600	203	79	2.4	2.0	4.2
Ibuprofen 400	4,703	56	2.4	2.3	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Bromfenac 100	95	62	2.6	1.8	4.9
Oxycodone immediate-release 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Ketorolac 10	790	50	2.6	2.3	3.1
Ibuprofen 200	1,414	45	2.7	2.5	3.1
Oxycodone immediate-release 10 + Paracetamol 1000	83	67	2.7	1.7	5.6
Piroxicam 20	280	63	2.7	2.1	3.8
Diclofenac 25	204	54	2.8	2.1	4.3
Dextropropoxyphene 130	50	40	2.8	1.8	6.5
Pethidine 100 (intramuscular)	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 550	169	46	3.0	2.2	4.8
Naproxen 220/250	183	58	3.1	2.2	5.2
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Paracetamol 500	561	61	3.5	2.2	13.3
Paracetamol 1500	138	65	3.7	2.3	9.5
Paracetamol 1000	2,759	46	3.8	3.4	4.4

Table 3. Continued

Analgesic in mg	Number of patients in comparison	Percentage with at least 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Oxycodone immediate- release 5 + Paracetamol 1000	78	55	3.8	2.1	20.0
Paracetamol 600 ⁄ 650 + Codeine 60	1,123	42	4.2	3.4	5.3
Ibuprofen 100	396	31	4.3	3.2	6.3
Paracetamol 650 + Dextropropoxyphene (65 hydrochloride or 100 napsylate)	963	38	4.4	3.5	5.6
Aspirin 600 ⁄ 650	5,061	38	4.4	4.0	4.9
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 + Codeine 60	598	25	5.3	4.1	7.4
Oxycodone immediate- release 5 + Paracetamol 325	149	24	5.5	3.4	14.0
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1,305	15	16.7	11.0	48.0
Placebo	> 10,000	18	N ⁄ A	N ⁄ A	N ⁄ A

NNT = number-needed-to-treat, N ⁄ A = not available.

When the cyclooxygenase-2 inhibitors first appeared in the market, some experts suggested that they might have inferior analgesic efficacy compared to traditional non-steroidal anti-inflammatory drugs (60, 132). However, as more clinical data has become available, it has become clear that many of the cyclooxygenase-2 inhibitors have equal or better analgesic efficacy compared with traditional non-steroidal anti-inflammatory drugs and this is reflected in the Oxford League Table (96, 100). In a recent meta-analysis of dental pain for rofecoxib 50 mg (1330 patients) compared with placebo (570 patients), the number-needed-to-treat was 1.9 (95% confidence interval 1.8–2.1) at 6 hours, 2.0 (1.8–2.1) at 8 hours, 2.4 (2.2–2.6) at 12 hours, and 2.8 (2.5–3.1) at 24 hours (34).

In general, non-steroidal anti-inflammatory drugs vary in their time of onset and their duration of analgesic effect; the longer the half-life of the drug, the slower the onset of effect. In addition, a higher dose has a faster onset, higher peak effect, and longer duration. It is advantageous to start with a high dose of a short half-life drug and then adjust the dose downward when analgesic efficacy has been achieved, e.g. ibuprofen. For management of persistent or chronic pain, the administration of non-steroidal anti-inflammatory drugs with long half-lives has clear advantages in allowing for once- or twice-a-day dosing, e.g. naproxen and cyclooxygenase-2 inhibitors. Strict adherence to a treatment schedule that requires drug administration many times a day can be difficult even for the most compliant patient.

Efficacy of opioids

From the Oxford League Table, opioids perform poorly in single doses on their own. For example, codeine phosphate 60 mg and tramadol 50 mg have numbers-needed-to-treat of 16.7 and 8.3, respectively. In the meta-analysis (100), the administration of 60 mg codeine produced only a 15% analgesic response (i.e. 15% of 1305 patients reported at least 50% pain reduction) and this response did not differ from a placebo tablet (18% response in > 10,000 patients). Tramadol produced dose-related analgesia at 50 mg (19% of 770 patients reported at least 50% pain relief). Oxycodone has 10- to 12-fold greater potency than codeine (10), and oxycodone 15 mg is the only opioid that has a number-needed-to-treat close to that of non-steroidal anti-inflammatory drugs (2.3) in the Oxford League Table, but there is a high incidence of reported adverse effects (33).

Oral opioids alone are a poor choice for acute dental pain because they provide relatively inferior analgesia and more adverse effects compared to non-steroidal anti-inflammatory drugs. However, opioids may be used as adjunctive analgesics and can be combined with acetaminophen to increase its efficacy. For example, combining codeine phosphate 60 mg with acetaminophen 1,000 mg increases its efficacy from a number-needed-to-treat of 16.7 to 2.2. Combining tramadol 75 mg with acetaminophen 650 mg increases its efficacy from a number-needed-to-treat of 8.0 to 3.0 (73).

Effects of formulation on the analgesic efficacy

The formulations of certain analgesics can have a profound effect on their efficacy. Certain formulations of non-steroidal anti-inflammatory drugs may enhance the onset of analgesia and efficacy. For example, the absorption of ibuprofen acid is influenced by formulation, and certain salts of ibuprofen (e.g. lysine and arginine), and solubilized formulations have an enhanced onset of activity. Ibuprofen lysine 400 mg produces faster onset and higher peak analgesia than a conventional tablet of ibuprofen acid 400 mg in dental pain (24). Solubilized liquigel ibuprofen 400 mg had more rapid onset than acetaminophen 1000 mg and had a longer duration of action than either acetaminophen 1000 mg or ketoprofen 25 mg (88). These differences can be clinically important because the median time to meaningful relief of pain was shorter after solubilized ibuprofen 400 mg than after acetaminophen 1000 mg (101). Diclofenac sodium softgel has also been shown to provide a very rapid onset of analgesic activity and prolonged analgesic duration compared with conventional diclofenac potassium (139). Many popular non-steroidal anti-inflammatory drugs, including ibuprofen, naproxen, and ketoprofen, undergo chiral conversion between active and inactive isomers. Variability in rates of conversion may help to explain differences in clinical response. Failure to achieve adequate pain relief with one non-steroidal anti-inflammatory drug may be followed by a trial of another non-steroidal anti-inflammatory drug from the same or different class. Good management of pain may be achieved with such a 'second choice' agent (75). If two non-steroidal anti-inflammatory drugs of two different classes have been tried individually, further attempts to obtain benefit from non-steroidal anti-inflammatory drugs are unlikely to succeed (75).

Opioids may be required when non-steroidal anti-inflammatory drugs and acetaminophen are contraindicated, e.g. because of allergy. However, many opioids have a short elimination half-life, which necessitates frequent administration (as frequent as every 2–4 hours). Sustained-release or controlled-release formulations have been developed which allow once- or twice-a-day dosing. Sustained-release oxycodone, codeine, and tramadol have been shown to be effective for the treatment of chronic pain (1, 52, 62). Therapeutic equivalence has been shown for the sustained-release and immediate-release formulations of tramadol and they are better tolerated with fewer adverse events for chronic low back pain (108). However, sustained-release or controlled-release formulations usually have a slower onset of action compared with immediate-release formulations. Hence, timed-release formulations are usually of limited value for treatment of acute pain and are more suited for chronic pain.

Improved clinical outcomes have been documented with combinations of analgesic agents, particularly those with complementary activities. However, because not all combinations or dose ratios lead to enhanced analgesia or reduced adverse events, each combination and dose ratio must be evaluated individually. Acetaminophen / opioid combinations, e.g. acetaminophen / codeine and acetaminophen / tramadol, have been shown in randomized controlled trials to have better analgesic efficacy than the single agent alone for dental pain without an increased incidence of adverse events (41, 74). An acetaminophen / non-steroidal anti-inflammatory drug combination has also been shown in two recent meta-analyses to act synergistically to improve analgesia for acute postoperative pain (35, 59). However, many studies have not been able to show that a non-steroidal anti-inflammatory drug / opioid combination is better than non-steroidal anti-inflammatory drugs alone for dental pain. Combinations of ibuprofen / codeine, ibuprofen / oxycodone, naproxen / codeine have failed to show any additive effects in many dental studies (28, 40, 49, 103, 133). Conversely, there are some studies that showed that ibuprofen / codeine and ibuprofen / oxcodone combinations have a better analgesic effect than ibuprofen alone, but with a higher incidence of side effects (68, 72). A recent meta-analysis shows that ibuprofen / codeine combination is superior to ibuprofen alone (107; including many studies for general surgical pain). Hence, it seems that the evidence for the efficacy of non-steroidal anti-inflammatory drug / opioid combinations vs.

non-steroidal anti-inflammatory drugs alone is still controversial.

Summary statement

The effectiveness of non-steroidal anti-inflammatory drugs for dental pain is overwhelming, as reflected in the Oxford League Table and in individual reviews (Tables 2 and 3). It can be seen from the Oxford League Table that few analgesics if any are better than non-steroidal anti-inflammatory drugs for acute pain. Moreover, non-steroidal anti-inflammatory drugs do differ in their analgesic efficacy. Traditional non-steroidal anti-inflammatory drugs, like ibuprofen, diclofenac, and naproxen, and cyclooxygenase-2 inhibitors, like rofecoxib, valdecoxib, and lumiracoxib, are among the most effective for dental pain. Opioids are relatively less efficacious than non-steroidal anti-inflammatory drugs for dental pain and should only be used when non-steroidal anti-inflammatory drugs are contraindicated. Despite the well-documented efficacy of non-steroidal anti-inflammatory drugs, some patients will not receive adequate pain relief from therapeutic doses of non-steroidal anti-inflammatory drugs. Combination analgesics such as acetaminophen / opioids or acetaminophen / non-steroidal anti-inflammatory drugs may be useful alternatives in this group of patients.

It should be noted that most of the analgesic studies used the impacted third molar model. The pain level after third molar surgery has been found to be higher than after other types of oral and periodontal surgery and hence is an extremely sensitive model for assessing the efficacy of analgesics (39). The less painful periodontal surgical model is less often used. However, a summary of the studies of the efficacy of analgesics for periodontal surgery supports the evidence from the third molar model that non-steroidal anti-inflammatory drugs are the drugs of choice for dental pain (Table 4).

Adverse effects of analgesics

Dentists need to know the likelihood of adverse effects of analgesics to assess the efficacy:risk ratio. This applies to both serious clinical effects that may cause significant morbidity or mortality, and to more 'trivial' symptoms that may affect quality of life and drug compliance. Lists of adverse effects can be obtained from reference texts or pharmaceutical companies, but details of frequencies are often not available. Systematic reviews of randomized controlled trials

and observational studies will be used to provide evidence on the frequencies of adverse effects.

Adverse effects of non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are associated with a number of side effects. The most common minor side effects include nausea, vomiting, diarrhea, dizziness, and headache. The serious side effects include prolonged bleeding after surgery, kidney failure, and gastrointestinal and cardiovascular adverse effects. The deleterious gastrointestinal effects of non-steroidal anti-inflammatory drugs are cause for concern because of their frequency and seriousness (120). Recent clinical trials have also demonstrated an apparent increased risk of cardiovascular adverse events in patients taking certain non-steroidal anti-inflammatory drugs, particularly cyclooxygenase-2 inhibitors (47). This section will discuss in detail the gastrointestinal and cardiovascular adverse effects of non-steroidal anti-inflammatory drugs.

Gastrointestinal risk of traditional non-steroidal anti-inflammatory drugs

There are two separate cyclooxygenase gene products, cyclooxygenase-1 and cyclooxygenase-2 that can initiate the metabolism of arachidonic acid to prostaglandins (29). Cyclooxygenase-1 is expressed in most tissues and governs the homeostatic function necessary to maintain physiological integrity, including gastric cytoprotection, whereas cyclooxygenase-2 is induced in response to inflammatory stimuli and is responsible for inflammation and pain. All traditional non-steroidal anti-inflammatory drugs inhibit cyclooxygenase-2 as well as cyclooxygenase-1 and are associated with an increased risk of gastrointestinal complications, including gastrointestinal hemorrhage, perforation, and obstruction (44, 48). The ulcerogenic properties of traditional non-steroidal anti-inflammatory drugs to a large extent relate to their capacity to inhibit cyclooxygenase-1 in the gastric mucosa (58). Less gastrointestinal toxic agents tend to be cyclooxygenase-1 sparing (i.e. cyclooxygenase-2 selective) and vice versa.

Three recent large-scale studies indicate that some traditional non-steroidal anti-inflammatory drugs are associated with higher gastrointestinal risks than others (46, 54, 69). The first is a meta-analysis of case–control studies, the second is a cohort study of

Table 4. Summary of studies for the efficacy of analgesics for periodontal surgery

Reference	Design of study	Drugs studied	Outcome measures	Results
Ettlin et al. (37)	Parallel double-blind RCT, 64 patients with chronic periodontitis for scaling and root planing	Preoperative 800 mg ibuprofen arginine or placebo 30 min before treatment	VAS pain scores at 1, 2, 4, 6, 8, 10, 24 hours after procedure	Average pain levels during treatment were lower following ibuprofen arginine (quartiles: 0.5, 4.5, 11) compared with placebo (2, 16, 26), corresponding to a percentage reduction in median pain of 72% ($P = 0.023$)
Betancourt et al. (11)	Cross-over design with 12 patients undergoing two periodontal surgeries in different quadrants	Preoperative combination of ibuprofen 400 mg with 5 mg of hydroxycodone vs. ibuprofen 400 mg used alone	VAS every 2 hours for the first 12 hours after surgery	More pain was reported with ibuprofen alone compared to the ibuprofen with hydrocodone combination ($P < 0.05$).
Pearlman et al. (102)	Parallel double-blind RCT, 127 patients undergoing periodontal surgery	Preoperative ibuprofen or placebo 30 minutes before surgery	Hourly VAS pain scores and total postoperative analgesic requirements	The ibuprofen group had significantly lower pain scores and analgesic requirements
O'Brien et al. (87)	Cross-over design with nine patients undergoing periodontal surgeries in different quadrants and measuring pain mediators and pain scores simultaneously	One quadrant with ibuprofen (800 mg 1 hour presurgery and 400 mg postsurgery) and one quadrant with a placebo	Immunoreactive prostaglandin E_2, leukotriene B_4 and patient's report of VAS pain scores for 4 hours	Mean tissue levels of pain mediators and pain scores increased continuously with time, peaking at 4 hours for placebo group. Mean tissue levels of pain mediators and pain scores in the ibuprofen group were significantly suppressed
Trombelli et al. (127)	Parallel double-blind RCT, patients undergoing periodontal surgery	Preoperative ketorolac 20 mg vs. placebo	Hourly VAS scores for 10-hour, time and dose of rescue analgesic	Preoperative ketorolac reduced pain scores and delayed the onset of postoperative pain and amount of rescue analgesic as compared to placebo
Tucker et al. (128)	Parallel single-blind RCT, 24 patients undergoing periodontal surgery	Preoperative etodolac vs. 'as needed' acetaminophen / hydrocodone	Hourly VAS scores for 8 hours, time and dose of rescue analgesic	Etodolac significantly delayed onset of postoperative pain. The pain scores and amount of rescue analgesic were similar
Vogel et al. (130)	Parallel double-blind RCT, 60 patients undergoing periodontal surgery	Group I: Preoperative ibuprofen 600 mg, Group II: Postoperative ibuprofen 600 mg, Group III: placebo	Hourly VAS pain scores for 8 hours	Group II significantly delayed onset of pain and decreased pain scores compared with group I. Both groups were also significantly better than placebo group
Gallardo et al. (45)	Parallel double-blind RCT, 63 patients undergoing periodontal surgery	Preoperative flurbiprofen 100 mg vs. acetaminophen 500 mg, vs. placebo	Hourly verbal rating scale of 0 to 3 for pain intensity	Flurbiprofen was superior to acetaminophen and placebo

SR = systematic review, RCT = randomized controlled trial, NNT = number-needed-to-treat, VAS = 100-mm visual analogue scale.

Table 5. Relative risk of gastrointestinal complications with traditional non-steroidal anti-inflammatory drugs, relative to ibuprofen or non-use

Drug	Case–control studies*	Cohort study†	Case–control study‡
Non-use			1.0
Ibuprofen	1.0	1.0	2.1 (0.6–7.1)
Fenoprofen	1.6 (1.0–2.5)	3.1 (0.7–13)	
Aspirin	1.6 (1.3–2.0)		
Diclofenac	1.8 (1.4–2.3)	1.4 (0.7–2.6)	2.7 (1.5–4.8)
Sulindac	2.1 (1.6–2.7)		
Diflusinal	2.2 (1.2–4.1)		
Naproxen	2.2 (1.7–2.9)	1.4 (0.9–2.5)	4.3 (1.6–11.2)
Indomethacin	2.4 (1.9–3.1)	1.3 (0.7–2.3)	5.4 (1.6–18.9)
Tolmetin	3.0 (1.8–4.9)		
Piroxicam	3.8 (2.7–5.2)	2.8 (1.8–4.4)	9.5 (6.5–13.8)
Ketoprofen	4.2 (2.7–6.4)	1.3 (0.7–2.6)	3.2 (0.9–11.9)
Azopropazone	9.2 (2.0–21)	4.1 (2.5–6.7)	
Ketorolac			24.7 (9.6–63.5)

Adapted with permission from *Henry et al. Br Med J 1996: 312: 1563-1566; †MacDonald et al. Br Med J 1997; 315: 1333-1337; and ‡Rodrigeuez et al. Arch Intern Med 1998; 158: 33–39.

Note that the Rodriguez et al. case–control study compares risk of gastrointestinal event with non-use, while the other two studies make the comparison with ibuprofen.

130,000 patients over 50 years of age in the UK, and the third is a case–control study of 780,000 patients from Italy. These three studies describe clear differences in gastrointestinal risks with the different traditional non-steroidal anti-inflammatory drugs, and some of these drugs are clearly associated with higher risks than others (Table 5). In general, ibuprofen has the lowest risk among the traditional non-steroidal anti-inflammatory drugs, diclofenac and naproxen have intermediate risks, and piroxicam and ketorolac carry the greatest risk. However, it should be noted that the advantage of 'low-risk' drugs may be lost once their dosage is increased.

The risk for gastrointestinal complications increases in the following patient groups, necessitating prudent drug choice in (136):

- patients above the age of 65 years.
- patients with a history of previous peptic ulcer disease.
- patients taking corticosteroids.
- patients taking anticoagulants.
- patients taking aspirin.

A recent meta-analysis of 18 case–control and cohort studies identified age and previous peptic ulcer disease, particularly if complicated, as the strongest predictors of absolute risks (55).

Furthermore, the risk develops in a time-dependent manner, such that 'chronic use' should be added to the list of risk factors. In their over-the-counter formulation, the use of traditional non-steroidal anti-inflammatory drugs is generally advised not to exceed 3 days for fever, and 10 days for analgesia. Short-term use of 5–10 days of over-the-counter traditional non-steroidal anti-inflammatory drugs has been shown in several studies to be extremely safe and well tolerated (56). Large-scale randomized controlled trials and meta-analyses have shown that over-the-counter naproxen (up to 660 mg/day) and ibuprofen (up to 1200 mg/day) have a side effect profile that is no different from that of acetaminophen or placebo (26, 66, 77, 110).

Although most of the gastrointestinal adverse effects of the traditional non-steroidal anti-inflammatory drugs develop with chronic use, there is evidence that short-term use can also have serious gastrointestinal effects. Two recent case–control studies showed that the use of high-dose short-term traditional non-steroidal anti-inflammatory drugs can be associated with serious gastrointestinal toxicity when administered for as little as 4 days (12, 67). In addition, risk of gastrointestinal bleeding was increased two- to three-fold among recent users of aspirin, ibuprofen, and other traditional non-steroidal anti-inflammatory drugs at over-the-counter doses, with risk increasing in a dose-related manner. Alcohol consumption was also a risk factor, which doubles the risks of gastrointestinal bleeding. However, it should be noted that these were observational studies and there may be other confounding factors responsible for the gastrointestinal effects. There is at least one case report of gastrointestinal perforation as the result of short-term non-steroidal anti-inflammatory drug use in dentistry (36).

Therapeutic approaches to reduce gastrointestinal toxicity of traditional non-steroidal anti-inflammatory drugs

Several strategies may be used to reduce the risk of gastrointestinal complications associated with traditional non-steroidal anti-inflammatory drug use. First, use a drug other than a traditional non-steroidal anti-inflammatory drug when possible (e.g. acetaminophen). Second, use the lowest effective dose because the risk is dose-dependent and the efficacy

of traditional non-steroidal anti-inflammatory drugs has a ceiling effect. Finally, anti-ulcer co-therapy and cyclooxygenase-2 inhibitors can be used in high-risk patients.

Use of anti-ulcer co-therapy

Four classes of drugs, namely proton pump inhibitor, prostaglandins, histamine H2-blockers, and antacids, are available for co-therapy for reducing traditional non-steroidal anti-inflammatory drug-associated gastrointestinal toxicity. Co-therapy with proton pump inhibitors, which inhibit acid secretion, has been demonstrated in large-scale randomized controlled trials to promote ulcer healing in patients with gastric ulcers related to use of traditional non-steroidal anti-inflammatory drugs (51, 138). Prophylactic use of proton pump inhibitors in patients with previous gastrointestinal events or in those at high risk for such events is considered appropriate by major treatment guidelines (30, 114). Clinical studies also support the efficacy of misoprostol (a synthetic prostaglandin E_1 analogue), which reduces gastric acid secretion as a strategy to prevent traditional non-steroidal anti-inflammatory drug-dependent gastropathy (53, 118). However, because of its non-specific mode of action, a significant proportion of patients reported treatment-related adverse events such as diarrhea, and discontinued the medication.

To date, there is no definitive evidence that the concomitant administration of histamine H2-blockers or antacids will either prevent the occurrence of gastrointestinal effects or allow continuation of traditional non-steroidal anti-inflammatory drugs when and if these adverse reactions occur (20, 120).

Use of cyclooxygenase-2 inhibitors

Evidence from several large-scale randomized controlled trials has shown that cyclooxygenase-2 inhibitors have reduced gastrointestinal toxicity compared to traditional non-steroidal anti-inflammatory drugs. The VIGOR, CLASS, TARGET, and SUCCESS-I trials have provided evidence that cyclooxygenase-2 inhibitors minimize risk for gastrointestinal events (13, 115, 117, 119). A recent meta-analysis has shown that treatment with etoricoxib was associated with a significantly lower incidence of gastrointestinal adverse events than was treatment with traditional non-steroidal anti-inflammatory drugs. The difference was consistent in subgroups of patients defined by a variety of known risk factors (109).

Cardiovascular risk of non-steroidal anti-inflammatory drugs

Evidence from several large-scale randomized controlled trials of structurally distinct cyclooxygenase-2 inhibitors has indicated that such compounds clearly elevate the risk of myocardial infarction and stroke (13, 15, 42, 57, 61, 86, 99, 121). This evidence has led to the recent worldwide withdrawal of rofecoxib and valdecoxib. Although it seems clear that cyclooxygenase-2 inhibitors increase the risk for cardiovascular events, the risk differs to some degree between individuals and across agents, is dose-related, and varies with the duration of therapy. For example, the APPROVe clinical trial showed that the risk was only apparent after 18 months of continuous intake of rofecoxib (15). Risk was highest among patients receiving the 50-mg dose, and less among patients receiving the 25-mg dose, and was not detected among those receiving 12.5 mg. In some high-risk patients, e.g. following coronary artery bypass graft, valdecoxib increased the cardiovascular events threefold even in short-term application for only 10 days (42, 86, 99). Some studies suggest that celecoxib, etoricoxib, and lumiracoxib have a better safety profile than other cyclooxygenase-2 inhibitors, which is why these drugs have remained on the market (115, 117, 134). Currently, celecoxib, etoricoxib, lumiracoxib, and parecoxib are still available in many countries and were approved for marketing because they fulfilled the requirements for drug registration based on internationally accepted guidelines.

Conversely, several recent studies have shown that some cyclooxygenase-2 inhibitors are not associated with increased cardiovascular risks. The SUCCESS-I trial found no increased cardiovascular risks with celecoxib compared to either diclofenac or naproxen in 13,274 patients with osteoarthritis (119). The TARGET trial found no significant difference in cardiovascular deaths between lumiracoxib and either ibuprofen or naproxen irrespective of aspirin use in 18,325 patients with osteoarthritis (117). The MEDAL trial also found no increased cardiovascular risks of etoricoxib compared to diclofenac in 34,701 patients with osteoarthritis (16).

With the recent findings of cardiovascular adverse effects of cyclooxygenase-2 inhibitors, a potential safety concern has been raised as to whether the increased cardiovascular events would be a class effect for all non-steroidal anti-inflammatory drugs. Unfortunately, we do not have placebo-controlled randomized trials addressing the cardiovascular safety of traditional non-steroidal anti-inflammatory

drugs, only observational studies, and the previously discussed traditional non-steroidal anti-inflammatory drug comparator randomized controlled trials. A recent meta-analysis of 14 observational studies suggests that some traditional non-steroidal anti-inflammatory drugs may increase the risk for myocardial infarction (120). In particular, diclofenac carries a higher risk than other traditional non-steroidal anti-inflammatory drugs (because it is more cyclooxygenase-2 selective); this was not the case for naproxen.

Based on the available data, the United States Food and Drug Administration has concluded that the increased risk of cardiovascular events may be a class effect for all non-steroidal anti-inflammatory drugs and recommended that all non-steroidal anti-inflammatory drugs will now carry stronger warnings for adverse side effects, including gastrointestinal and cardiovascular adverse effects (64). These serious warnings for all non-steroidal anti-inflammatory drugs may have been exaggerated and have definitely, and perhaps needlessly, frightened non-steroidal anti-inflammatory drug users, because current literature supports the enhanced cardiovascular toxicity of cyclooxygenase-2 inhibitors over traditional non-steroidal anti-inflammatory drugs.

Adverse effects of acetaminophen

Generally, acetaminophen has a safer profile than non-steroidal anti-inflammatory drugs. A recent meta-analysis of 47 randomized controlled trials that enrolled 4186 patients using single-dose acetaminophen for postoperative pain shows no statistically significant differences in the frequency of reported adverse effects between acetaminophen and placebo (6).

However, acetaminophen overdose can cause hepatotoxicity (65). Severe hepatotoxicity has been reported even after therapeutic doses in patients with risk factors such as chronic alcohol consumption, human immunodeficiency virus infection, and hepatitis C virus infection (79). Hence, rational prescribing is equally important for a 'safe' analgesic like acetaminophen.

Adverse effects of opioids

Two recent meta-analyses for the adverse effects of opioids in pain management showed that about one-third of patients abandoned treatment because of adverse events. Dry mouth (affecting 25% of patients), nausea (21%), and constipation (15%) were most common (43, 83). Another meta-analysis of analgesics for dental pain shows that codeine and codeine combinations were associated with a significant increase in patients suffering adverse events compared with non-steroidal anti-inflammatory drugs alone (5). The frequency of adverse events with opioids is more common than with non-steroidal anti-inflammatory drugs and acetaminophen, making them a poor choice for dental pain. In view of the frequency of adverse effects, softening laxatives and anti-emetics (e.g. metoclopromide) should be made available at the same time when required for opioid prescriptions.

Summary statement

The overall risk of analgesics when used in dentistry is low. A recent systematic review has shown that non-steroidal anti-inflammatory drugs have an extremely safe profile when used for acute dental pain as compared with general chronic pain (92). The mean number of patients reporting minor adverse effects was 9.9%. The most common were nausea, diarrhea, drowsiness, and vomiting. No serious adverse effects were reported.

On balance of the evidence for gastrointestinal and cardiovascular safety, it seems that ibuprofen and naproxen are the safest traditional non-steroidal anti-inflammatory drugs. However, it is possible that gastrointestinal and cardiovascular adverse effects can occur even with short-term use of non-steroidal anti-inflammatory drugs, especially when used in high doses. Hence, it is prudent to prescribe anti-ulcer co-therapy with traditional non-steroidal anti-inflammatory drugs and to avoid cyclooxygenase-2 inhibitors in high-risk patients in the treatment of dental pain.

Techniques of analgesic administration

There are a variety of techniques for administering analgesics. Both the routes and timing of analgesic administration will be discussed in this section.

Routes of administration

It is a common belief that parenteral non-steroidal anti-inflammatory drugs would be more efficacious

than the oral route. Many doctors use injected or rectal non-steroidal anti-inflammatory drugs even when the oral route can be used. Reasons for choosing these routes are based on pharmaco-kinetics, that is the rate of drug absorption may influence efficacy and onset of analgesia. A recent meta-analysis of 26 randomized controlled trials (2225 patients) compared the analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain (125). The authors concluded that there was a lack of evidence for any difference in analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes. However, the intramuscular and rectal routes were more likely to have specific local adverse effects. The intravenous route was also reported to increase the risk of postoperative bleeding. In addition, the parenteral route has the same risks of gastrointestinal toxicity as the oral route. The only possible exception is the topical route, which is not associated with any of the gastrointestinal effects seen with other routes (84). Hence, the oral route should be used whenever possible.

Severe local reactions associated with intramuscular injection of non-steroidal anti-inflammatory drugs have been reported. Necrotizing fasciitis is a life-threatening infection of the superficial muscle fascia and the adjacent deep layer of subcutaneous tissue that has been reported with the injection of intramuscular diclofenac and ketorolac (98, 106). Although rare, these serious complications should be considered when intramuscular injection of non-steroidal anti-inflammatory drugs is contemplated.

Preoperative vs. postoperative administration

Traditionally, analgesics were given after surgery when patients experienced moderate to severe pain. At this time, the nociception may be upregulated through both peripheral and central sensitizations, leading subsequently to more intense postoperative pain. Preoperative analgesic interventions may prevent this upregulation of the nociceptive system (137). The idea that analgesia given before the injury would be more effective than the same analgesia given after the injury was termed pre-emptive analgesia (131). Many randomized controlled trials were conducted over the past decade to test the efficacy of pre-emptive analgesia for postoperative pain with conflicting results. A recent meta-analysis of 66 randomized controlled trials (3261 patients) has concluded that pre-emptive analgesia is effective for

non-steroidal anti-inflammatory drugs but not for opioids (89). Recent dental pain studies have also demonstrated the efficacy of non-steroidal anti-inflammatory drugs as a preoperative analgesic (91, 94, 96, 97, 113).

One possible caveat of pre-emptive analgesia is the theoretical risk of complications when certain drugs were administered preoperatively. This is exemplified by the possible increased risk of postoperative bleeding problems from the use of preoperative non-steroidal anti-inflammatory drugs. However, existing data from randomized controlled trials on the incidence of peri-operative bleeding complications caused by non-steroidal anti-inflammatory drugs have been conflicting (122). A recent meta-analysis of 25 randomized controlled trials (1853 patients) concluded that the evidence that non-steroidal anti-inflammatory drugs increase the incidence of bleeding after tonsillectomy remains ambiguous (78).

Summary statement

The evidence indicates that preoperative oral non-steroidal anti-inflammatory drugs are probably the best analgesic technique for the management of acute dental pain for patients with no contraindication to their use. The choice of non-steroidal anti-inflammatory drugs should be based on the efficacy:risk ratio. The lower risk non-steroidal anti-inflammatory drugs should be used first and the more toxic non-steroidal anti-inflammatory drugs should only be used in the event of a poor clinical response.

Drug interactions

This section will focus on analgesic drug interactions of greatest clinical significance. Prescriber ignorance is likely to be a major determinant of many adverse drug interactions and may be limited by rational prescribing.

Non-steroidal anti-inflammatory drug interactions

Most non-steroidal anti-inflammatory drug interactions relate to the antiplatelet and gastrointestinal effects. A key concern is the interaction between aspirin and non-steroidal anti-inflammatory drugs. Although low-dose aspirin is cardioprotective, evidence suggests that concomitant use with certain

non-steroidal anti-inflammatory drugs (in particular ibuprofen) may reduce its cardioprotective benefits and increase gastrointestinal risk (17, 70). Ibuprofen prevents the irreversible platelet inhibition induced by aspirin. This effect may be responsible for a statistically and clinically significant increase in risk of mortality in users of aspirin plus ibuprofen compared with users of ibuprofen alone. In contrast, sustained exposure to diclofenac, rofecoxib, or acetaminophen did not influence the effects of aspirin on platelet function (17).

The gastroprotective benefit of cyclooxygenase-2 inhibitors is partially or, in some patients, totally lost if aspirin is used for cardiovascular prophylaxis (115, 117). Evidence also suggests that concurrent use of non-steroidal anti-inflammatory drugs with corticosteroids or warfarin may increase gastrointestinal risk (9, 85).

The following are some examples of other possible drug interactions with non-steroidal anti-inflammatory drugs:

- Angiotensin-converting enzyme inhibitors – non-steroidal anti-inflammatory drugs antagonize the antihypertensive effects of angiotensin-converting enzyme inhibitors. The risk of renal impairment or hyperkalemia is increased when patients are treated with these two classes of drugs simultaneously.
- Anticoagulants – warfarin levels are likely to be increased if patients are treated with non-steroidal anti-inflammatory drugs because of competition for protein-binding sites.
- Antidiabetics – the antidiabetic effects of the oral sulfonylureas are increased by the co-administration of non-steroidal anti-inflammatory drugs.
- Corticosteroids – the risk of peptic ulceration with associated perforation and bleeding is increased in patients taking both drugs.
- Diuretics – nephrotoxicity is increased, which is probably the result of reduced extracellular fluid volume. The diuretic effect is antagonized and an elevation in serum potassium can occur.
- Methotrexate – levels of methotrexate can be increased because of the direct competition for renal excretion of the two drugs.

Acetaminophen interactions

Generally, acetaminophen has the fewest drug interactions. As acetaminophen is metabolized in the liver, drugs that increase the action of liver enzymes that metabolize acetaminophen (e.g. carbamazepine) may decrease the action of acetaminophen. The potential for acetaminophen to harm the liver is increased when it is combined with alcohol or with drugs that also harm the liver.

Opioid interactions

Most opioid interactions stem from the drug's effects on the liver enzymes, which are largely responsible for the elimination of drugs. These interactions can either slow down or speed up that elimination. An example of the former is the sometimes-fatal interaction between pethidine and monoamine oxidase inhibitor antidepressants, an interaction that can cause an extreme increase in body temperature and seizures. An example of the latter is the withdrawal symptoms reported in patients maintained on methadone when they are given phenytoin.

An algorithm for decision making in pain management

Analgesics do vary in their efficacy, duration of action, and ability to cause adverse effects. In view of non-steroidal anti-inflammatory drugs' efficacy for dental pain, they should be used as the first-line analgesic, especially for severe dental pain where there are no contraindications to non-steroidal anti-inflammatory drugs. The primary factor to consider for the choice of a non-steroidal anti-inflammatory drug should be its efficacy and adverse effect. The most efficacious and least toxic agent should be used first. The other factors to consider are availability, cost, and length of action. If pain is likely to be persistent over a long period of time, it may be logical to choose an agent with a long half-life and prolonged clinical effect. Hence, ibuprofen should be used as a first-line agent for dental pain of short duration. When other traditional non-steroidal anti-inflammatory drugs are required, naproxen should be used because it has intermediate risks of adverse events. Mucosa-protective agents should be added for those at high risk of developing adverse gastro-intestinal effects because of the possibility of adverse events even in short-term use. Cyclooxygenase-2 inhibitors have a place in treatment of high gastrointestinal risk patients who cannot take mucosa-protective agents. In addition, if patient compliance is a problem, the once or twice daily formulation is beneficial (e.g. cyclooxygenase-2 inhibitors and naproxen).
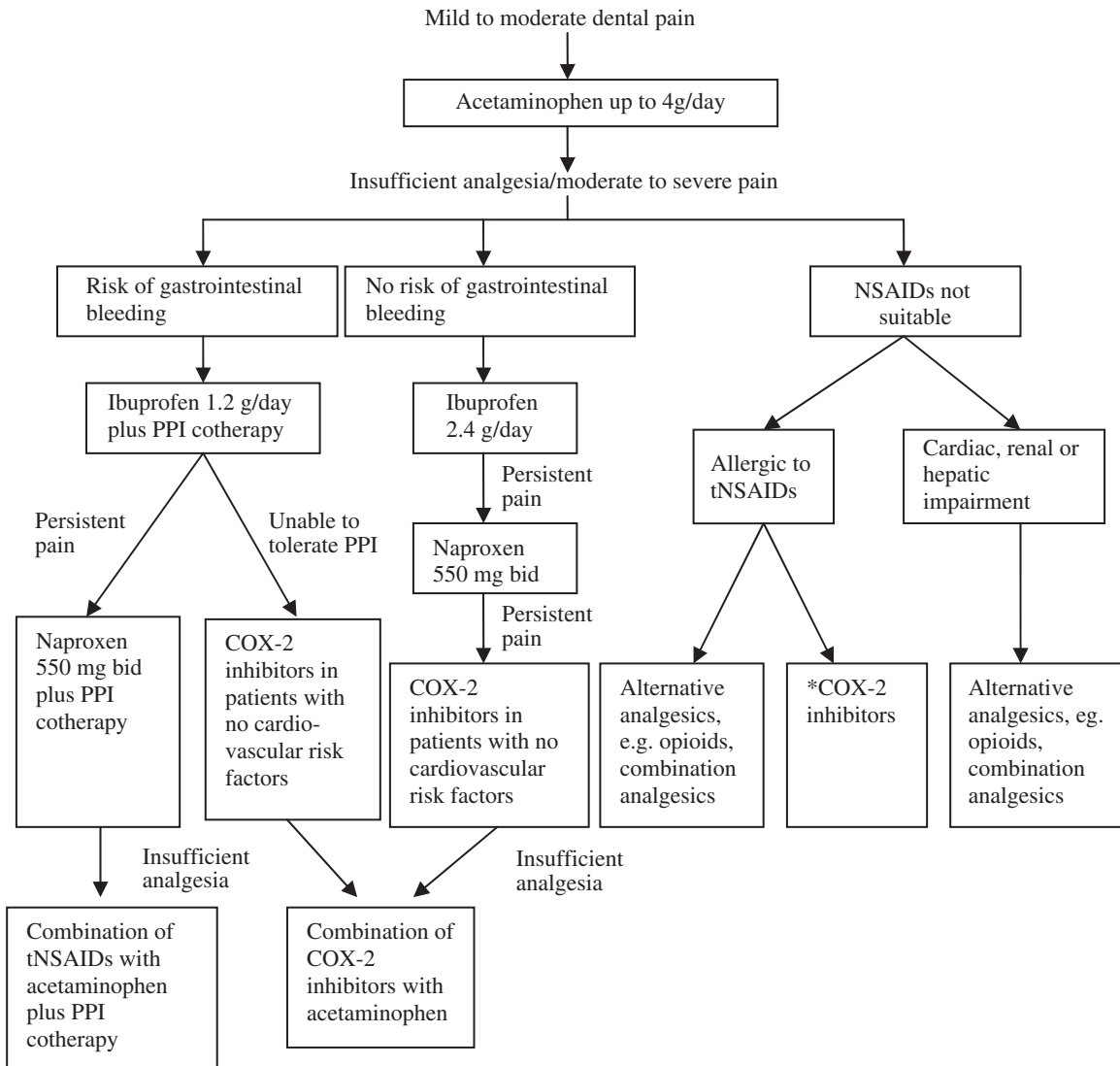
Fig. 1. Dental pain management algorithm. Proceed down the algorithm on the basis of inadequate pain control. Ibuprofen and naproxen are recommended on the basis of extensive evidence supporting efficacy and safety. For management of chronic ∕ persistent pain, administration of non-steroidal anti-inflammatory drugs (NSAIDs) with long half-lives has clear advantages in allowing for once- or twice-a-day dosing, e.g. naproxen and cyclooxygenase 2 (COX-2) inhibitors. Acetaminophen may be added if pain control is inadequate when using non-steroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors. In addition, analgesics may be given pre-emptively to prevent pain. Asterisk indicates that the treatment should be given only after assessing their specific tolerability in a properly performed provocation test. PPI, proton pump inhibitor.

When non-steroidal anti-inflammatory drugs are not appropriate, acetaminophen should be used and can be combined with opioids to increase its efficacy. Opioids should not be used as a sole agent in view of the high frequency of adverse events and their lack of efficacy in dental pain (only indicated when both non-steroidal anti-inflammatory drugs and acetaminophen are contraindicated). Of particular interest is that cyclooxygenase-2 inhibitors have been reported to be well tolerated by patients who are intolerant of traditional non-steroidal anti-inflammatory drugs (18, 19, 104). Most adverse traditional non-steroidal anti-inflammatory drug-induced respiratory and skin allergic reactions appear to be precipitated by the inhibition of cyclooxygenase-1 (73). It has been suggested by some authors that cyclooxygenase-2 inhibitors may safely be used by patients with traditional non-steroidal anti-inflammatory drug intolerance (18, 19, 104). However, we recommend that cyclooxygenase-2 inhibitors be used as alternative drugs in patients with such intolerance only after assessing their specific tolerability in a properly performed provocation test.

An algorithm for decision-making for dental pain is proposed in Fig. 1. Participation by a fully informed patient in the decision-making process is an essential element of good dental practice. Postoperative pain following dental procedures should decrease over the course of 3–5 days as the inflammatory process subsides. The presence of persistent pain even after continuous analgesic therapy should be evaluated to determine the cause of the pain, e.g. infection or misdiagnosis, and treated on the basis of the diagnosis.

Conclusion

Clinical decision-making for analgesic use involves more than simply taking published studies directly to the chair-side. Dentists need to consider how similar their patients are to those in published studies, taking into account both the preferences of their patients and their own experience. Selecting the most appropriate analgesic is an issue of efficacy, safety, and cost. No analgesic, dose, or combination will work for all patients. Rather, the dentist has to periodically assess patient's pain and intervene as needed to adjust medications to balance analgesic efficacy against adverse effects. Rational prescribing will result in good pain management with minimal side effects.

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