An Update on Analgesics for the Management of Acute Postoperative Dental Pain

(Mise à jour sur l'utilisation d'analgésiques pour le traitement des douleurs dentaires postopératoires aiguës)

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Sommaire

L'acétaminophène, les anti-inflammatoires non stéroïdiens (AINS) et les opioïdes sont des analgésiques pouvant être utilisés en dentisterie, et à chacun correspondent des avantages, des inconvénients, des indications et des contre-indications qui leur sont propres. Cet article propose un bref aperçu du rôle de ces substances dans le traitement de la douleur postopératoire aiguë.

Mots clés MeSH : *analgesics/therapeutic use; pain, postoperative/drug therapy; toothache/prevention & control*

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Managing acute postoperative pain is inherent to dental practice. Numerous analgesics are available, and the recent introduction of new agents provides even more options from which to choose. The purpose of this article is to provide a brief review of the drugs that should be considered for the management of acute postoperative dental pain.

Acetaminophen

The first drug to consider is acetaminophen, which is indicated for the management of mild to moderate pain. Acetaminophen is very safe if used in therapeutic doses, as listed in Table 1. Its favourable risk/benefit balance makes it the analgesic of choice for acute postoperative dental pain in adults and children. Acetaminophen has analgesic and antipyretic properties, and is devoid of the side effects that accompany the nonsteroidal anti-inflammatory drugs (NSAIDs). It is therefore also the analgesic of choice if there is a contraindication to an NSAID. Excessive doses can lead to irreversible liver damage and thus caution must be exercised in patients with a history of liver disease or alcoholism. Long-term use should be avoided as it may lead to renal toxicity. For the management of severe pain acetaminophen is usually insufficient by itself, although it may be used in combination with an opioid such as codeine or oxycodone.

NSAIDs

NSAIDs have been used increasingly as analgesics, not just as anti-inflammatory agents, since the mechanism of action of acetylsalicylic acid (ASA) was discovered approximately 30 years ago.[1] Clinical trials have shown repeatedly that, by themselves, NSAIDs are effective for the management of any level of dental pain, whether mild, moderate or severe.[2-5] Optimal use of these drugs resides in understanding their mechanism of action on the arachidonic acid cascade, which is summarized in Fig. 1. NSAIDs block the cyclooxygenase enzymes, which exist in 2 forms known as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for the synthesis of several mediators, including the prostaglandins that protect the gastric mucosa and that regulate renal blood flow, and the thromboxanes that initiate platelet aggregation. Leukotrienes also promote inflammation and can cause bronchospasm. Tissue damage such as pulpitis or periodontitis, or tissue damage resulting from surgery, will induce the production of COX-2, which, in turn, leads to the synthesis of the prostaglandins that sensitize pain fibres and promote inflammation.[3] Traditional NSAIDs block both COX-1 and COX-2, but in recent years, new NSAIDs have been developed that are much more selective for COX-2. These selective COX-2 inhibitors were developed to be less damaging to the gastric mucosa, and the evidence supports this contention.[6,7]

Effects of NSAIDs

The therapeutic and adverse effects of NSAIDs are summarized in Table 2. Analgesic and anti-inflammatory actions are their main properties. These actions, combined with their inhibition of uterine contraction, make them effective for the management of menstrual pain. ASA is a well-known antipyretic and is widely used for its antiplatelet action for prophylaxis of myocardial infarction in patients with a history of unstable angina pectoris or with a history of myocardial infarction.[8]

NSAIDs are associated with many adverse effects, which lead to a number of contraindications (Table 2).[9] Inhibition of prostaglandin synthesis will diminish the protective effect of prostaglandins on the gastric mucosa. This inhibition may lead to dyspepsia, and more seriously, to gastric bleeding. Gastrointestinal toxicity is a major problem associated with NSAIDs, as it is reported that there are over 16,500 NSAID-related deaths per year in the United States.[10] Therefore, NSAIDs should not be given to any patient with active gastric ulcers or gastric bleeding. Acetaminophen is the analgesic of choice for these patients. Enteric-coated formulations may reduce the likelihood of dyspepsia, but will not prevent gastric damage and subsequent bleeding. If acetaminophen is insufficient, one can consider a selective COX-2 inhibitor, as these inhibitors are much less likely to induce gastric bleeding than traditional NSAIDs. Celecoxib (Celebrex) and rofecoxib (Vioxx) are 2 agents in this class that are available. Rofecoxib, when given as a 50-mg dose per day, has been shown to provide analgesia equivalent to ibuprofen 400 mg.[11] Celecoxib provides analgesia that is slightly less efficacious, in that it is similar to ASA 650 mg but less effective than therapeutic doses of naproxen or ibuprofen.[11] New COX-2 inhibitors likely to be released in the near future include valdecoxib, etoricoxib and parecoxib, the latter being an injectable.

NSAID-induced inhibition of thromboxane synthesis results in a decrease in platelet aggregation. For most NSAIDs this effect is reversible within 24 hours. ASA is unique in that it irreversibly damages cyclooxygenase for the life of the platelet; if doses are high, one could consider withdrawing ASA for at least one week before surgery. ASA is more commonly used for prophylaxis of myocardial infarction and is usually taken in a low dose — no more than 325 mg per day. Individual clinical judgment must be used in these cases, but usually patients should be advised to continue taking their low-dose ASA.

A patient may have a true allergy to ASA or other NSAIDs, but of even more concern is the possibility of an allergy-like, i.e. anaphylactoid, reaction. Bronchospasm and other allergy signs and symptoms can occur in susceptible patients as a result of redirecting the arachidonic acid breakdown into the leukotriene pathway, as shown in Fig. 1. Therefore, history of an allergy-like reaction to ASA, particularly an asthmatic reaction, rules out not only ASA, but also any other NSAID. Furthermore, ASA and NSAIDs are best avoided in patients with severe asthma.

Monographs for NSAIDs list numerous potential drug interactions, yet only a few of these interactions may be relevant in dentistry, as our prescribing of these agents is usually short term.[12,13] The effect on reducing blood pressure of antihypertensive drugs that belong to the angiotensin-converting enzyme inhibitor class (such as enalapril), diuretic class (such as hydrochlorothiazide), and beta-blocker class (such as

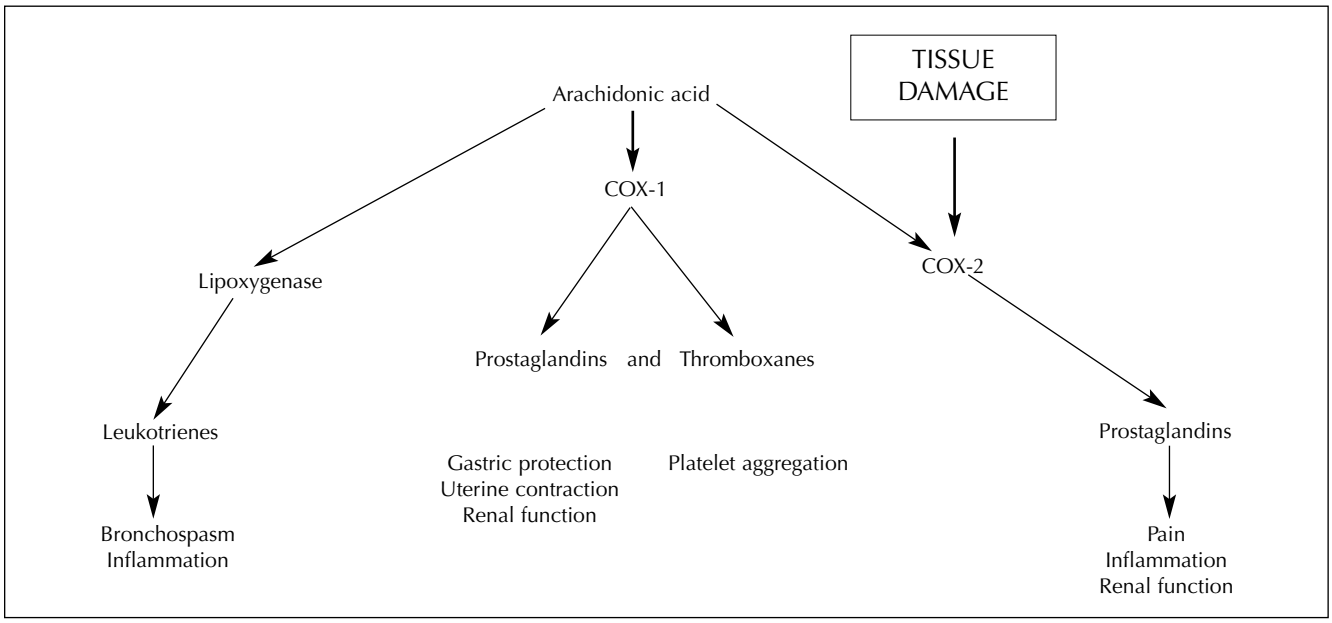

Figure 1: *Arachidonic acid cascade. This illustration is a summary of part of the biochemical response that occurs during inflammation. Cyclooxygenase-1 (COX-1) is constitutive to maintain normal function, whereas cyclooxygenase-2 (COX-2) is induced when there is tissue damage. Traditional NSAIDs act by blocking both cyclooxygenase enzymes. The COX-2 inhibitors are much more selective for this latter enzyme.*

Table 1 **Acetaminophen and NSAID dosing regimens for dental pain**

Drug (brand name[a])	Dose (mg)	Frequency	Daily maximum (mg)
Adults			
Acetaminophen	500–1,000	q4–6h	4,000
Acetylsalicylic acid (Aspirin)	325–1,000	q4–6h	4,000
Celecoxib (Celebrex)	200	once/day	400
Diflunisal (Dolobid)	500	q12h	1,500
Etodolac (Ultradol)	200–400	q6–8h	1,200
Floctafenine (Idarac)	200–400	q6–8h	1,200
Flurbiprofen (Ansaid)	50	q4–6h	300
Ibuprofen (Advil, Motrin)	400	q4–6h	2,400
Ketoprofen (Orudis)	25–50	q6–8h	300
Ketorolac (Toradol)	10	q4–6h	40 (5 days max.)
Naproxen (Anaprox, Naprosyn)	275/250	q6–8h	1,375
Rofecoxib (Vioxx)	50	once/day	50 (5 days max.)
Children			
Acetaminophen (Tylenol, Tempra)	10–15 mg/kg	q4–6h	65 mg/kg[b]
Ibuprofen (Children's Advil)			
age 2–12	10 mg/kg	q6–8h	
over age of 12	200–400 mg	q4h	1,200

[a] Brand names are included only as examples and not to promote any one product. The manufacturers are as follows: Aspirin, Bayer Consumer; Advil, Whitehall-Robins; Motrin, McNeil Consumer Healthcare; Ansaid, Pharmacia; Dolobid, Frosst; Anaprox, Roche; Naprosyn, Roche; Toradol, Roche; Orudis, Aventis Pharma; Idarac, Sanofi-Synthelab; Ultradol, Procter & Gamble Pharmaceuticals; Vioxx, Merck Frosst; Celebrex, Pharmacia; Tylenol, McNeil Consumer Healthcare; Tempra, Mead Johnson Nutritionals.

[b] Not to exceed the adult dose

propranolol), may be diminished if NSAIDs are taken over the long term. It is acceptable to coprescribe NSAIDs as long as the duration is kept to 4 days or less.[13] Calcium-channel blockers are not a concern. NSAIDs are also best avoided with the other agents listed in Table 2. Patients on an anticoagulant will be susceptible to increased bleeding, and ASA in particular must be avoided. NSAIDs should be avoided with high-dose methotrexate, as used for cancer therapy, whereas low-dose methotrexate, as used for arthritis, is not a concern. Concurrent ingestion of alcohol may predispose to gastric bleeding. Long-term use of NSAIDs in combination with other NSAIDs or acetaminophen may lead to nephrotoxicity, and must be avoided. All the interactions listed in Table 2 apply to ASA. In addition, ASA should be avoided in diabetic patients taking oral hypoglycemics.

Prescribing Considerations

Dosing regimens for the NSAIDs tested in a dental pain model are listed in Table 1. Studies have shown that NSAIDs may be all that is required to manage any level of postoperative pain.[2-4] It has been suggested[14] that NSAIDs can be more effective analgesics if they are given early enough and in sufficient doses to prevent the synthesis of prostaglandins, as opposed to prescribing them to deal with pain once prostaglandins are already formed. Therefore, one should consider an initial loading dose, such as double the maintenance dose, which will allow therapeutic levels to be reached more rapidly. Preoperative administration of NSAIDs may reduce the need for analgesics postoperatively. Consideration can thus be given to either preoperative dosing or at least to beginning the dosing immediately after surgery, before the offset of local anesthesia. Preoperative dosing may not be prudent in cases where bleeding is a concern and is probably best reserved for NSAIDs other than ASA or ketorolac. Another consideration is to prescribe the NSAID on a regular basis for the first 1 to 2 days following the procedure, such as every 4 hours, as opposed to on an "as required" (prn) basis. The analgesic can then be taken on a prn basis following this initial period. Finally, although numerous adverse effects exist, these are more easily tolerated in the healthy patient than the adverse effects of opioids. Therefore, it is best to maximize the nonopioid, i.e. acetaminophen or an NSAID, before adding an opioid.

Opioids

Opioid analgesics may be used to manage dental pain.[15] They should be considered if acetaminophen or an NSAID alone will not be sufficient.

Effects of Opioids

Analgesia is the primary action of opioids, affecting both the pain threshold and pain reaction. Although high doses can be very effective for the relief of severe pain, opioids are most often accompanied by unacceptable side effects, which are summarized in Table 3. All opioids induce dose-dependent respiratory depression, sedation, constipation, nausea and vomiting. The nausea is characteristically exacerbated if the patient is ambulatory and can often be relieved if the patient is advised to lie down. Mood alteration may manifest as either euphoria or, alternatively, as an unpleasant reaction known as dysphoria. Chronic use may lead to tolerance or physical dependence. Addiction may occur in patients predis-

Table 2 Effects and contraindications of NSAIDs

Therapeutic effects
Analgesic
Anti-inflammatory
Antipyretic
Antidysmenorrheal
Antiplatelet action (ASA only)
Adverse effects
Dyspepsia
Gastric mucosal damage
Increased bleeding
Possible renal impairment
Anaphylactoid reactions
Contraindications[a]
Gastric ulcers or gastrointestinal inflammatory disease
ASA or other NSAID-induced hypersensitivity
ASA-induced asthma and nasal polyps
Bleeding concerns
Third-trimester pregnancy
Significant renal disease
Children (for ASA only)
Concurrent use of the following drugs:
antihypertensives such as angiotensin-converting enzyme inhibitors, diuretics or beta-blockers: NSAIDs may be coprescribed if required for 4 days or less
lithium
anticoagulants (warfarin)
antineoplastic doses of methotrexate
alcohol
digoxin if patient is elderly or has renal disease
other NSAIDs or acetaminophen; long term
oral hypoglycemics (for ASA only)

[a] *This section is adapted from information provided in the* Compendium of Pharmaceuticals and Specialties[9]

Table 3 Effects and contraindications of opioids

Effects
Analgesia
Antitussive
Sedation
Nausea
Vomiting
Constipation
Mood alteration (euphoria/dysphoria)
Respiratory depression
Tolerance if long term
Physical dependence if long term
Addiction potential
Miosis (except for meperidine)
Contraindications
Severe chronic respiratory disease
Severe inflammatory bowel disease
Concurrent use of alcohol
For meperidine only: monoamine oxidase inhibitor use within the past 14 days

Table 4 Opioid dosing regimens for dental pain

Drug (brand name)	Dose (mg)	Frequency	Daily maximum
Adults			
Codeine, with acetaminophen or an NSAID	30–60	q4–6h	
Oxycodone (Percodan, DuPont Pharma; Percocet, DuPont Pharma)	5–10	q4–6h	
Children			
Codeine, with acetaminophen or an NSAID	0.5–1 mg/kg	q4–6h	3 mg/kg

posed to chemical dependency. Allergy to codeine, morphine, oxycodone or hydromorphone contraindicates use of any other opioid in this structural class. If an opioid is required for patients with such allergies, the pure synthetics, meperidine or pentazocine, could be considered. Additional contraindications are listed in Table 3.

Prescribing Considerations

Prescribing opioids for dental pain should be considered only in combination with an NSAID or acetaminophen, in doses listed in Table 4. Opioids can be prescribed alone if the patient already has a prescription for an NSAID or is taking acetaminophen appropriately. If an opioid is necessary, codeine should be the first to consider. Formulations combining acetaminophen or ASA with codeine are available and popular because of ease of administration. However, ease of administration may be the only advantage of these formulations as the relative doses of nonopioid to opioid are often inappropriate. When using these combination analgesics one should still follow the principle of maximizing the nonopioid before adding the opioid. As an example, 3 tablets of Tylenol No. 2 with Codeine (McNeil Consumer Healthcare) will provide 900 mg acetaminophen with 45 mg codeine, which is preferable to one Tylenol No. 4 With Codeine, which will provide 300 mg acetaminophen with 60 mg codeine.

If codeine is insufficient, the next opioid to consider is oxycodone. This drug is most commonly available with either ASA (in Percodan) or acetaminophen (in Percocet).

Other opioids should be used only rarely for postoperative dental pain. Meperidine (Demerol, Sanofi-Synthelab), a synthetic opioid, is chemically distinct from codeine and oxycodone. Meperidine for dental pain should be reserved for the patient who is allergic to morphine and codeine derivatives, but who still requires an opioid. Although effective when given by injection, oral meperidine has increased risks of

Table 5 Analgesic use in pregnancy or lactation[a]

Drug	FDA category for drug use in pregnancy	May be used during pregnancy	May be used while breast-feeding
Acetaminophen	B	yes	yes
ASA	C/D[b]	do not use in third trimester	caution
Diflunisal	C/D	do not use in third trimester	caution
Flurbiprofen	B/D	do not use in third trimester	yes
Ibuprofen	B/D	do not use in third trimester	yes
Ketorolac	B/D	do not use in third trimester	yes
Ketoprofen	B/D	do not use in third trimester	yes
Naproxen	B/D	do not use in third trimester	yes
Codeine	C	low dose, short duration is acceptable	yes
Oxycodone	B	low dose, short duration is acceptable	yes
Hydromorphone	B	low dose, short duration is acceptable	yes
Meperidine	B	low dose, short duration is acceptable	caution
Pentazocine	B	low dose, short duration is acceptable	caution

[a] *Adapted from Haas and others*[16]
[b] *Where B/D or C/D is listed, the first letter refers to the category for the first 2 trimesters, while the second letter refers to the category for the third trimester.*

adverse effects, as its metabolites can lead to toxicity. Oral meperidine is therefore a very poor choice. The adult dose is 100 mg every 4 hours as required. Pentazocine (Talwin, Sanofi-Synthelabo) is similar to meperidine in that it is also a pure synthetic, but is unique in that it is an agonist-antagonist. The adult dose for pentazocine is 50 mg every 4 hours as required. Hydromorphone (Dilaudid, Abbott) is the most potent opioid discussed in this review and should be reserved for only those situations where other agents and local measures have been tried, but have failed to relieve pain. Hydromorphone should be prescribed for a very short duration only, with an adult dose of 2 to 4 mg every 4 hours as required. There appears to be little justification to use propoxyphene (Darvon, Lilly) today.[15]

Use of Analgesics in Pregnancy and Lactation

The use of analgesics during pregnancy has been recently reviewed, and the findings are summarized in Table 5.[16] Optimal management of dental pain during pregnancy is removal of the source of pain using local anesthesia. If, however, postoperative pain is present, an analgesic may be necessary and should be made available. Acetaminophen is clearly the analgesic of choice in all stages of pregnancy. The use of NSAIDs, including ASA, is less favourable, particularly late in pregnancy. NSAIDs may predispose to ineffective contractions during labour, increased bleeding during delivery or premature closure of the ductus arteriosus of the heart. NSAIDs are therefore contraindicated in the third trimester.

If acetaminophen is insufficient, opioids are considered acceptable during pregnancy provided they are given for a short duration. Chronic opioid use can result in fetal dependence, premature delivery and growth retardation.

As with pregnancy, acetaminophen is the analgesic of choice in lactation. ASA and diflunisal may increase bleeding and should be avoided if possible. Opioids are considered safe in lactation.

Use of Analgesics for Pediatric Patients

ASA is contraindicated for the young patient because it can potentially induce Reye's syndrome. Acetaminophen, administered in appropriate doses as shown in Table 1, may be considered the drug of choice for the pediatric patient. For pain of a higher level, either ibuprofen or codeine can be used, both being available in an elixir form to facilitate administration.

Use of Analgesics for Elderly Patients

Acetaminophen is the analgesic of choice in the elderly. NSAIDs are a major concern due to the potential for gastrointestinal bleeding, which becomes more likely with increasing age, if there is a history of gastric bleeding, and if high doses of NSAIDs or multiple NSAIDs are used. This further emphasizes the need to avoid multiple NSAIDs. Therefore, nonselective NSAIDs are best avoided in the older patient. If they are necessary, one should greatly reduce doses and avoid concurrent use of 2 or more NSAIDs. If the analgesic effect of acetaminophen is insufficient, it is reasonable to consider a selective COX-2 inhibitor such as rofecoxib or celecoxib over other NSAIDs. Opioid analgesics have an increased likelihood of more profound adverse effects as well as prolonged durations of action. Therefore it is best not to select an opioid. If it is necessary, reduced doses must be utilized.

Overall Prescribing Recommendations

A protocol, or algorithm, for analgesic use is presented in Fig. 2. This algorithm should be considered in conjunction with the general guidelines listed in Table 6. NSAIDs have repeatedly been shown to be more effective than opioids in the doses used in dentistry.[2] For mild to moderate pain, a reasonable first consideration is acetaminophen in doses of 500 mg to 1,000 mg every 4 hours. Alternatives include any of the NSAIDs listed in Table 1. If the maximum dose of a nonopioid is ineffective, then consider adding an opioid. The first choice is codeine, but severe pain can warrant oxycodone.

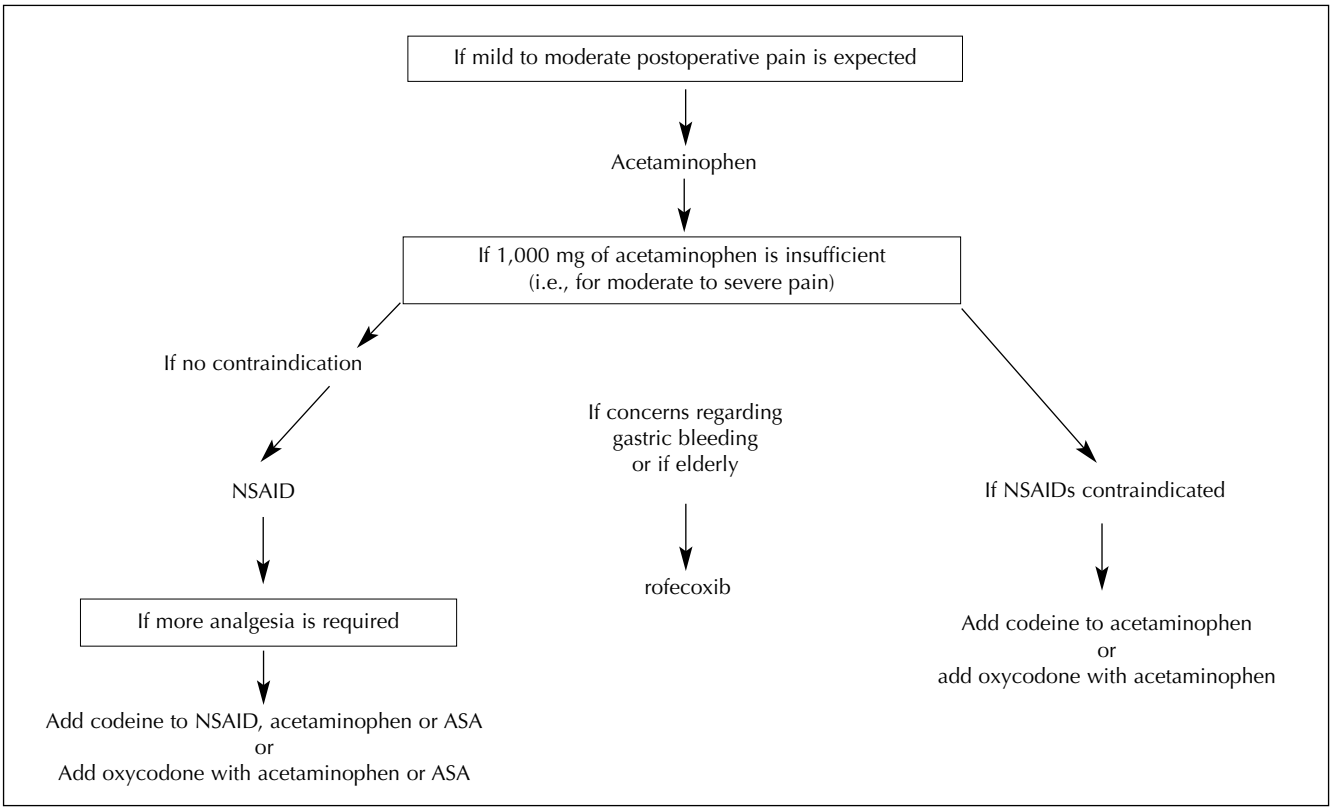

Figure 2: *Algorithm for analgesic use. This algorithm should be considered to manage acute postoperative pain in the adult.*

Table 6 General guidelines for the use of analgesics[9]

Eliminate the source of pain, if at all possible
Individualize regimens based on pain severity and medical history
Maximize the nonopioid before adding an opioid
Optimize dose and frequency before switching
For NSAIDs, consider:
• preoperative dose
• loading dose
• prescribing round-the-clock instead of prn on first day
Avoid chronic use of any analgesic whenever possible
Reduce the dose and duration of any NSAID or opioid in the elderly

One must remember that analgesics are a second-best means of managing pain; the best means is to remove the source as quickly as possible. Therefore, if the patient is able to present to the dental clinic and local anesthesia can be achieved, then the source of pain should be dealt with, whether by means of a pulpectomy, an extraction or incision and drainage. We have numerous analgesics at our disposal. Our goal should be to use these drugs optimally to treat pain most effectively. ➧

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