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Non-steroidal anti-inflammatory drugs for pain after oral surgery

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Abstract

Aim: To describe the role of non-steroidal anti-inflammatory drugs (NSAIDs) in the management of pain after oral surgery.
Materials and methods: A review of the literature describing the pharmacokinetics, benefits and harms of NSAIDs in terms of systematic review evidence, interactions, use in children, pregnancy and breastfeeding.
Results: Twelve Cochrane reviews were identified describing the efficacy of NSAIDs for pain after oral surgery. Ibuprofen 400 mg is an effective analgesic [number needed to treat (NNT) = 2.3 in tablet form and 1.8 in soluble form]. Cyclooxygenase-2 (COX-2)-selective NSAIDs also demonstrate low NNTs, based on smaller studies of post-operative pain. There is association with gastrointestinal, cardiovascular and renal adverse effects.
Conclusions: NSAIDs are effective analgesics for moderate pain after oral surgery. The routine use of COX-2-selective NSAIDs is not recommended. Careful patient selection is important.

Clinical relevance

Scientific rationale

This article provides an update for oral surgeons on the use of non-steroidal anti-inflammatory drugs (NSAIDs) for post-operative pain control.

Principal findings

There are many NSAIDs that are currently licensed around the world, and they have different indications and modes of action. We recommend ibuprofen and diclofenac as the most effective NSAIDs for pain after oral surgery.

Practical implications

NSAIDs are very useful analgesics for managing post-operative pain; however, their adverse effects must be borne in mind when prescribing, and it is advisable to use the lowest effective dose for the shortest possible duration.

Introduction

This third article in the series discusses the use of NSAIDs in the management of pain in patients undergoing oral surgery procedures in primary and secondary care. Other articles in this series describe pain pathways and the use of paracetamol and opioids in the management of pain following oral surgery and pain measurement[1–4].

Background

There are now over 50 different non-steroidal anti-inflammatory drugs (NSAIDs) on the global market. These drugs have analgesic, antipyretic and, at higher doses, anti-inflammatory actions. In UK primary care in 2007 there were 4.5 million prescriptions for ibuprofen, most commonly for 400 mg tablets (2.6 million). These numbers do not include over-the-counter sales, which are considerable, with over 7 million packs sold annually in the UK in 2000[5]. Prescriptions for diclofenac are even more common, with almost 8 million prescriptions being issued in the UK in 2007[6]. This is probably due to only small doses of diclofenac being available in over-the-counter prepa-

rations. Anti-inflammatory drugs were developed in the latter part of the 20th century, with cortisone first synthesised in 1948, followed by non-steroidal drugs in the 1960s. Ibuprofen was the first NSAID to be marketed, in 1969, with diclofenac following in 1974[6]. Since then, more NSAIDs have been developed, along with specific drugs for neuropathic pain[7].

Ibuprofen is widely available without prescription throughout the world. It has been shown to be an effective analgesic in the control of post-operative dental pain in a number of clinical trials[8–10], including a recent Cochrane review[5] that included 72 studies of post-operative pain (57 of which used the third-molar pain model). The review concluded that ibuprofen is an effective analgesic for the treatment of post-operative pain based on a substantial amount of high-quality evidence; this will be discussed in further detail later in this article.

Overall, NSAIDs are safe and well tolerated by patients undergoing outpatient and day surgery and are often considered the first choice in analgesics for patients undergoing these procedures[11].

Other than ibuprofen, commonly used NSAIDs include the following[12,13]:

- *Aspirin* is now mainly used alone for cardiovascular treatment; it is a component of many over-the-counter preparations. Its half-life is 15 min.
- *Naproxen* has good efficacy with a low incidence of side effects, though more than ibuprofen. Its half-life is 12–15 h.
- *Fenoprofen* is as effective as naproxen and may well be slightly more effective; however, it produces slightly more gastrointestinal side effects than ibuprofen.
- *Ketoprofen* and *dexketoprofen* have anti-inflammatory properties similar to those of ibuprofen but with more side effects; dexketoprofen has been introduced for the short-term relief of mild to moderate pain.
- *Diclofenac* and *aceclofenac* have similar efficacy to naproxen. Diclofenac potassium is immediate-release and diclofenac sodium is slow-release. Diclofenac potassium was developed to manage migraine pain[10]. Diclofenac sodium is far more frequently prescribed than the potassium derivative of the drug[2]. The immediate-release preparation is of more use in the management of post-operative pain.
- *Etodolac* has comparable efficacy to naproxen; it is licensed for symptomatic relief of arthritis. Its half-life is 7 h.
- *Indometacin* has equal or superior efficacy to naproxen, but with a higher incidence of side effects, including headache, dizziness and gastrointestinal disturbances. Its half-life is 4.5–6 h.
- *Mefenamic acid* has minor anti-inflammatory properties; it can be associated with diarrhoea and haemolytic anaemia. Its half-life is 3–4 h.
- *Meloxicam* is licensed for short-term pain relief in osteoarthritis and long-term treatment of rheumatoid arthritis and ankylosing spondylitis. Its half-life is 13–20 h.
- *Nabumetone* has effects comparable with those of naproxen.
- *Phenylbutazone* can be used for ankylosing spondylitis but is associated with serious side effects; use is restricted to specialists for severe cases where other treatments have failed.
- *Piroxicam* is as effective as naproxen, with a long duration of action that permits once-daily administration. It has more gastrointestinal side effects than most NSAIDs and is associated with severe skin reactions. Its half-life is 30–86 h.
- *Sulindac* is similar to naproxen.
- *Tenoxicam* has similar activity and tolerance to naproxen; its long duration of action allows for once-daily administration.
- *Tolfenamic acid* is used for treatment of migraine.
- *Ketorolac* and *parecoxib* are licensed for the short-term management of post-operative pain. Parecoxib is cyclooxygenase-2 (COX-2)-selective.
- *Celecoxib* and *etoricoxib* are COX-2-selective and are licensed for the relief of pain in arthritis and ankylosing spondylitis; etoricoxib is also licensed for acute gout.

The uses of these and other NSAIDs are shown in Table 1.

Key NSAIDs for post-operative oral surgery pain

Ibuprofen

In the UK, ibuprofen is available in the following formulations[12]:

- 200 mg, 400 mg, 600 mg and 800 mg (slow-release) tablets
- 100 mg/5 mL oral suspension (available in sugar-free preparations)
- 600 mg effervescent sachets
- Topical preparations

The recommended dosage for adults and children over 12 years is 300–400 mg 3–4 times daily, increased if necessary to maximum of 2.4 g daily, administered by mouth.

Diclofenac

In the UK, diclofenac sodium is included in the Dental Practitioner's Formulary; diclofenac potassium is not.

Table 1 Recommended usage of NSAIDs by treatment type[12,13]

Drug	COX selectivity	PO	MS	OA	RA	HM	AS	DM	G
Aceclofenac				✓	✓		✓		
Acemetacin		✓	✓	✓	✓				
Aspirin	Weak COX-1								
Azopropazone					✓		✓		✓
Dexibuprofen				✓			✓	✓	
Dexketoprofen		✓				✓		✓	
Etodolac				✓	✓				
Fenbufen			✓	✓	✓				
Fenoprofen		✓	✓	✓	✓				
Ibuprofen	Weak COX-1	✓	✓	✓	✓	✓		✓	
Indometacin	Weak COX-1	✓	✓	✓	✓	✓		✓	✓
Ketoprofen		✓	✓	✓	✓				✓
Ketorolac	High COX-1	✓							
Mefenamic acid		✓		✓	✓			✓	
Meloxicam				✓	✓		✓		
Nabumetone				✓	✓				
Naproxen	Weak COX-1	✓	✓	✓	✓			✓	✓
Tenoxicam			✓	✓	✓				
Tiaprofenic acid			✓	✓	✓				
Tolfenamic acid						✓			
Celecoxib	Moderate COX-2			✓	✓	✓			
Diclofenac	Weak COX-2	✓	✓	✓	✓				✓
Etoricoxib	High COX-2			✓	✓				✓
Parecoxib	Moderate COX-2	✓							
Piroxicam	Weak COX-2	✓	✓	✓	✓				✓
Sulindac	Weak COX-2		✓	✓	✓				✓

AS, ankylosing spondylitis; DM, dysmenorrhoea; G, gout; HM, headache and migraine; MS, musculoskeletal; OA, osteoarthritis; PO, post operative; RA, rheumatoid arthritis.

Diclofenac potassium is more expensive and has fewer routes of administration, although it is available over the counter in 12.5 mg tablets for 3-day usage.

Diclofenac sodium is available in the following formulations in the UK[12]:

- 12.5 mg, 25 mg and 50 mg tablets
- 75 mg and 100 mg slow-release formulations
- Dispersible tablets (50 mg equivalent)
- 12.5 mg, 25 mg, 50 mg and 100 mg suppositories
- 75 mg intramuscular injection
- 75 mg intravenous infusion
- Topical preparations

The recommended dosage for adults is 75–150 mg per 24 h in two or three divided doses, administered via mouth or rectum.

Pharmacokinetics

All NSAIDs exert their dominant effects by inhibiting the COX enzyme, which plays a crucial role in the enzymatic processing of arachidonic acid to produce prostaglandins and thromboxane[14]. Two isoforms of COX are described, COX-1 and COX-2. COX-1 regulates normal cellular processes, in particular platelet function, gastrointestinal mucosal protection and protection of the stressed or inadequately perfused kidney[15,16]. The COX-2 enzyme is activated by several cytokines and cell mediators, and its activation leads to the production of inflammatory states and plays a major role in pain. NSAIDs produce their analgesia as a result of the inhibition of prostaglandin production[17] but are also responsible for the loss of gastric protection and the consequent ulceration and bleeding that may occur (Table 2).

Absorption of NSAIDs is swift and comprehensive. Absorption occurs primarily in the upper sections of the small intestine, with a small amount occurring in the stomach. Food intake and gastrostasis associated with acute pain can delay the delivery of the drug to the small intestine, leading to a slower onset of analgesia. Drug absorption can occur across any mucous membrane, and NSAIDs given in a suppository can be of use in the management of acute pain in the post-operative setting, especially in children when swallowing tablets is impractical[19].

The half-life of ibuprofen is approximately 2 h with peak plasma concentrations being achieved within 45 min of dosing (when taken on an empty stomach) or 1–2 h if taken with food, although these times vary

Table 2 Roles of COX-1 and COX-2

	COX-1	COX-2
Constitutive roles	GI protection Platelet aggregation Blood flow regulation Central nervous system function	Renal function Central nervous system function Tissue repair and healing (including gastrointestinal tract) Reproduction Uterine contraction Blood vessel dilation Inhibition of platelet aggregation
Pathological/ adverse roles	Pain Involvement in inflammation Raised blood pressure	Inflammation Pain Fever Blood vessel permeability Alzheimer's

Source: Adapted from Waller[18].

with differing doses and formulations. Ibuprofen is excreted via the kidneys[20].

Diclofenac has a half life of 1–2 h with peak plasma concentrations being reached within 20–60 min of drug administration. The plasma concentrations show a linear relationship to the size of the dose, and the drug undergoes first-pass metabolism and is extensively metabolised[19,21].

The COX-2 selective inhibitors were developed to target only the COX-2 enzymes whilst sparing the COX-1 enzymes, thereby avoiding the COX-1-related adverse effects observed with non-selective NSAIDs. COX-2-selective and non-selective NSAIDs have similar analgesic efficacy, and both exhibit a 'ceiling effect' as seen with paracetamol. COX-inhibiting nitric oxide donators (CINODs) are another new class of drugs designed to provide analgesic efficacy through COX inhibition and gastrointestinal safety through the protective effects of controlled nitric oxide donation. Clinical studies assessing their efficacy are encouraging[22].

The COX-2-selective agents are not completely selective. Celecoxib has only moderate COX-2 selectivity, and its gastrointestinal safety profile has not been consistently shown to be better than that of diclofenac, which has a slight selectivity towards COX-2 inhibition[13,23]. Parecoxib is an injectable prodrug of valdecoxib that is rapidly converted in the liver and associated with a slightly increased risk of renal dysfunction and hypertension[24].

Benefits

Approximately 60% of patients will respond to any NSAID; the remaining 40% may well respond to another if they do not respond to the first. Pain relief starts soon after taking the first dose of the analgesic, and full analgesic effect is achieved within a week. The anti-inflammatory effect may not be achieved for up to 3 weeks; if appropriate responses are not obtained within these time frames, another NSAID should be tried[12].

The 'number needed to treat' (NNT) is commonly used to measure the efficacy of an analgesic. NNT represents the number of patients given an analgesic who achieve at least 50% pain relief as compared with a placebo. The smaller the NNT, the more effective the analgesic. Tables 3 and 4 are based on post-operative pain models using single doses of the trial drug versus placebo.

Use of COX-2-selective agents for post-operative oral surgery pain

The COX-2-selective NSAIDs clearly show advantages over non-selective agents in terms of limiting gastrointestinal toxicity and bleeding. In this section, we will look at the evidence for the use of COX-2-selective agents for post-operative pain management in oral surgery by comparing their analgesic efficacy with that of the non-selective NSAIDs (Figs. 1 and 2).

Celecoxib

In a recent Cochrane review[25], the authors concluded that a 400 mg single dose of celecoxib given post-operatively had a similar effect to 400 mg ibuprofen. One serious event probably linked to celecoxib was noted from the trials included.

Etoricoxib

A recent trial studying the effects of analgesics beyond the 'traditional' 24 h period post-dosing and extending the monitoring period to 3 days showed that etoricoxib had a lower proportion of patients requiring dosing on days 2 and 3 compared with ibuprofen, paracetamol and placebo following third-molar surgery[34]. This COX-2-selective NSAID has been found to have the lowest NNT of all NSAIDs based on Cochrane data, with an NNT of only 1.6 (95% CI 1.5–1.8) based on four dental pain studies with 500 participants in total. Etoricoxib has a very long half-life of 22 h, which is considerable when compared with other NSAIDs. In spite of these beneficial properties, two important practical considerations have to be taken into account when prescribing etoricoxib, the first being that it is not licensed for use in post-operative pain in the UK[12] and

Table 3 Summary of results for COX-2-selective NSAIDs (based on Cochrane reviews)

Drug	Number of trials (number using dental pain model)	Number of participants	Dose (mg)	NNT (95% CI)	Notes
Celecoxib[25]	8 (7)	1380	200	4.2 (3.4–5.6)	One serious adverse event probably linked to drug
			400	2.5 (2.2–2.9)	
			200†	3.2 (2.7–3.9)	
			400†	2.5 (2.2–2.9)	
Etodolac[26,27]	9 (7)	1459	100	4.8 (3.5–7.8)	Very limited information on the extended-release formulations
			200	3.3 (2.7–4.2)	
			100†	4.7 (3.4–7.6)	
			200†	3.3 (2.7–4.2)	
			400†	2.2 (1.7–2.9)	
Etoricoxib[27,28]	6 (5)	1214	120†	1.6 (1.5–1.8)	Insufficient data for other doses to draw conclusions
Lumiracoxib[29]	4 (3)	629	400	2.4 (2.1–2.8)	Drug was found to have a relatively long duration of action
			400†	2.1 (1.8–2.7)	
Rofecoxib[30]	27 (24)	2636	50	1.9 (1.8–2.0)	Drug withdrawn in September 2004

Publication bias was judged to be adequately low in the above studies; studies with fewer than 100 participants were excluded, as were those that found NNTs of greater than 10.
†Dental studies only.

Table 4 Summary of results for non-selective NSAIDs (based on Cochrane reviews)

Drug	Number of trials (number using dental pain model)	Number of participants	Dose (mg)	NNT (95% CI)	Notes
Aspirin[27,31]	67 (48)	5743	600/650	4.2 (3.9–4.8)	Milligram for milligram, aspirin has almost the same efficacy as paracetamol
			900/1000	3.8 (3.0–5.1)	
			1200	2.7 (2.0–3.8)	
			600/650†	4.5 (4.0–5.2)	
			1000†	4.2 (3.2–6.0)	
Ibuprofen[5,27]	72 (57)	9186	50	4.7 (3.3–8.0)	Largest number of trials focus on 200 mg and 400 mg doses
			100	4.3 (3.2–6.4)	
			200	2.7 (2.5–3.0)	
			400	2.5 (2.4–2.6)	
			600	2.7 (2.0–4.2)	
			800	1.6 (1.3–2.2)	
			200†	2.7 (2.5–3.0)	
			400†	2.3 (2.2–2.4)	
Ibuprofen[5,27] (soluble)	9 (9)	959	200†	2.1 (1.9–2.4)	
			400†	1.8 (1.7–2.0)	
Diclofenac potassium[6,27]	15 (9)	1512	50	2.1 (1.8–2.4)	
			100	1.9 (1.7–2.2)	
			50†	2.1 (1.8–2.4)	
			100†	1.9 (1.7–2.2)	
Diclofenac sodium[6,27]	3 (3)	313	50†	6.7 (4.2–17)	
			100†	4.5 (3.2–7.6)	
Ketoprofen[27,32]	14 (12)	968	25	2.0 (1.8–2.3)	Results comparable with those of ibuprofen
			50	3.3 (2.7–4.3)	
			100	2.1 (1.7–2.6)	
			12.5†	2.4 (1.9–3.1)	
			25†	1.9 (1.7–2.3)	
			50†	1.8 (1.5–2.2)	
			100†	1.6 (1.4–2.0)	
Naproxen[27,33]	15 (9)	1509	500/550	2.7 (2.3–3.2)	
			500/550†	1.8 (1.6–2.1)	

†Dental studies only.

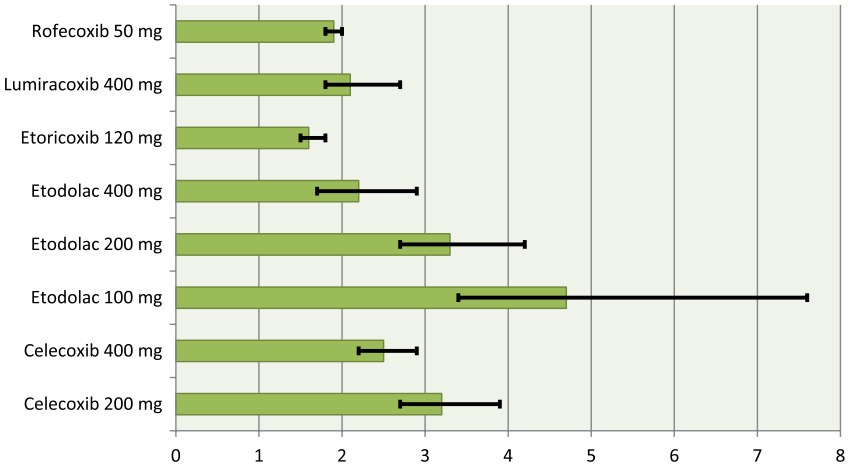

Figure 1 Mean number needed to treat for various COX-2-selective NSAIDs. Bars represent 95% confidence intervals.

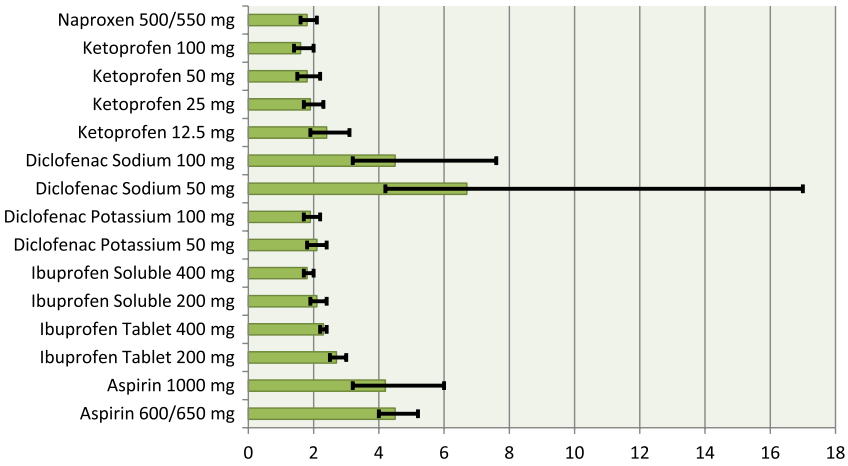

Figure 2 Mean number needed to treat for non-selective NSAIDs (based on Cochrane reviews). Bars represent 95% confidence intervals.

the second being that the evidence base for the NNT is fairly weak, based on data from only four trials, compared with 49 for ibuprofen 400 mg, with 10 times the total number of participants.

Harm and interactions

Bleeding

In some fields of surgery there has been concern about the preoperative and intra-operative use of NSAIDs because of impaired coagulation and consequent perioperative bleeding. This is not considered to be a problem for patients undergoing oral surgery. COX-2-selective inhibitors may have an advantage because they do not affect platelet function and may be safely administered preoperatively before, for example, tonsillectomy and plastic surgery[35,36]. The COX-2 inhibitors are generally more expensive and their use more difficult to justify for short-term use in pain management after oral surgery.

Cardiovascular effects

There have been increasing concerns recently that the anti-inflammatory drugs may be associated with cardiovascular adverse effects. The COX-2 inhibitor rofecoxib was reported in a systematic review of observational trials to increase the risk of cardiovascular events and was withdrawn from the worldwide market in 2004[32,37]. Celecoxib did not show any increased risk. There may also be increased risk with non-selective NSAIDs[37,38]. However, short-term use, such as for post-operative pain, has shown a similar incidence of cardiovascular event to placebo. The issue is more relevant for patients who need long-term drug

use, such as those with arthritis pain. NSAIDs should be avoided in patients at high risk, that is, with a history of myocardial infarction, unstable angina, congestive heart failure or suspected or known atherosclerotic disease. All NSAIDs are thought to weakly increase the risk of thrombotic events when used long-term, with the possible exception of naproxen[7].

Gastrointestinal effects

All NSAIDs are associated with gastrointestinal toxicity. It is recommended that NSAIDs with a low risk of toxicity be used and that they be used at the lowest recommended dose[12]. From highest to lowest risk, NSAIDS associated with significant gastrointestinal toxicity include ketoprofen, ketorolac, diclofenac, naproxen and ibuprofen.

COX-2-selective NSAIDs have a lower risk of gastrointestinal toxicity, and when non-selective NSAIDs are used for treatment of long-term inflammatory conditions such as arthritis, they are often prescribed alongside a proton pump inhibitor.

Patient-related risk factors for gastrointestinal complications in patients taking NSAIDs include the following[7]:

- Age > 65 years
- Previous history of ulcer
- *Helicobacter pylori* infection
- Severe comorbidities

Treatment-related risk factors include the following:

- NSAID dose
- Combination of >1 NSAIDs
- Concomitant use of aspirin
- Concomitant use of corticosteroids
- Concomitant use of anticoagulants and antiplatelet agents

Renal effects

NSAIDs can cause renal insufficiency and 'analgesic-associated nephropathy'[13] and should be avoided if possible or used at the lowest effective dose for the shortest duration possible in patients with renal impairment[12]. However, in adults with normal renal function preoperatively, NSAIDs used for post-operative pain management make a small, transient reduction in renal function that is clinically unimportant[39]. In one Cochrane review, the authors studied the outcomes of 23 trials with 1459 participants; no cases of renal failure requiring dialysis were identified, and no significant reduction in urine production was observed across the trials. The risk of renal failure is higher in elderly patients and those with dehydration or hypovolaemia; the latter two situations are unlikely to be encountered in routine oral surgery practice[19].

Use in children

Not all NSAIDs are licensed for use in children; aspirin must be avoided in children under the age of 12 because of the risk of Reye's syndrome[12,19].

Recommended doses for ibuprofen in children are as follows[12]:

- 3–6 months (body weight over 5 kg): 50 mg 3 times daily (maximum 30 mg/kg daily in 3–4 divided doses)
- 6 months–1 year: 50 mg 3–4 times daily (maximum 30 mg/kg daily in 3–4 divided doses)
- 1–4 years: 100 mg 3 times daily (maximum 30 mg/kg daily in 3–4 divided doses)
- 4–7 years: 150 mg 3 times daily (maximum 30 mg/kg daily in 3–4 divided doses)
- 7–10 years: 200 mg 3 times daily (up to 30 mg/kg daily, maximum 2.4 g, in 3–4 divided doses)
- 10–12 years: 300 mg 3 times daily (up to 30 mg/kg daily, maximum 2.4 g, in 3–4 divided doses)

Recommended doses for diclofenac in children (6 months–18 years) are as follows[12]: by mouth, 0.3–1 mg/kg (maximum 50 mg) 3 times per day; by rectum, 12.5 mg twice daily for a maximum 4 days (children 8–12 kg in body weight) or 1 mg/kg (maximum 50 mg) 3 times daily for a maximum 4 days (children over 12 kg).

Pregnancy

Manufacturers advise against using NSAIDs during pregnancy, unless the benefit outweighs the potential risk. The use of NSAIDs during the third trimester causes increased risk of closure of the fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension in the newborn. In addition, the onset of labour may be delayed and its duration increased through NSAID use[12]. Additionally, regular use of NSAIDs in early pregnancy is associated with an increased risk of miscarriage[40].

Breastfeeding

NSAIDs are not readily transferred into breast milk and are considered to be safe for short-term use; however, aspirin should be avoided due to the risk of Reye's syndrome, as discussed previously. At present, there is insufficient information on the use of COX-2-selective agents during lactation[19].

Asthma

NSAIDs should be used with caution in patients who have any degree of asthma. Approximately 5% of patients will experience 'aspirin-sensitive asthma'; the exact mechanism for this is unknown but is possibly related to the inhibition of COX enzymes. Aspirin desensitisation can be used to decrease this effect; incremental doses of aspirin or topical administration of soluble lysine-aspirin are used to desensitise the patient[41]. It is also thought that COX-2-selective NSAIDs, namely celecoxib, are less likely to cause exacerbations of asthma; however, the safety of COX-2 inhibitors during acute exacerbations is unproven[42,43].

Interactions

There are many interactions associated with the use of NSAIDs listed in the British National Formulary[12]; in this article, we will concentrate on the major known interactions between NSAIDs and other drugs[19], which are listed in Table 5.

Aside from the interactions listed in the table, ibuprofen is thought to block the cardioprotection offered by aspirin[44].

Table 5 Major known interactions between NSAIDs and other drugs

Interaction	Drugs
Increased risk of peptic ulceration	Corticosteroids
Reduced renal excretion	Aminoglycosides, lithium, methotrexate, digoxin
Increased nephrotoxicity	Aminoglycosides, ciclosporin, diuretics
Decreased antihypertensive efficacy	Angiotensin-converting enzyme inhibitors, beta-blockers
Increased severity of gastrointestinal bleeding	Warfarin
Impaired diuresis	Diuretics
Reduced metabolism	Phenytoin

Therapeutics

According to the evidence base, the best NSAIDs for managing post-operative oral surgery pain are the following:

- Ketoprofen 100 mg; NNT = 1.6 (95% CI 1.4–2.0)
- Etoricoxib 120 mg; NNT = 1.6 (95% CI 1.5–1.8)
- Naproxen 500/550 mg; NNT = 1.8 (95% CI 1.6–2.1)
- Ibuprofen soluble 400 mg; NNT = 1.8 (95% CI 1.7–2.0)
- Diclofenac potassium 100 mg; NNT = 1.9 (95% CI 1.7–2.2)
- Ibuprofen tablet 400 mg; NNT = 2.3 (95% CI 2.2–2.4)

The NNTs for these NSAIDs are compared graphically in Figure 3. Figure 4 shows the number of trials on which each NNT is based.

Summary

There is overwhelming evidence demonstrating that 400 mg ibuprofen is an effective analgesic (NNT = 2.3 for the tablet form and 1.8 for the soluble form), and 100 mg diclofenac potassium gives the best NNT for dental pain. It would therefore seem appropriate to use one of these NSAIDs. The routine use of COX-2-selective NSAIDs for post-operative pain relief for oral surgery is not advised; instead, where the risks of prescribing NSAIDs (gastric toxicity, bleeding, interactions, intolerance) outweigh the benefits, we would recom-

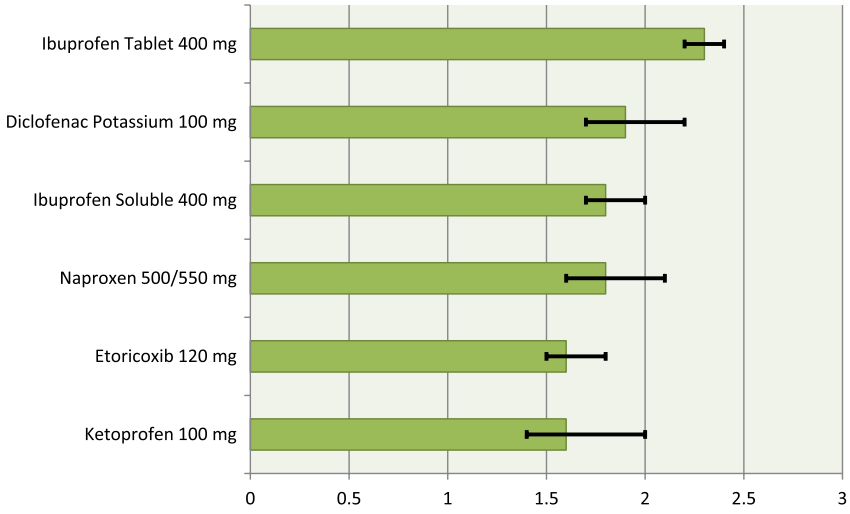

Figure 3 Mean number needed to treat for the most effective NSAIDs. Bars represent 95% confidence intervals.

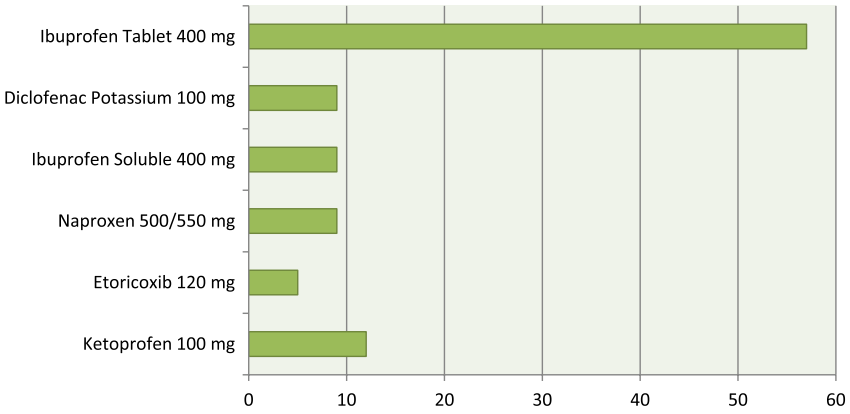

Figure 4 Number of trials used to determine number needed to treat for the most effective NSAIDs.

mend prescribing paracetamol alongside a weak opiate such as codeine or tramadol[2]. In summary, the NSAIDs are very useful analgesics for managing post-operative pain; however, their adverse effects must be borne in mind when prescribing, and it is advisable to use the lowest effective dose for the shortest duration in post-operative pain.

The side effects of these drugs should always be borne in mind when prescribing, but that is not to say that they should prevent prescribing of these effective drugs. The more severe side effects (such as GI bleeding and increased risk of thrombotic events) appear to only occur in long-term use of the drugs for chronic inflammatory conditions, not for short-term use for post-operative pain as required after oral surgery.

The use of COX-2-selective NSAIDs should be considered in patients with high risk of gastrointestinal toxicity and bleeding, and it is important to remember that NSAIDs only show clinically relevant levels of anti-inflammatory action when used for 3 weeks or more.

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References

1. Coulthard P, Bailey E, Patel N, Coulthard MB. Pain pathways, preemptive and protective analgesia for oral surgery. Oral Surg 2014;7:74–80.
2. Patel N, Bailey E, Coulthard P. Opioids for pain after oral surgery. Oral Surg DOI: 10.1111/ors.12076. Epub ahead of print.
3. Coulthard P, Patel N, Bailey E, Coulthard MB. Measuring for pain after oral surgery. Oral Surg DOI: 10.1111/ors.12075. Epub ahead of print.
4. Coulthard P, Bailey E, Patel N. Paracetamol (acetaminophen) for pain after oral surgery. Oral Surg 2014;7:81–86.
5. Derry CJ, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database Syst Rev 2009;(3)CD010210.
6. Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database Syst Rev 2011;(11)CD004768.
7. Beaulieu P, Lussier D, Porreca F, Dickenson AH. Pharmacology of Pain. Seattle: IASP Press, 2010.
8. Winter L, Bass E, Recant B, Cahaly JF. Analgesic activity of ibuprofen (Motrin) in postoperative oral surgical pain. Oral Surg Oral Med Oral Path 1978;45:159–66.
9. Seymour RA, Frame J, Negus TW, Hawkesford JE, Marsden J, Matthew IR. The comparative efficacy of aceclofenac and ibuprofen in postoperative pain after third molar surgery. Br J Oral Maxillofac Surg 1998;36:375–9.
10. Hersh EV, Levin LM, Cooper SA, Doyle G, Waksman J, Wedell D *et al*. Ibuprofen liquigel for oral surgery pain. Clin Ther 2000;22:1306–18.
11. Bromley L, Brandner B. Oxford Pain Management Library: Acute Pain. Oxford: Oxford University Press, 2010.
12. British Medical Association/Royal Pharmaceutical Society. British National Formulary 65. London: British Medical Association/Royal Pharmaceutical Society, 2013.
13. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology, 7th edition. Edinburgh: Elsevier Churchill Livingstone, 2012.
14. Dubois RN, Abramson SB, Crofford L. Cyclooxygenase in biology and disease. FASAB J 1998;12:1063–73.
15. Lipsky PE, Abramson SB, Crofford L. The classification of cyclooxygenase inhibitors. J Rheumatol 1998;25:2298–303.

16. Patrono C, Dunn MJ. The clinical significance of inhibition or renal prostaglandin synthesis. Kidney Int 1987;32:1–12.
17. Malmberg AB, Yaksh TL. Antinociceptive effects of spinal non-steroidal anti-inflammatory agents on the formalin test in the rat. J Pharmacol Exp Ther 1992;263:136–46.
18. Waller DG, Renwick AG, Hillier K. Medical Pharmacology and Therapeutics, 3rd edition. London: Saunders, 2009.
19. Macintyre PE, Walker SM, Rowbotham DJ. Clinical Pain Management: Acute Pain, 2nd edition. London: Hodder Arnold Press, 2008.
20. Medicines and Healthcare Products Regulatory Agency. MHRA Public Assessment Report: Ibuprofen. Available from URL: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con071215.pdf [accessed 20 April 2013].
21. Medicines and Healthcare Products Regulatory Agency. MHRA Public Assessment Report: Diclofenac Potassium. Available from URL: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con076429.pdf [accessed 20 April 2013].
22. Hill CM, Sindet-Pederson S, Seymour RA, Hawkesford JE, Coulthard P, Lamey P *et al*. Analgesic efficacy of the cyclooxygenase-inhibiting nitric oxide donor AZD3582 in postoperative dental pain: comparison with naproxen and rofecoxib in two randomized, double-blind, placebo-controlled studies. Clin Ther 2006;28:1279–95.
23. Esser R, Berry C, Du Z. Preclinical pharmacology of lumiracoxib: a novel selective inhibitor of cyclooxygenase-2. Br J Pharmacol 2005;144:538–50.
24. Zang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events – meta-analysis of randomised trials. J Am Med Assoc 2006;296:1619–32.
25. Derry S, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2012;(3)CD004233.
26. Tirunagari SK, Derry S, Moore RA, McQuay HJ. Single dose oral etodolac for acute postoperative pain in adults. Cochrane Database Syst Rev 2010;(12)CD007357.
27. Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev 2011;(9)CD004309.
28. Clarke R, Derry S, Moore RA. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2012;(4)CD006865.
29. Roy YM, Derry S, Moore RA. Single dose oral lumiracoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2012;(6)CD004604.
30. Bulley S, Derry S, Moore RA, McQuay HJ. Single dose oral rofecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2010;(12)CD002067.
31. Derry S, Moore RA. Single dose oral aspirin for acute postoperative pain in adults. Cochrane Database Syst Rev 2012;(4)CD007355.
32. Barden J, Derry S, McQuay HJ, Moore RA. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. Cochrane Database Syst Rev 2011;(11)CD004234.
33. Derry CJ, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. Cochrane Database Syst Rev 2011;(11)CD008659.
34. Brown JD, Daniels SE, Bandy DP, Ko AT, Gammaitoni A, Mehta A *et al*. Evaluation of multiday analgesia with etoricoxib in a double-blind, randomized controlled trial using the postoperative third-molar extraction dental pain model. Clin J Pain 2012;0:1–7.
35. Gajraj NM, Joshi GP. Role of cyclooxygenase-2 inhibitors in postoperative pain management. Anesthesiol Clin North America 2005;23:49–72.
36. Gilron I, Milne B, Hong M. Cyclooxygenase-2 inhibitors in postoperative pain management. Anesthesiology 2003;99:1198–208.
37. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: studies of selective and non-selective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44.
38. Kearney PM, Baigent C, Godwin J. Do selective cyclooxygenase 2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. Br Med J 2006;332:1302–8.
39. Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. Cochrane Database Syst Rev 2009;(3)CD002765.
40. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute Pain Management: Scientific Evidence, 2nd edition. Melbourne: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, 2005.
41. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl Med J 2002;347:1493–9.
42. Power I. Aspirin-induced asthma. Br J Anaesth 1993;71:619–21.
43. Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J *et al*. Biochemical and clinical evidence that aspirin intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgesic drug celecoxib. J Allergy Clin Immunol 2003;111:1116–21.
44. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003;361:573–74.