



Back to the future: postoperative pain management beyond COX-2 inhibitors

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Abstract

In the aftermath of the heated dispute on COX-2 selective nonsteroidal anti-inflammatory drugs (NSAID) that led to the national and international withdrawal of several of the recently introduced coxibs a balanced discussion of pros and cons for their short term use is warranted. Further debate and research has highlighted risks with both classical NSAIDs and coxibs when administered to patients with cardiovascular disease. For several decades discussion about indications, risks and contraindications for the perioperative use of classical NSAIDs has been ongoing. The COX debate has further added some uncertainty amongst practitioners. With a vast amount of research available on this topic, it should however be feasible to reach some consensus for the perioperative use of NSAIDs as well as for coxibs. This would ensure that the right patients take advantage of our present knowledge of NSAIDs as part of a multimodal and balanced perioperative analgesic regimen and at the same time that the patients at risk are not prescribed such drugs. Rational use of NSAIDs in the perioperative period would benefit a major group of patients who at present are deprived of such therapy due to unfounded fears of side effects and lack of knowledge among prescribers. This review highlights some of the aspects of short term (i.e. less than 5 days) perioperative use of NSAIDs.

Recent debate has highlighted severe cardiovascular side effects from COX-2 selective nonsteroidal anti-inflammatory drugs (COX-2 inhibitors or coxibs). This has led to a withdrawal from the New Zealand (NZ) market of rofecoxib and valdecoxib in accordance with international recommendations.

The bulk of evidence for the potentially harmful effects of COX-2 inhibitors is based on long-term trials in rheumatoid populations. An extensive database is available on the analgesic efficacy of COX-2 inhibitors for postoperative pain.¹ While only a few studies have focused on adverse effects of the short-term perioperative use (1–5 days) of these drugs, the main impression seems to be of a high general tolerability apart from a cluster of cardiovascular adverse events reported after coronary by-pass surgery.^{2–6}

Anaesthetists have been advocates of the COX-2 inhibitors as they have allowed more patients to get the benefits from a nonsteroidal anti-inflammatory drug (NSAID) as part of a multimodal perioperative analgesic regimen offering superior analgesia with opioid sparing effect and reduced opioid-related side effects.

In the aftermath of the recent COX-2 debate it is however appropriate to revisit the rationale perioperative use of NSAIDs. The extent upon the prolonged use of NSAIDs outside the perioperative period will not be elaborated.

Pharmacology

The synthesis of prostaglandins is the primary target of all NSAIDs. Prostaglandins are known to be involved in numerous physiological systems (Table 1). The regulation of vascular tone and platelet aggregation is affected by endothelial prostacyclin and platelet-derived thromboxane. Prostaglandins of the E-series exert protective effects on the gastric mucosa.⁷⁻¹¹ Prostaglandins are also of major importance in the regulation of the inflammatory cascade and they act as sensitisers of peripheral nociceptors.¹²

The synthesis of prostaglandins (PG-series), thromboxane, and the leucotrienes is initiated (e.g. after tissue trauma) by the conversion of arachidonic acid to intermediate PGG₂ and PGH₂, which are the substrates for the several other prostaglandins (Figure 1).

The two first metabolic steps are catalysed by cyclo-oxygenase (COX) which is the enzyme responsible for the velocity of the reaction and thus the rate limiting factor. Cyclo-oxygenase is known to be present in at least two isomeric forms (COX-1 and COX-2) with different physiological effects.^{9,10}

Table 1. Prostaglandins: their organ-specificity and effects

Prostaglandin type	COX-1	COX-2	Organ specificity	Effects
PGE ₁	++ ++ ++ -	+ + ++ ++	CNS / peripheral nerves GI-tract Kidney Peripheral tissues	Sensitisation and hyperalgesia Motility, mucosa protection Medullary blood flow, Na ⁺ -K ⁺ exchange Inflammatory response
PGE ₂	++ - - ++	+ ++ + ++	CNS / peripheral nerves Peripheral tissues GI-tract Uterus	Sensitisation and hyperalgesia Inflammatory response Mucosa protection, H ⁺ secretion Labour onset
PGI ₂	- ++ ++ ++	++ ? + ++	Vessel wall Coagulation GI-tract Kidney	Smooth muscle relaxation Fibrinolysis, platelet aggregation Mucosa protection, H ⁺ secretion Cortical and glomerular blood flow
TXA ₂	++ ++ ++	- + -	Platelets Vessel wall Kidney	Pro-aggregatory Contraction GFR regulation
PGF _{2α}	- -	++ ++	Uterus Kidney	Contractility ↑ in labour Na ⁺ /water excretion

The predominant COX-enzyme involved in their metabolism is marked ++; + indicates that the enzyme is present but in lower concentrations under normal non-inflammatory conditions; GFR=glomerular filtration rate; GI=gastrointestinal; CNS=central nervous system.

COX-1 is a constitutive enzyme (i.e. “daily household”) and is involved in the production of “physiological” prostaglandins. COX-2 is classically described as inducible and is expressed in inflamed/traumatised tissues, but is lacking in others (e.g. platelets) (Figure 2). Recent evidence, however, points to a more complex picture, with the COX-2 enzyme being constitutively expressed in several tissues as e.g. brain and kidney (cf. Table 1). A third isomeric form (COX-3) has recently been proposed as being expressed in the restitutional phase of inflammation.¹³

The classic, non-selective NSAIDs are not more specific for either isomeric form of the COX enzyme as opposed to the newer and selective COX-2 inhibitors. A hydrophilic side-pocket unique to the COX-2 isoenzyme allows the active site to accommodate only the coxibs due to their added side chain. Classic NSAIDs block arachidonic acid access to both isoforms. However the degree of COX-1 or COX-2 selectivity (i.e. COX-1: COX-2 inhibitory ratio) warrants caution in the interpretation due to methodological differences of currently available test systems, of which biological models have more clinical relevance. Of the various coxibs, celecoxib has a ratio of 1:30 whereas rofecoxib, for example, has a ratio of 1:276 and lumiracoxib a ratio of 1:433.

The analgesic effects of NSAIDs are ascribed primarily to COX-2 inhibition, whereas several adverse effects are believed to be mediated by COX-1 inhibition. The inhibition of COX-1 prolongs the bleeding time due to an inhibition of TXA₂ synthesis from platelets and may lead to the formation of gastric ulcerations due to PGE₂ inhibition. COX-1 inhibition may, under certain circumstances, decrease renal glomerular filtration rate. COX-2 selectivity may theoretically attenuate such adverse effects.¹⁴

Figure 1. Tissue injury activates the arachidonic acid cascade through membrane bound phospholipase A2 (PA2). Through the action of cyclooxygenase various prostaglandins (PG) are formed according to tissue specific pathways. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the COX enzyme.

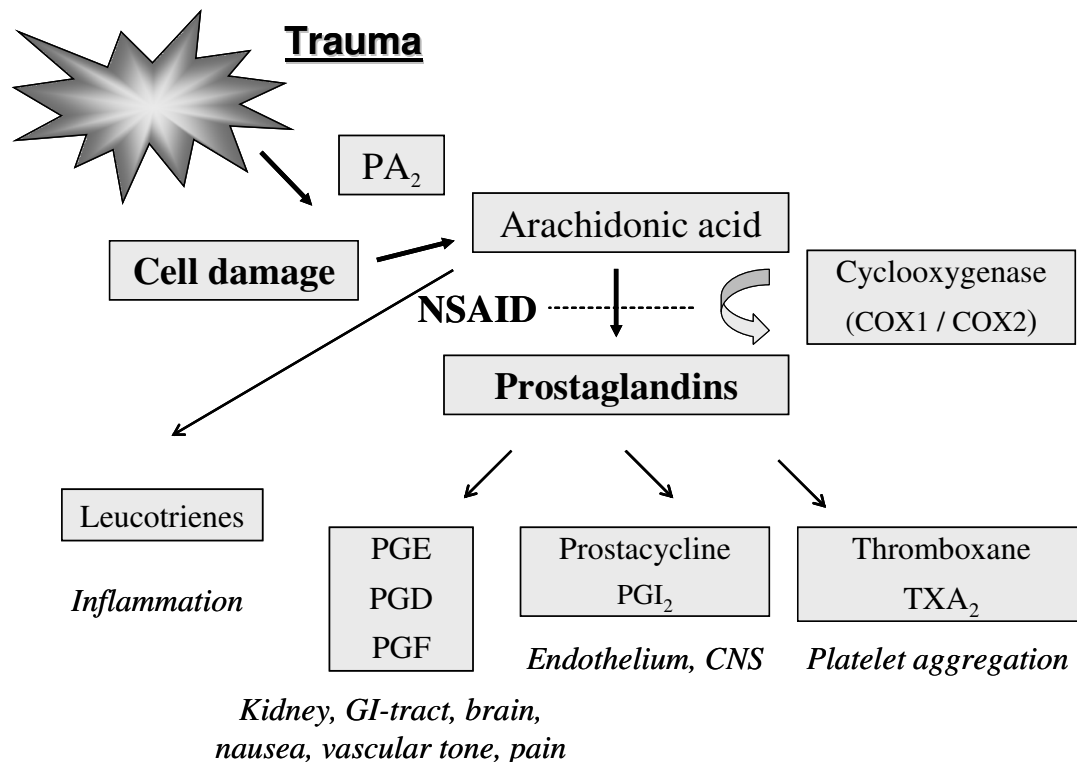
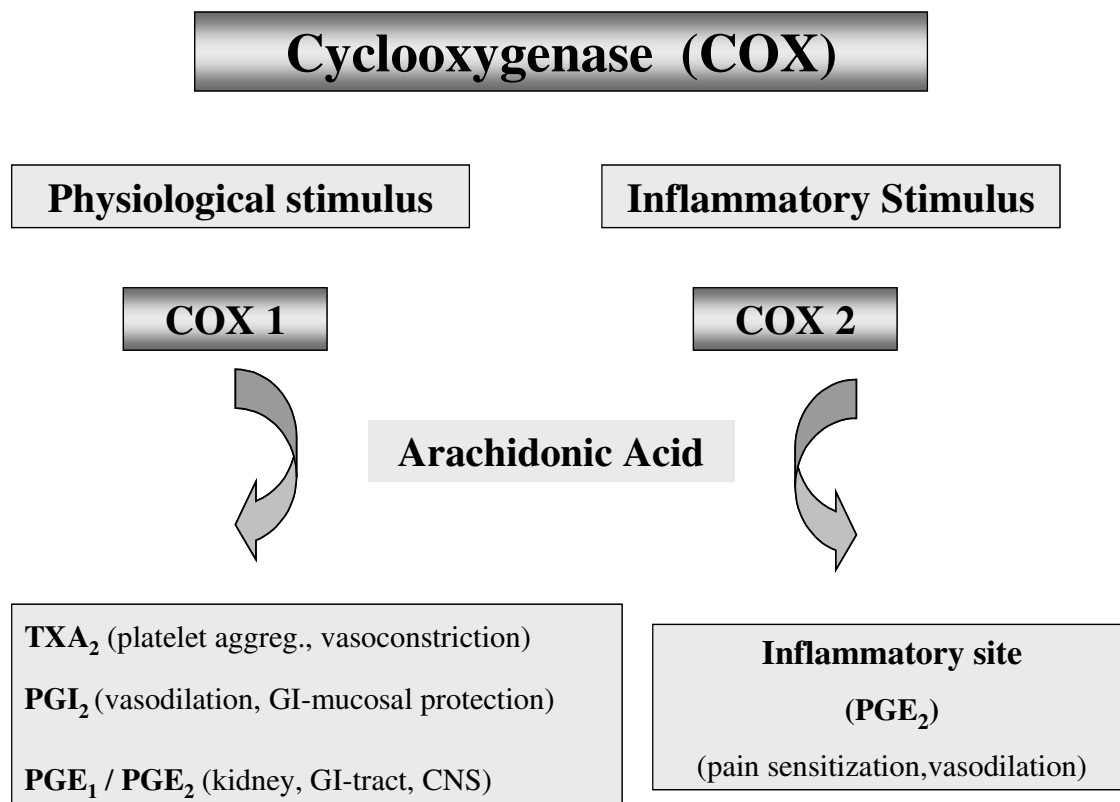


Figure 2. Cyclo-oxygenase (COX) exists in at least two forms (COX-1 / COX-2). In a simplified model, various normal physiological stimuli induce COX-1 activity and inflammation induces COX-2 activity. By the enzymatic action of COX, arachidonic acid is converted into prostaglandins (TXA₂=thromboxane; PGI₂=prostacyclin; PGE=prostaglandin E)



Inhibition of COX-3 by the non-selective NSAIDs may theoretically interfere with restitution after tissue trauma but the clinical relevance remains to be elucidated.¹³ The above mentioned pharmacological effects of NSAIDs are widely accepted. Central (CNS) effects have recently been suggested but the exact mechanism has not been fully clarified. NSAIDs are strongly ionized at physiological pH, and have difficulties passing the blood-brain barrier. However endothelial cells in the brain were recently shown to possess interleukin receptors coupled to COX-2 activity.

Provided the proper stimulus (e.g. interleukin 1), such receptors would allow PGs to be expressed in the brain. An inhibition by NSAIDs at this level could explain an intracerebral effect. Finally, an interaction with opioid receptors in the CNS has been suggested.¹⁵⁻¹⁸

Selective COX-2 antagonism affects the balance between PGI₂ and TXA₂ in favour of TXA₂, and might thus act as a prothrombotic principle due to unopposed inhibition of endothelial PGI₂.^{19,20} Early warnings of this potential mechanism were given by several groups but it took larger patient materials in order to realize that COX-2 antagonism might increase cardiovascular events in predisposed patients.

Several recent large-scale studies have unraveled this side effect and have led to a heated debate on the use of these new drugs and to the withdrawal of some (but not all) coxibs.²¹⁻²⁵

The inherent potential for serious cardiovascular events with the use of coxibs seems to be a class effect but may still differ among the coxibs (e.g. rofecoxib >> celecoxib). However, as would be expected, it becomes evident in patients at risk of such events.

Recent debate has focussed on an interference of coxibs with the mechanisms of myocardial preconditioning (i.e. a preceding minor ischaemic episode offering protection towards a following ischaemic event) and on the impact of coxibs on renal physiology as underlying coxib-induced adverse cardiovascular events.²⁴ Indeed, the increased cardiovascular risks are acknowledged in the recent national and international recommendations on the continued use of COX-2 inhibitors.²⁶

To paraphrase George Orwell, *all NSAIDs are not created equal*. Indeed, possibly due to several variant forms of the COX enzyme,²⁷ NSAIDs differ in their effects and side effects profile. Of the four major pharmacological groups of classical NSAIDs (salicylic acid, propionic acid, acetic acid, and oxicams), there are differences in platelet inhibitory activity (e.g. diclofenac being less active than comparator NSAIDs) and in gastrointestinal side effects profile (e.g. ibuprofen showing best GI tolerability).²⁸

Interaction (e.g. decreased effect) with low-dose regimens of salicylic acid is seen with some but not with others (e.g. ibuprofen may interact whereas e.g. diclofenac does not).²⁹ Furthermore, NSAID-induced side effects show a strong dose, time, and age dependence.

Clinical use of COX-2 inhibitors

So in which patients are COX-2 inhibitors indicated for perioperative pain management?

As an inflammatory tissue response to surgery is involved in sensitisation of peripheral and central pain pathways, NSAIDs / coxibs should be used as facilitating analgesics as part of a multimodal regimen. Coxibs should be used at the lowest recommended dosage and for short periods of time only (i.e. < 5 days). A lower “ulcerogenic” potential and a platelet-sparing effect must be taken into consideration.

Where the nature of the surgical intervention “contraindicates” use of classic NSAIDs due to risk of bleeding (e.g. ENT surgery, plastic surgery, or neurosurgery) coxibs may well be used.³⁰

There is, however, no valid evidence for any superior analgesic benefits of the coxibs as opposed to the classic NSAIDs in the majority of surgical patients.^{1,31-34}

In NZ, there is access to five COX-2 selective NSAIDs: meloxicam, etoricoxib, lumericoxib, celecoxib, and parecoxib. The latter is for parenteral use and is the only available intravenous (iv) COX-2 inhibitor in NZ. Primarily used by anaesthetists during the immediate perioperative period, it has not proven superior to any classical iv NSAIDs.

Meloxicam has a long record as anti-inflammatory drug with a relatively long half-life (~20 h) and a favourable gastrointestinal (GI) profile (ulcerogenicity and GI bleeding)

in long-term studies in osteoarthritis. The database for its perioperative use is limited, and its COX-2 selectivity at clinically relevant perioperative doses has been questioned (Virtual Anaesthesia Textbook: <http://www.virtual-anaesthesia-textbook.com>).

Etoricoxib has not been trialled in the perioperative setting. Lumericoxib was recently introduced, but is only scarcely documented for postoperative pain.

This leaves us with celecoxib as the only available true COX-2 selective, oral NSAID for perioperative analgesia. A one-off premedication dose of 400 mg (as opposed to 200 mg) of celecoxib (elimination $T_{1/2} \sim 4-8$ hr), followed by 200 mg once to twice daily for postoperative analgesia, has recently been advocated as optimal in adults (cf. Straube et al 2005). Intraoperatively, the only available intravenous COX-2 inhibitor is parecoxib (elimination $T_{1/2} \sim 8$ hr) at a normal adult dose of 40 mg. No further NSAIDs should be administered until after at least 12 hours.

Contraindications and adverse effects of NSAIDs

Anecdotes and myths are often quoted when discussing NSAIDs. Clear and updated guidelines for the perioperative use of NSAIDs (including COX-2) are imperative to ensure that patients get the full benefit of their inclusion into a multimodal analgesic regimen. There are, however, some clear contraindications to the use of NSAIDs and some more controversial relative contraindications (Table 2).

The national advisory board of NZ (Medsafe: <http://medsafe.govt.nz/hot.htm>), in agreement with international consensus, recommends that COX-2 NSAIDs are contraindicated in patients undergoing cardiac or vascular surgery, and in patients at high risk of cardiovascular disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing major surgery.

Table 2. Absolute contraindications to NSAIDs

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| <ul style="list-style-type: none">• Ischaemic cardiovascular disease• Severe hypertension• Severe liver disease• Severe diabetes• Allergy to NSAIDs / (sulphonamide ~ COX-2)• Peptic ulcer disease (COX-1) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

There is, however, no indications as to the severity of such risk factors and the perioperative team is left with a recommendation to weigh the risks and benefits in each individual case and an obligation to inform the patient of any intended perioperative use of coxibs.

It is worth remembering that all NSAIDs hold a potential to aggravate any pre-existing heart failure and hypertension due to fluid retention through renal effects. It is

also worth noting that patients should continue low-dose acetylsalicylic acid if a COX-2 inhibitor is prescribed to maintain a cardioprotective / antiplatelet effect, as this is not offered by COX-2 inhibitors.

Ibuprofen and indomethacin may impede access of aspirin to platelet COX-1 enzyme and inhibit this protective effect. Furthermore, the addition of low-dose acetylsalicylic acid will remove any “gastroprotective” effect of the COX-2 inhibitor.

Patients with a history of peptic ulcer disease may well benefit from the perioperative use of coxibs if a NSAID is indicated. An alternative approach to coxib prescription for the patient with gastrointestinal intolerance to NSAIDs is the concomitant use of a proton inhibitor or misoprostol as mucosal protection.³⁵ Patients on continued perioperative acetylsalicylic acid should also receive gastroprotection during COX-2 inhibitor treatment.

Another major concern of perioperative NSAID use is the potential for renal impairment. Both COX-1 and COX-2 activity is expressed in the kidney, and in the marginally failing kidney, any class of NSAIDs may cause deterioration of such failure. It has been stated that the physiological function of COX-1 in the kidney is mainly in maintaining the glomerular filtration rate (GFR), whereas COX-2 is primarily involved in water and electrolyte haemostasis.³⁶

Side effects such as acute renal failure, papillary necrosis, and nephrotic syndrome are extremely rare with NSAID therapy in the uncompromised patient. Although mild side effects such as hyperkalaemia and fluid retention, and minor increases in blood pressure, are seen they are readily reversible with discontinuation of the drug. Furthermore, interactions with antihypertensives and diuretics warrant caution in patients concomitantly treated with these drugs.

Patients who should not receive either non-selective nor COX-2 selective anti-inflammatories are the ones with preoperative renal dysfunction or a renal perfusion compromise (e.g. hypovolaemia, severe liver or heart failure, and advanced hypertension or diabetes).

Continuous perioperative monitoring of creatinine and urea during NSAID therapy is warranted in patients with hypertension and mild diabetes and also in the very elderly. There are some indications, however, that COX-2 inhibitors may prove safer in these patient groups, but more data is needed before any recommendations can be made.³⁷

NSAIDs are contraindicated in patients with a known allergy to this group of drugs. As celecoxib and parecoxib contain a sulphonamide moiety, they are contraindicated in patients with a known allergy to sulphonamides. Of the asthmatic population, only 10–15% are actually reactive to the effect of NSAIDs, partly related to their diversion of the arachidonic acid cascade towards bronchoconstrictory leucotrienes.³⁸

A simple questioning of the patient prior to surgery of any NSAID usage in the past will often solve the concern. If the patient is an asthmatic and never challenged with NSAID, the perioperative period is perhaps not the ideal time to test the system. In addition, COX-2 selectivity does not seem to confer any advantage in these patients.

The use of NSAIDs in orthopaedic surgery is controversial—some experimental work points to NSAIDs having an inhibitory effect on bone healing. However long experience and a widespread use of NSAIDs after fracture surgery has not highlighted any clinical problem.

Some evidence points to a negative impact of NSAIDs after spinal fusion surgery but most of the scarce literature has not corrected for confounders such as smoking which has a major impact on bone and soft tissue healing.^{39–41} Whilst awaiting prospective, randomised clinical trials, no clear recommendations can be given, although the prudent healthcare professional might consider avoiding NSAIDs in orthopaedic cases involving bone grafting

As the coxibs may interfere with the cytochrome P-450 enzymatic system, other drugs depending on this enzyme for their metabolism may be adversely affected.⁴² Anticoagulation therapy with warfarin can thus be potentiated and the dosage may have to be adjusted in those cases where a NSAID (COX-2) is deemed of major benefit—but the classic NSAIDs are contraindicated due to their antihaemostatic effect.

The risk of haematoma formation with the use of neuraxial blocks (i.e. spinal and epidurals) and the concomitant use of NSAIDs has been a matter of concern. International consensus holds that non-selective NSAIDs (including acetylsalicylic acid) do not *per se* contraindicate neuraxial techniques. But as combined with low-molecular weight heparins and/or other “weak” anticoagulants, the risks of bleeding does increase.

Full anticoagulation (e.g. coumarins) contraindicate neuraxial techniques irrespective of NSAIDs. Combination of NSAIDs and the newer anti-platelet drugs (e.g. clopidogrel, ticlopidine) markedly increase the risk of perioperative bleeding and should be avoided. Interestingly, several complementary and alternative medicines (e.g. garlic, ginko, ginseng) are platelet inhibitors so it is currently recommended that their use is stopped before surgery and that they are not used together with classic NSAIDs.⁴³

Perioperative use of classic NSAIDs

NSAIDs are an integral part of a multimodal and preventive, perioperative analgesic regimen. It is, however, only a relatively small proportion of patients who will benefit from selective COX-2 inhibition for perioperative analgesia.

Gastric ulcer disease (GI intolerance to non-selective NSAIDs) or surgical request for minimal platelet inhibition (e.g. plastic surgery, neurosurgery, ENT surgery) may warrant the use of perioperative selective COX-2 inhibition. The combined use of NSAIDs and paracetamol has proven highly cost-effective and with a desirable opioid sparing effect, not least in day-case surgery.^{1,37,44–45}

Of the classic NSAIDs, ibuprofen in appropriate oral dose (i.e. 400–800 mg tds), diclofenac (50 mg tds), and iv tenoxicam (e.g. 20–40 mg intraoperatively) have a long and well-established place in perioperative analgesia. Together with paracetamol, a NSAID can be incorporated into a cost-effective “take-home pack” for day-case surgical patients (e.g. paracetamol 1 g qid with ibuprofen 400 mg tds for 3 days’ use).

It is notable that merely being a child is no contraindication to the use of NSAIDs. Indeed, no evidence suggests that paediatric surgery patients tolerate NSAIDs to any lesser extent than adults; otherwise healthy children may well benefit from the perioperative use of NSAIDs, often in combination with paracetamol.

Judicious consideration of indications, side effects, and contraindications is as appropriate as in the adult surgical patient.^{46,47} Interestingly, a recent study showed less analgesic efficacy of a COX-2 inhibitor (rofecoxib) than ibuprofen in a paediatric tonsillectomy population although any potential haemostatic advantage of a COX-2 inhibitor was not further discussed.⁴⁸ COX-2 selective NSAIDs are currently not recommended in NZ for age groups under 18 due to lack of valid data on dose-effect relations.

Supplemental drugs such as α_2 -agonists (e.g. clonidine), NMDA receptor antagonists (e.g. ketamine), tramadol, and gabapentin are emerging as facilitating perioperative analgesics and their possible combination with NSAIDs is under intense scrutiny. A more procedure-specific approach to perioperative analgesia has recently been suggested.⁴⁹ Eventually, recommendations for analgesic regimens involving or not involving NSAIDs or COX-2 inhibitors may emerge.

We may have gone two steps forward and one step back, but the judicious use of the entire group of NSAIDs (selective and non-selective) in postoperative pain remains to be determined in the future.

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