Discovery and development of NSAIDs

In the late 1800s, German chemists looking at derivatives of aspirin that had anti-inflammatory properties came very close to discovering cyclo-oxygenase-2 (COX-2) inhibitors, however, these agents lacked the necessary sulfur moity. The next big step, in the early 20th century, was the discovery of cortisone. For the first time a drug had specific anti-inflammatory effects and could be used to treat rheumatoid disease. There are many anecdotes of people whose lives were changed by treatment with cortisone, one of whom was the artist Raoul Dufy who was unable to paint without taping his paint brush to his hand. Once he began treatment he was able to go back to painting, but unfortunately he died after 12 months from gastrointestinal bleeding, an unfortunate adverse effect associated with cortisone.1

Subsequently, pharmacologists aimed to develop a drug with specific anti-inflammatory properties that was not a steroid. As often happens, different researchers across the world developed a variety of anti-inflammatories all at about the same time. In Europe, Gerhard Wilhelmi at Ciba-Geigy developed phenylbutazone.1 In the US, T.Y. Shen and Charles Winter at Merck, Sharp & Dohme and Parke-Davis came up with indomethacin, while in the UK, Boots chemist Stewart Adams developed ibuprofen.2

NSAID pharmacology

NSAIDs are known to be potent inhibitors of COX enzymes and subsequent prostaglandin synthesis, which gives them their anti-inflammatory properties and probably explains much of their analgesic activity.3 However, their speed of action has always been a puzzle. Drugs that work by inhibition of enzyme systems often take a long time to have an effect, yet the analgesic actions of NSAIDs are evident within half an hour. This suggests there may be more going on than we think. In addition to the prostaglandin-dependent effects of NSAIDs, other mechanisms that are not COX dependent, and whose effects are unknown, are evident.3 These include the scavenging of free radicals, the inhibition of nitric oxide formation, an effect on cannabinoid receptors, and anti-inflammatory effects through modulation of caspase inhibitors.

Ibuprofen is an enantimoric compound composed of two stereoisomers, only the S isomer provides activity while the R isomer must be converted through inversion to the S isomer and probably contributes to prolonged activity of racemic ibuprofen.4 Ibuprofen is rapidly absorbed orally, and both peak plasma concentrations and maximal analgesic onset are achieved within 90 minutes of oral administration.5 It is highly metabolised to inactive metabolites, with modest stereoselectivity favouring the S isomer for metabolite formation.5 Ibuprofen also has a relatively small volume of distribution as it is highly protein bound.

NSAID analgesic efficacy

Oral NSAIDs such as ibuprofen are “surprisingly effective in moderate-to-severe postoperative pain”5 and provide “a high standard of effectiveness” against which more complex methods of delivering analgesia must be judged.6 As an analgesic agent, ibuprofen has a number of advantages:7

- Significant opioid sparing effect
- Lack of sedation
- Lack of respiratory depression
- Low potential for abuse
- No interference with bladder or bowel function
- Efficacy for both pain at rest and movement
- No withdrawal symptoms on cessation of treatment
- Not a controlled S8 drug, so saves on nursing time.

The efficacy of ibuprofen for acute postoperative pain relief has been demonstrated by the Bandolier group, who showed an increasing efficacy with dosage when expressed either as percentage of patients with 50% pain relief (Figure 1) or as number needed to treat (NNT; Figure 2).6
Gastrointestinal effects

Gastrointestinal effects are a major cause of mortality in long-term NSAID users; however, the risk (among other things) is directly related to the duration of treatment. Gastric erosions can be seen after as little as 1 week of treatment with NSAIDs, but these are usually of little clinical significance, and in the post-surgical context these agents are only prescribed for a few days. In comparison to other non-selective NSAIDs, ibuprofen is relatively low risk for gastrointestinal complications (Figure 3). The mechanism for the development of these gastrointestinal adverse effects is almost certainly due to prostaglandin-dependent pathways that include the inhibition of COX, reduction of mucous production, reduction of gastromucosal blood flow and reduced bicarbonate production. There may also be some prostaglandin-independent pathways including NSAID effects on nitric oxide and hydrogen sulfide production, and an ion "trapping" effect (NSAIDs are weak acids so they cannot ionise in the stomach but once absorbed into epithelial cells they ionise and are trapped), but it is likely that the prostaglandin effects are the most important. So therefore, will giving NSAIDs by routes other than oral reduce gastrointestinal effects? - Probably not!

Anti-platelet effects

The effect of NSAIDs on reducing platelet adhesiveness is reversible, transient, and related to the half-life of the drug. In preadmission, we usually tell patients to stop NSAIDs 10 days before surgery, but in fact for most NSAIDs, cessation of administration could be tailored to the half-life of the drug and for diclofenac and ibuprofen this could be quite close to the surgery date. In fact, one review has suggested that during an 8-hour dosing interval, there may be an anti-platelet effect lasting perhaps one hour.

Limitations of oral ibuprofen

In general, NSAIDs vary in the time of onset and the duration of analgesic effect. The longer the half-life of the drug, the slower the onset of effect. A higher dose has a faster onset, higher peak effect and a longer duration. It is therefore advantageous to start with a high dose of a short-life drug (e.g. ibuprofen) and then adjust the dose downward when analgesic efficacy has been achieved. Commonly, it is recommended that NSAIDs are taken with food to avoid some of the gastrointestinal adverse effects, but recent studies have shown that food also alters the pharmacokinetics of immediate release oral formulations of aspirin, dipyrdone and NSAIDs. Taking NSAIDs without food results in higher early plasma levels, better early pain relief, better overall pain relief, longer lasting pain relief, and lower rates of remedication.

This seems like a good idea, but there are problems associated with this approach. Does taking NSAIDs on an empty stomach result in increased nausea and vomiting? Does it increase gastric adverse effects? What if patients can’t, perioperatively, or won’t, postoperatively, swallow tablets? Initiation of NSAID treatment is often delayed in the immediate postoperative period.

Adverse events

There are three main types of adverse events associated with NSAIDs, renal, gastrointestinal and anti-platelet.

Renal Effects

The renal effects are feared, but can generally be avoided by careful prescribing. One of the questions that is often raised is why are surgical patients at particular risk? Prostaglandins are not associated with regulation of renal blood flow under normal conditions where it is mainly controlled by intrinsic myogenic responses, but in the post-surgical patient who is volume depleted, with borderline renal function and exposed to agents such as aldosterone, ADH and other vasoactive compounds, prostaglandins do play a role in maintaining renal perfusion. These are the patients in which the use of NSAIDs can be problematic. However, it is relatively simple to avoid renal problems by limiting prescribing to 2-3 days, ensuring adequate hydration and choosing an agent with a short half-life, so that treatment can be stopped as necessary and renal blood flow return to normal.
**IV preparation of ibuprofen [Caldolor®]**

This is where the concept of IV ibuprofen [Caldolor®] comes into focus. Caldolor® has predictable pharmacokinetics, can achieve high blood levels and as a concentrated injection (800 mg/8 mL or 100 mg/mL) provides an option to fill the gap in perioperative/postoperative pain management. However, the study is not powered sufficiently to confirm the ITT population. 

In Australia, Caldolor® is indicated for the management of acute mild-to-moderate postoperative pain and moderate-to-severe postoperative pain with adjunctive reduced morphine dosage, where an intravenous route of administration is considered clinically necessary, and for the reduction of fever in adults where an intravenous route of administration is considered clinically necessary.

It is critical that the following provisos are adhered to. The concentrated solution of Caldolor® 800 mg (in 8 mL) must be diluted prior to administration and infused over 30 minutes. In most normal electrolyte solutions (0.9% sodium chloride injection, 5% glucose injection) the dilution is 800 mg in at least 200 mL to achieve a final concentration of 4 mg/mL. With Hartmann’s solution, the dilution is 800 mg in at least 250 mL to achieve a final concentration of 3.2 mg/mL (data on file August 2016, Cumberland Pharmaceuticals Inc.).

Administration of Caldolor® takes advance planning and care, because some short procedures may take only 30 minutes, so the infusion needs to start early. A potential risk with Caldolor® is thrombophlebitis as it is a venous irritant, hence the need for dilution and a prolonged infusion period.

**Key pivotal trials**

Three multicentre, randomised, double-blind, placebo-controlled trials supported the registration of Caldolor® in Australia. The first was Southworth et al’s dose ranging study in 111 orthopaedic and 295 abdominal surgery patients. The patients were randomised to Caldolor® 400 mg (n = 134) or 800 mg (n = 138) or placebo (n = 134) every 6 hours plus patient-controlled analgesia with morphine 1-2 mg every 5 minutes. The first dose of Caldolor® or placebo was administered intraoperatively at the initiation of wound closure, and thereafter every 6 hours. The primary endpoint was reduction in morphine consumption in the first 24 hours after surgery.

The results of the trial (Figure 4) demonstrate that Caldolor® 800 mg reduced postoperative morphine use by 22% (relative reduction) versus placebo (35.5 vs 45.3 mg; p = 0.03), but Caldolor® 400 mg (44.0 mg) did not differ significantly from placebo. There was no significant difference in number of patients experiencing serious adverse events versus placebo, or in the proportion of patients with bleeding or renal events versus placebo. The most common adverse events in patients given at least one dose of Caldolor® or placebo were nausea, vomiting and constipation. There was a significant reduction in the proportion of patients reporting combined gastrointestinal adverse events versus placebo.

The second trial was Singla et al’s study in 185 patients aged 45-80 years undergoing elective hip or knee replacement, reconstruction or arthroplasty. Patients were randomised to receive either Caldolor® 800 mg or placebo plus patient-controlled analgesia with morphine 1-2 mg every 5 minutes, with Caldolor® first administered at induction of anaesthesia (preoperatively*), then every 6 hours for 24 hours, and then as needed. The primary endpoint was a reduction in pain intensity on movement as measured by the 100 mm Visual Analogue Scale (VAS) from 6-28 hours postoperatively.

The study demonstrated a 26% (p = 0.003) relative reduction in pain on movement versus placebo, along with a 32% (p = 0.012) relative reduction in pain at rest (see Figure 5). Furthermore, patients experienced early postoperative pain relief when receiving a preoperative* dose of Caldolor®. There was also an average relative reduction of 31% in morphine use (41.1 mg vs 59.5 mg; p < 0.001) in Caldolor® versus placebo recipients.

The third trial, by Kroll et al., examined the use of Caldolor® 800 mg at the initiation of wound closure then every 6 hours, plus patient controlled analgesia with morphine 1-2 mg every 5 minutes, versus placebo in 319 adults undergoing elective single site abdominal hysterectomy surgery. The primary endpoint was reduction in morphine consumption in the first 24 hours after surgery. Caldolor® 800 mg once again produced a relative reduction (19%) in morphine use compared to placebo in these patients (43.5 mg vs 54.0 mg; p < 0.001); see Figure 6.
### Reference:

**BibTeX**

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  title={Immediate-release ibuprofen for acute postoperative pain in adults},  
  author={Derry, C.},  
  journal={Cochrane Database Syst Rev},  
  volume={2},  
  number={4},  
  pages={CD003168},  
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