Simple Analgesics and NSAIDs

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Both on and off-prescription the non-opioid analgesics are one cornerstone of pain management (another of course is opioids). It is astonishing that we remain so ignorant as to where and how the non-opioid analgesics work. Aspirin after all was discovered many years ago, and preparations of willow have been used in herbal and folk medicine for thousands of years. After reviewing the two big current questions, the isoforms of cyclo-oxygenase COX-1 and COX-2 and the enantiomeric R and S forms the chapter focuses on the relative efficacy and safety of the different alternatives.

**Where and how do they work?**

The classic explanation of how NSAIDs work was that they inhibit the enzyme cyclo-oxygenase, which in turn decreased the pain-sensitivity effect of prostaglandins (PGS). Textbooks ascribe a peripheral site of action, but this does not fit easily with the antipyretic effects, or indeed aspirin’s ability to produce tinnitus, which seem likely to be occurring inside the nervous system.

The cascade on which the NSAIDs are thought to work is shown in Figure 1.

**COX-1 AND COX-2**

COX-1 and COX-2 are different isoforms of cyclo-oxygenase, responsible for the breakdown of arachidonic acid via PGG₂ and PGH₂ to prostaglandins and thromboxanes (Figure 1). It was suspected 25 years ago from the different effects of different NSAIDs on prostaglandin formation that there might be different pools of COX in the cell, and this has been proved correct. COX-1 is described as the ‘constitutive’ isoform, meaning that it is present for normal functions, and it is found in most cell types, mainly in the endoplasmic reticulum. COX-2 is believed to be induced by inflammation, called up to synthesise more prostanoids. COX-2 constitutive expression (i.e. under normal conditions) is, however, found in brain, testis and lung. COX-2 activity is mostly round the nucleus.

So we have COX-1 occurring normally to organise prostanoid synthesis and COX-2 triggered by inflammation to make more. It is possible to antagonise one without the other? Dexamethasone does just this, selectively inhibiting COX-2 without affecting COX-1.

So the enticing future is finding NSAIDs which do what we want, providing analgesia, without producing the adverse effects, renal failure (acute use) and gastrointestinal haemorrhage (chronic). Most of the NSAIDs we use now inhibit both COX-1 and COX-2 pretty much equally. That is they are not selective. There are selective COX-2
inhibitors in development. The catch may be that if COX-2 is required (i.e. is constitutive) in brain and reproductive organs then there may be new adverse effect issues.

**ENANTIOMERIC R & S FORMS - SEPARATING ANALGESIA AND ANTI-INFLAMMATORY ACTIONS**

One of the clinical enigmas surrounding NSAIDs is the extent to which the analgesic and anti-inflammatory actions are separate. A further stage to this question is that if these two actions can be separated are they generated at the same sites or at different sites?

Separation of the analgesic and anti-inflammatory actions has been shown with the R and S enantiomers of flurbiprofen. The S form has both anti-inflammatory and analgesic action. The R form blocks nociception but has little effect on PG formation and inflammation. In addition while the S form is ulcerogenic the R form is said to have negligible effect.

**ACETAMINOPHEN SITE OF ACTION**

Nobody knows precisely where acetaminophen works in the brain. The standard explanation is that it acts as a prostaglandin synthetase inhibitor. This makes sense as an explanation of both the analgesic and the antipyretic actions. The fact that acetaminophen is not anti-inflammatory may be because it does not act on peripheral cyclo-oxygenase. There is perhaps a parallel with the flurbiprofen R enantiomer mentioned above.

**The clinical use of simple analgesics and NSAIDs**

In recent years there has been a fundamental shift away from opinion-based to evidence-based clinical decision making. That sentence may still sound odd, but the reality is that empirical and theoretical work have combined to make us aware of potential lapses in how we use information. We are exhorted to use the best quality of evidence, and increasingly that best-quality evidence comes from systematic reviews of the highest quality clinical trials. When we have it, then it has to be combined with the unique biology of our patients and the society in which we work in order to make the best possible decision on treatment. That decision may well be different in the UK or USA from many other parts of the world. At its simplest, there is no point in saying
we must use a particular analgesic because it is “the best” when it is not licensed where we are working.

**PAIN MEASUREMENT**

In order to understand what follows, comparisons of the relative efficacy of these drugs, it is necessary to have some idea as to how the information is gathered and processed. Pain is a personal experience which makes it difficult to define and measure. It includes both the sensory input and any modulation by physiological, psychological and environmental factors. Not surprisingly there are no objective measures - there is no way to measure pain directly by sampling blood or urine or by performing neurophysiological tests. Measurement of pain must therefore rely on recording the patient's report. The assumption is often made that because the measurement is subjective it must be of little value. The reality is that if the measurements are done properly, remarkably sensitive and consistent results can be obtained. Rules have been developed to do this consistently, and the most important is that if pain is not of moderate or severe intensity, then measuring an analgesic effect is likely to be unreliable. There are contexts, however, when it is not possible to measure pain at all, or when reports are likely to be unreliable. These include impaired consciousness, young children, psychiatric pathology, severe anxiety, unwillingness to cooperate, and inability to understand the measurements. Such problems are deliberately avoided in trials.

**Measurement Scales**

Most analgesic studies include measurements of pain intensity and/or pain relief, and the commonest tools used are categorical and visual analogue scales.

**Categorical and visual analogue scales**

Categorical scales use words to describe the magnitude of the pain. They were the earliest pain measure. The patient picks the most appropriate word. Most research groups use four words (none, mild, moderate and severe). Scales to measure pain relief were developed later. The commonest is the five category scale (none, slight, moderate, good or lots, and complete).

For analysis numbers are given to the verbal categories (for pain intensity, none=0, mild=1, moderate=2 and severe=3, and for relief none=0, slight=1, moderate=2, good or lots=3 and complete=4). Data from different subjects is then combined to produce means (rarely medians) and measures of dispersion (usually standard errors of means).
The validity of converting categories into numerical scores was checked by comparison with concurrent visual analogue scale measurements. Good correlation was found, especially between pain relief scales using cross-modality matching techniques. Results are usually reported as continuous data, mean or median pain relief or intensity. Few studies present results as discrete data, giving the number of participants who report a certain level of pain intensity or relief at any given assessment point. The main advantages of the categorical scales are that they are quick and simple. The small number of descriptors may force the scorer to choose a particular category when none describes the pain satisfactorily.

Visual analogue scales (VAS), lines with left end labelled "no relief of pain" and right end labelled "complete relief of pain", seem to overcome this limitation. Patients mark the line at the point which corresponds to their pain. The scores are obtained by measuring the distance between the no relief end and the patient's mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms and provide many points from which to choose. More concentration and coordination are needed, which can be difficult post-operatively or with neurological disorders.

Pain relief scales are perceived as more convenient than pain intensity scales, probably because patients have the same baseline relief (zero) whereas they could start with different baseline intensity (usually moderate or severe). Relief scale results are then easier to compare. They may also be more sensitive than intensity scales. A theoretical drawback of relief scales is that the patient has to remember what the pain was like to begin with.

### Analysis of scale results - summary measures

In the research context pain is usually assessed before the intervention is made and then on multiple occasions. Ideally the area under the time-analgesic effect curve for the intensity (sum of pain intensity differences; SPID) or relief (total pain relief; TOTPAR) measures is derived.

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\text{SPID} = \sum_{t=0}^{n} \text{PID}_t \quad \text{TOTPAR} = \sum_{t=0}^{n} \text{PR}_t
\]

Where at the \( t \) th assessment point, \((t= 0, 1, 2, \ldots, n)\) \( \text{P}_t \) and \( \text{PR}_t \) are pain intensity and pain relief measured at that point respectively, \( \text{P}_0 \) is pain intensity at \( t=0 \) and \( \text{PID}_t \) is the pain intensity difference calculated as \( (\text{P}_0 - \text{P}_t) \).
These summary measures reflect the cumulative response to the intervention. Their disadvantage is that they do not provide information about the onset and peak of the analgesic effect. If onset or peak are important then time to maximum pain relief (or reduction in pain intensity) or time for pain to return to baseline are necessary.

**Efficacy**

In measuring efficacy, the best available evidence comes from systematic reviews of randomised, double-blind trials. A systematic review is one that searches for all published (and possibly unpublished) trials of a particular intervention. If trials are not randomised estimates of treatment effect may be exaggerated by up to 40%. In a systematic review of transcutaneous electrical nerve stimulation (TENS) in postoperative pain, 17 reports on 786 patients could be regarded unequivocally as RCTs in acute postoperative pain. Fifteen of these 17 RCTs demonstrated no benefit of TENS over placebo. Nineteen reports had pain outcomes but were not RCTs; in 17 of these 19, TENS was considered by their authors to have had a positive analgesic effect. The therapeutic effect may be exaggerated by up to 20% in trials with deficient blinding.

Pooling of information from many clinical trials is important. Single trials are statistically powered only to measure the direction of an effect - whether the analgesic truly is better than placebo. But that is insufficient information to measure the magnitude of the analgesic effect - how much better than placebo is it? About ten times as much information is needed to measure the magnitude of the analgesic effect, which is perhaps the most compelling reason why systematic reviews are important. The contrary message is that a single trial powered only for directional significance, even when performed to the highest standards, may produce a magnitude of effect that is inaccurate.

Pooling information from different studies is facilitated if there is a common outcome, and methods have been developed which allow the different pain measurement methods discussed above to be reported as the proportion of patients given a treatment who have at least 50% pain relief over four to six hours. This is a high hurdle, and few patients in clinical trials achieve this level of analgesia.

Increasingly a common method of expressing treatment efficacy is the number needed to treat, or NNT (Figure 2). In the context of postoperative pain, the NNT as we use it here will describe the number of patients who have to be treated with an analgesic for one of them to have at least 50% pain relief over four to six hours who would not have pain relief of that magnitude with placebo. That does not mean that pain relief of a lower intensity will not occur. The best NNT will be 1, but NNTs in the range of 2 to 5 signify effective treatments. There are circumstances, like the use of aspirin after
myocardial infarction, where an NNT of 40 will be good, because it means that using aspirin in 40 patients (which is cheap and without much harm) will prevent one of the 40 patients dying.

It has been shown that the NNT for pain relief in postoperative pain is relatively insensitive to the magnitude of the pain relief between about 20% and 60% pain relief (Figure 3). Where the NNT is good, as for tramadol 150 mg in the Figure, the NNT does not change very much with the use of different cut points. Where the NNT is poor, as with codeine 60 mg, the NNT rises (gets worse) rapidly as the quality of pain relief required increases. At 50% pain relief we obtain a point at which there is excellent sensitivity to distinguish between effective and less effective analgesics, and, of course, the concept of half pain relief is one easily understood.

Questions have been raised in the past about the wisdom of combining information gathered in analgesic trials using different pain models (dental versus postoperative or episiotomy pain), or different pain measurements, or different durations of observation. Analysis of the great mass of information on aspirin has shown that none of these variables has any effect on the magnitude of the analgesic effect.

**HOW WELL DO NSAIDS AND ACETAMINOPHEN WORK - BY MOUTH?**

Figure 4 shows the information we have on oral acetaminophen, acetaminophen plus codeine, aspirin, ibuprofen, diclofenac, naproxen and bromfenac from systematic reviews of randomised controlled trials of single-doses in postoperative pain. It shows the dose with the largest amount of information for each drug, except for acetaminophen where significant information was available for two doses. It is clear that the four NSAIDs do extremely well in this single-dose postoperative comparison. They all have NNT values of between 2 and 3, and the point estimate of the mean is below that of (i.e. better than) 10 mg of intramuscular morphine, even though the confidence intervals overlap.

The simple analgesics, aspirin and acetaminophen are significantly less effective than 10 mg intramuscular morphine. The point estimates of the NNT are higher, and there is no overlap of the confidence intervals. Analgesic efficacy of the simple analgesics is improved by combination with weak opioids. Combination of acetaminophen 600/650 mg with codeine or dextropopoxyphe lowering the NNT of the combination to levels which are similar to that of 10 mg intramuscular morphine.

Figure 5 presents the NNT data in a graphical form. A league table like this is easy to take in, and as more systematic reviews compile similar data on other analgesics, it can
be extended to make comparison and choice of drugs based on more evidence-based efficacy. The league table is legitimate only because it uses information on similar patients with valid inclusion criteria (pain of moderate or severe intensity), similar measurement methods, similar outcomes, and a common comparator, placebo. While it can be argued that head-to-head comparison between analgesics would be better, the problem is that few such head-to-head comparisons exist, and randomised trials to detect small differences in efficacy between two analgesics would need to be massive to be able to detect differences in direction, let alone in the magnitude of the difference.

Systematic reviews of clinical trials of simple analgesics and NSAIDs can also provide important insights into the dose-response relationships of these analgesics in clinical practice (Figure 6). The dose-response for aspirin and acetaminophen are very similar. Those for diclofenac and ibuprofen are different. While diclofenac produces little additional analgesia above a dose of 50 mg, perhaps because of insufficient data, ibuprofen continues to generate additional analgesia at doses of 600 mg and 800 mg, when the NNT approaches 1, which is the theoretical perfect NNT (Figure 2).

**How well do NSAIDs and acetaminophen work - by injection or other routes of administration?**

We know that topical NSAIDs are effective in strains and sprains and in arthritic conditions from a systematic review of 86 randomised controlled trials involving 10,160 patients. Measures approximating at least half pain relief were used with analysis at 1 week for acute and 2 weeks for chronic conditions. In acute pain conditions placebo controlled trials had a NNT of 3.9 (3.4 to 4.4). Analysing by drug (at least three trials), ketoprofen (NNT 2.6), felbinac (3.0), ibuprofen (3.5) and piroxicam (4.2) had significant efficacy. Benzydamine and indomethacin were not distinguished from placebo. In chronic pain conditions placebo controlled trials had NNT of 3.1 (2.7 to 3.8).

We do not have the same league table of analgesic efficacy for injected or rectal NSAIDs in postoperative or other acute pain states. The reason for this is that almost all trials of injected or rectal NSAIDs have been conducted where the analgesic has been given where there is no pain - before the operation begins, for instance. This has become fashionable partly because there is a belief that if pain can be pre-empted then the need for analgesics postoperatively is reduced. Pre-emptive analgesia is beyond the scope of this chapter, but reviews have both questioned the methodological validity of most trials that have been conducted, and have shown that analysis of valid studies does not support the theory. Certainly most randomised trials comparing the same intervention given before or after pain begins have not shown clinical advantage of
so-called pre-emptive analgesia. The injectable form of paracetamol, propacetamol, undoubtedly works, but as yet there are too few published 'modern' trials to allow meta-analysis.

What we do have is a review of twenty-six randomised controlled trials (2225 analysed patients), published between 1970 and 1996, which have examined the difference in analgesic efficacy and adverse effects of NSAIDs given by different routes of administration. Fourteen trials were in postoperative pain (1268 patients), four in renal colic (647 patients), one in acute musculoskeletal pain (77 patients), one in dysmenorrhoea (32 patients), and six in rheumatoid arthritis (201 patients). Different doses of eight different NSAIDs (diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, piroxicam, tenoxicam), given by intravenous, intramuscular, intrawound, rectal and oral route, were tested in 58 single-dose or multiple-dose comparisons. Fifteen trials (58% of all analysed trials) were relevant to the review because they compared the same drug by different routes. In nine of them (35% of all trials) the same drug was compared at the same dose.

Of the ten relevant trials which reported a significant difference between routes, or which reported equivalence but had an index of internal sensitivity (i.e. which were valid), five were in postoperative pain, three were in renal colic, one was in dysmenorrhoea, and one was in rheumatoid arthritis.

**Postoperative pain**

Of 14 trials in postoperative pain, five were valid direct comparisons comparing diclofenac or ketorolac across routes.

In one trial, diclofenac 1 mg/kg injected intravenously at induction of anaesthesia led to significantly lower pain intensity scores 30 minutes after surgery than the same dose given intramuscularly at induction. In two other trials no difference was found between ketorolac 30 mg given either intravenously or intramuscularly at induction. In one of these trials inguinal hernia repair was done under local anaesthesia with very low pain scores during the postoperative observation period whether or not an NSAID or no treatment was given. In the same trial both intramuscular and intravenous ketorolac 30 mg at induction led to significantly lower pain scores and less rescue analgesics at 90 minutes after surgery than the same dose taken orally, but one hour before surgery. Group sizes in this trial were small (i.e. 14 patients per group) and no double-dummy design was used. Another trial with larger groups (50 patients per group), but again without a double-dummy design, reported less pain and rescue analgesics at discharge with diclofenac 75 mg intramuscularly compared with the same drug given orally but at a lower dose (50 mg). Yet another trial compared diclofenac 150
mg taken orally with 50 mg intramuscularly plus 100 mg orally. The drugs were given as a premedication using a double-dummy design, and group sizes were large (50 patients per group). No difference was found between the two forms of administration.

**Renal colic**

Of four trials in renal colic, there were three valid direct comparisons comparing dipyrrone, diclofenac, and indomethacin given by different routes.

In one trial pain relief was tested with dipyrrone 1 g or 2 g, and diclofenac 75 mg, given intramuscularly compared with intravenously. At 10 and 20 minutes after administration of the drugs the proportion of patients with at least 50 percent improvement was significantly in favour of the intravenous route with each drug and dose.

In the two other trials intravenous indomethacin 50 mg was compared with the same drug given rectally but double the dose. Despite there being only half the intravenous dose both trials reported significant improvement (less pain intensity, less rescue analgesics) with the intravenous route compared with the rectal. Again these differences were apparent only at 10 or 20 minutes. A simple clinical conclusion is that we lack convincing evidence that the same dose of NSAID is any more effective when given by injection than when given at the same dose by mouth. One might then argue that it makes little sense to give that dose by injection instead of by mouth to a patient who can swallow.

**Safety**

NSAIDs can cause a number of minor adverse effects at recommended doses, but can also cause major adverse effects at recommended doses. Acetaminophen can also cause minor adverse effects at recommended doses, but no major adverse effects. It is only in overdose that acetaminophen is dangerous, with the potential to cause hepatic failure.

In acute pain the main concerns with NSAIDs are renal and coagulation problems. Acute renal failure can be precipitated in pre-existing heart or kidney disease, those on loop diuretics, or those who have lost more than 10% of blood volume. NSAIDs cause significant lengthening (by about 30%) of the bleeding time, usually still within the normal range. This can last for days with aspirin, but hours with non-aspirin NSAIDs. Whether or not NSAIDs cause significant increases in blood loss is something that remains contentious, and for which better evidence is awaited.
Oral route

Adverse effects from single-dose oral acute pain studies have been examined systematically for acetaminophen, ibuprofen and aspirin. The common adverse effects like nausea, dizziness or drowsiness are reported more commonly when diaries are used, and drowsiness is reported more commonly in dental rather than other pain models. The incidence of any adverse effect with any single dose of analgesic is low, but for acetaminophen and ibuprofen, but not aspirin, was statistically greater than placebo (Figure 7). Individual adverse effects with commonly used doses are rarely statistically significant (Figure 8), the most important being the finding that gastric irritation is two to three times more common with aspirin rather than placebo, with a number needed to harm of 22 (95% confidence interval 22 to 174).

Other routes

For injected and rectal administration commonly reported adverse effects independent of the route of administration were nausea, vomiting, dizziness, drowsiness, sedation, anxiety, dyspepsia, indigestion, and dry mouth. Two studies reported bleeding time changes. In 12 patients with rheumatoid arthritis treated with indomethacin 100-150 mg orally and rectally, respectively, in a cross-over design for two weeks, endoscopically diagnosed gastric mucosal damage was independent of the route of administration.

Adverse effects related to the route of administration were most often reported for intramuscular and rectal regimens. Discomfort at the site of injection was the most frequent complaint in relation to intramuscular injections. After rectal administration, diarrhoea, rectal irritation, and non-retention of suppositories were reported.

For topical NSAIDs, both acute and chronic pain local and systemic adverse events, and drug-related study withdrawal, had a low incidence and were no different from placebo.

Longer-term adverse effects

Oral NSAIDs cause ulcers in some people. In some of those who have ulcers, some also have symptoms, which include bleeding ulcers. In some of those who have bleeding ulcers, the bleeding is sufficiently severe to result in hospital admission, and may cause death. The variables are drug and dose, duration of exposure, and patient characteristics. The total burden is large, with some 76,000 NSAID-related hospital admissions and 7,600 deaths in the USA every year.
Age and sex are the major risk factors for serious gastrointestinal complications with NSAIDs (Figure 9), though a history of previous ulcers and heart disease are also important. Of the different NSAIDs, some are implicated more than others, though case-control and cohort studies give somewhat different estimates (Figure 10). Both types of study indicate that ibuprofen is among the safest of the NSAIDs.

The size of the problem of gastrointestinal emergencies associated with oral NSAID use is large. Two recent UK studies, each on about 1% of the UK population, indicate, first, that 1.9% of NSAID users might be admitted to hospital each year with upper gastrointestinal emergencies, and, second, that one episode of ulcer bleeding in the elderly will be expected for each 2,823 prescriptions. Another way of putting this is that if oral NSAIDs are taken for at least two months, the risk of an endoscopic ulcer is 1 in 5, of a symptomatic ulcer is about 1 in 70, of a bleeding ulcer is about 1 in 150, and of a death from a bleeding ulcer about 1 in 1300. None of these risks is associated with topical NSAIDs, which have much lower plasma concentrations.

**Conclusion**

Simple analgesics and NSAIDs are clinically highly effective analgesics. The fact that they can be taken by mouth with the same efficacy as injections or rectal routes simplifies administration and makes them ideal candidates for postoperative analgesia, and especially for day-case surgery. The advent of new COX-2 selective inhibitors which are not associated with gastrointestinal adverse effects opens the door to the possibility that much better analgesia will be achievable.

**Bibliography - selected further reading**


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