

NSAIDs and Coxibs: clinical use

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Summary

Simple analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are clinically highly effective. The introduction of the cyclooxygenase-2-inhibitory non-steroidal anti-inflammatory drugs (Coxibs), selective inhibitors of cyclooxygenase (Cox)-2, has resulted in large quantities of safety and efficacy data. While there are differences in efficacy between NSAIDs and paracetamol, the efficacy of classical NSAIDs and Coxibs is similar, both in single doses used to treat acute postoperative pain and in the chronic situation for treatment of musculoskeletal disorders such as osteoarthritis. The highest doses of NSAIDs produce numbers needed to treat (NNTs) for 50% pain relief that approach 1, which is the theoretically perfect NNT. The major differences are in safety. NSAIDs and Coxibs can cause gastrointestinal bleeding, and can precipitate renal failure or congestive heart failure at therapeutic dose. If oral NSAIDs are taken for at least 2 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. Coxibs reduce the gastrointestinal bleeding risk compared with NSAIDs. The odds ratio for acute renal failure is 1.6–2.0 with chronic NSAID therapy. The risk of congestive heart failure is twice as high with chronic NSAID therapy, and increases to over 20 in patients with a previous history. Coxibs do not reduce the renal or heart failure risks compared with NSAIDs. Paracetamol is safe at therapeutic dose, but a little less effective. This balance between efficacy and safety is critical to optimal use of the drugs in all therapeutic areas.

The NSAIDs, Coxibs, and other non-opioid analgesics are important in pain management, both on and off prescription. People use paracetamol and NSAIDs off prescription to treat pain and fever. NSAIDs and Coxibs are prescribed as part of the analgesic ladder.

The phrase *analgesic ladder* is slightly misleading when it comes to optimal use of these drugs. Unlike on a real ladder, where the climber goes up or down the rungs, best pain relief may be obtained if all the rungs on the analgesic ladder are used simultaneously, in the sense that the non-opioid analgesics work through different mechanisms compared with the opioids, and the analgesia from one drug class adds to the analgesia provided by the other class—hence the importance of the non-opioid analgesics.

The development of the Coxibs has given us a clearer picture of the mechanism of NSAID action, but we are still ignorant as to precisely where, and in some cases how, the non-opioid analgesics work, even though aspirin was after all discovered in 1753 (at Chipping Norton near Oxford), and preparations of willow have been used in herbal and folk medicine for thousands of years.

Beyond understanding where and how the non-opioid analgesics work, the clinical questions about their pharmacology are intriguing. These drugs work as analgesics, but we need to know which is the most and which is the least effective, and whether different routes of

administration offer any efficacy advantage. The choice of drug to prescribe, given that they all work, has to take into account their relative safety. The safety issues include adverse effects at therapeutic dosage (gastrointestinal, cardiac and renal); the impact of the drugs on other diseases, such as asthma, or on processes such as bone healing; and drug–drug interactions with warfarin or prophylactic aspirin.

While the major focus of this chapter is on NSAIDs and Coxibs, there is also brief mention of paracetamol, dipyron and nefopam.

Basics

NSAIDs: Cox-1 and Coxib

The classic explanation of how NSAIDs work was that they inhibited the constitutive enzyme Cox, decreasing prostaglandin synthesis, which in turn reduced the pain-sensitizing effect of the prostaglandins. Cox was believed to be expressed with constant levels in individual tissues. This was unlikely to be the complete story, because of observations such as the increase in Cox activity in inflammation, the ability of corticosteroids to block this increase, and the analgesic efficacy of the drugs in conditions that do not involve inflammation. Similarly, a solely peripheral site of action does not fit easily with the antipyretic effects or aspirin's ability to produce tinnitus, which seems likely to be occurring centrally.

The research that followed the identification of two isoforms of Cox, Cox-1 and Cox-2, has made some of the mechanisms of action clearer (Hawkey 1999). The two enzymes are very similar. Both are membrane-associated. Arachidonic acid released from neighbouring damaged membranes is converted by the enzymes into prostaglandins. The differences between the two enzymes are in their internal configuration, which dictates which drugs bind to each; in their distribution in different body tissues; and in their relative preponderance in normal conditions (constitutive) and in response to inflammation (induced). The broad distinction between the two systemic isoforms, Cox-1 and Cox-2, is that Cox-1 is mainly expressed constitutively and gives rise to prostaglandins that mediate normal cellular processes, whereas Cox-2 is generally considered to be an inducible enzyme, induced by inflammation and called up to synthesize more prostanoids. Cox-1, as the constitutive isoform, is necessary for normal functions and is found in most cell types. Cox-2, despite being the inducible isoform, is expressed constitutively (i.e. under normal conditions) in a number of tissues, which probably include brain, testis and kidney.

It is because these prostanoids play a variety of important roles in the normal physiology and functioning of the gastrointestinal tract, the renal system, and the cardiovascular system that NSAID and Coxib therapy, by inhibiting prostaglandin and thromboxane production, can interfere with prostaglandin-mediated maintenance of these systems, resulting in a range of potential adverse effects.

Paracetamol, dipyron and nefopam

Nobody knows precisely where paracetamol, dipyron or nefopam work. The standard explanation for paracetamol is that it acts as a Cox inhibitor in the brain, explaining both its analgesic and its antipyretic actions. The lack of clinical anti-inflammatory activity may be because paracetamol is not active on peripheral Cox. Similar comments are made for dipyron. Nefopam, while undoubtedly an analgesic, has neither opioid nor NSAID-like activity. It is neither anti-inflammatory nor antipyretic, and, like paracetamol and dipyron, its site of action is presumed to be in the central nervous system.

Clinical efficacy

How well does the intervention work?

Clinicians need to know how well the intervention works: the size of the effect or its clinical significance. Knowing only that an intervention works is much, much less helpful, especially when a range of similar interventions are available. The information on relative efficacy given here uses the NNT as the measure of clinical significance, with data derived from quantitative systematic reviews. The NNT describes the difference between active treatment and control, and in Figs 30.1 to 30.4 this is the difference between active drug and placebo in the proportion of patients who achieve at least 50% pain relief over 6 h following a single postoperative dose of the drug.

By deriving the NNT for different analgesics from comparisons with placebo, the relative efficacy can be compared, and such league tables (Fig. 30.1) are easy to understand. As more trials are reported and systematic reviews compiled, giving similar data on other analgesics, the league table can be extended and refined, allowing drug

comparison on a credible evidence base. 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, and similar outcomes, using placebo as a common comparator, and in circumstances where we know that pain model makes no difference (Barden et al 2004). 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 randomized 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.

Oral non-opioids

Figure 30.1 shows the NNT, confidence intervals, and numbers of patients in the trials at each oral single dose for selected NSAIDs, Coxibs, paracetamol, tramadol and intramuscular morphine. The data came from systematic reviews of randomized controlled trials of single doses in postoperative pain. It is clear that the NSAIDs and Coxibs do extremely well in this single-dose postoperative comparison. They have NNT values of between 2 and 3, meaning that of two or three patients given that drug at that dose one will achieve at least 50% pain relief, a high hurdle.

These NSAID and Coxib NNTs at these doses are lower (i.e. better) than that achieved by 10 mg of intramuscular morphine, even though the confidence intervals overlap. It has been known for many years from single trials that oral NSAIDs can provide similar analgesia to that provided by 10 mg of intramuscular morphine, and these data confirm those observations. The limited data we have on 20 mg of intramuscular morphine give an NNT of less than 2.

Coxibs achieve as good or better (lower) NNTs than the NSAIDs. The Coxibs have been used for postoperative trials at doses several

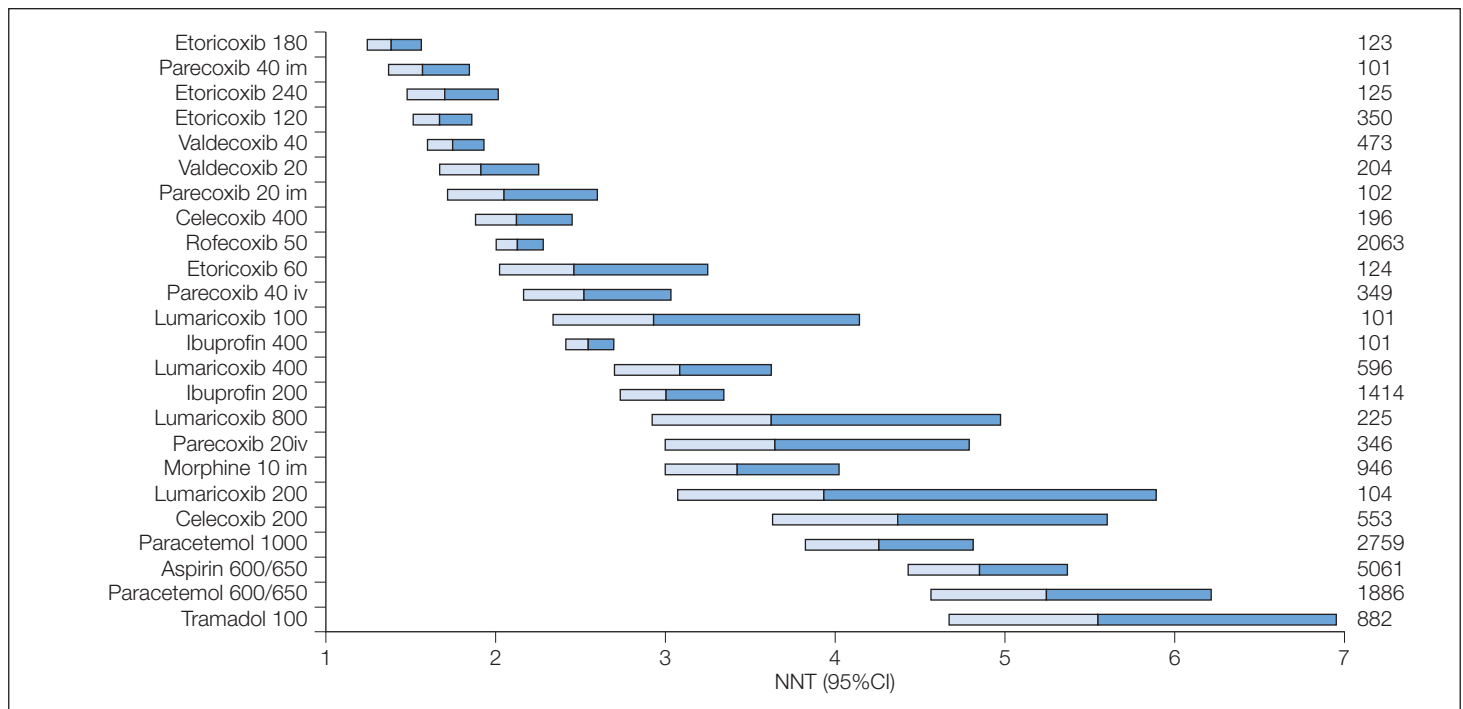


Fig. 30.1 Numbers needed to treat (NNTs) for 50% pain relief in postoperative pain (single dose) for 6 h post dose. NNT point estimate is at the junction of the shaded and unshaded bar segments. Shaded bar segment is the lower 95% confidence interval; unshaded is the upper. Number of patients studied shown on the right.

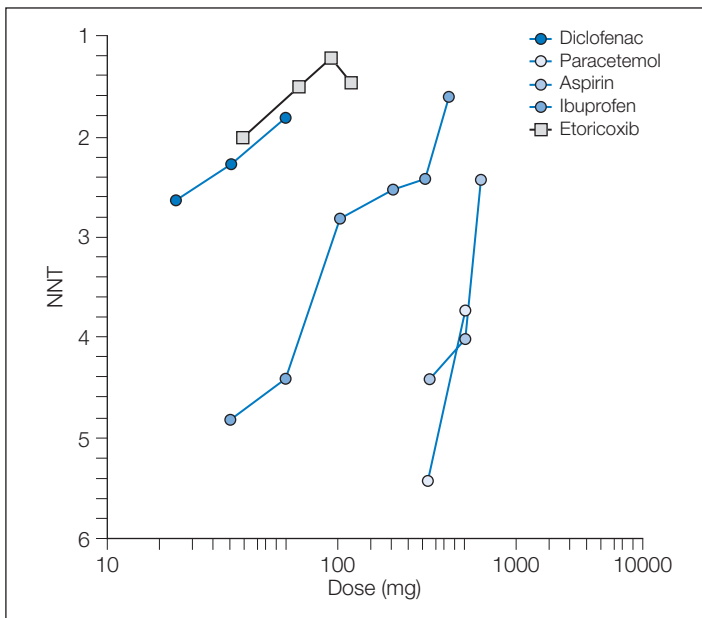


Fig. 30.2 NSAID and Coxib 6-h dose-response relationships for numbers needed to treat (NNTs) for 50% pain relief in postoperative pain (single dose).

multiples of the chronic pain dose, whereas the NSAIDs were tested at doses close to the chronic pain dose, so the efficacy difference between Coxibs and NSAIDs in this 6-h efficacy comparison is largely a function of dose (Fig. 30.2). There is no reason to expect any greater analgesia from the Coxibs than from the NSAIDs—which were after all designed specifically to reduce gastrointestinal haemorrhage rather than because they offered greater efficacy—unless the doses are increased relative to the NSAIDs.

Aspirin 600 or 650 mg and paracetamol 1000 mg are significantly less effective than 10 mg of intramuscular morphine. The point estimates of the NNT are higher, and there is no overlap of the confidence intervals. The original trial results of Houde and Wallenstein suggested milligram for milligram equianalgesic equivalence between aspirin and paracetamol in postoperative pain, and this is borne out by our results. Dipyron 500 mg oral has an NNT of 2.4 (1.9–3.2) from data on only 143 patients (Edwards et al 2001). It too is an effective drug. We have no NNT for nefopam.

These NNTs were derived from single-dose pain studies. It is not possible from these analyses to comment on speed of onset of analgesia, but we know from single trials that oral normal-release formulations of the original NSAIDs start to work at roughly half an hour, with peak effect between 60 and 90 min. Duration of analgesia with NSAIDs and Coxibs is a function of dose (and kinetics). Bigger doses will give analgesic effect longer than the 4–6 h expected from standard therapeutic dose. The large Coxib doses used in these postoperative trials should therefore result in longer duration of analgesia. Most multiple-dosing studies have been performed in arthritis, and the relative efficacy data shown here from single doses seem to tally well with the multiple-dosing studies.

Another old observation from single trials was that the dose-response for analgesia with NSAIDs was flat, meaning that the increase in analgesia from increasing the dose was less marked than was seen with a similar relative increase in dose for, say, morphine. The results from the systematic reviews of single doses (Fig. 30.2) show very similar dose-responses for aspirin and paracetamol, reflecting

the milligram for milligram efficacy equivalence, and show the greater potency, more analgesia at lower milligram dosage, of diclofenac, ibuprofen and etoricoxib.

The largest doses of etoricoxib, diclofenac and ibuprofen produce NNTs approaching 1, which is the theoretically perfect NNT. Dose is plotted in Fig. 30.2 as the logarithm. This perhaps emphasizes the clinical perception of the ceiling to non-opioid analgesia. For diclofenac and etoricoxib, the doses shown are on the upper (flatter) part of the sigmoid dose-response curve; further dose increase can produce little improvement in NNT. The steeper slopes for aspirin and paracetamol suggest the steep portion of the sigmoid curve; better NNTs could be achieved with bigger doses if it was safe to give bigger doses.

Analgesic efficacy of the non-opioid analgesics is improved by combination with weak opioids (Fig. 30.3) (Edwards et al 2002). Combination of paracetamol 600 or 650 mg with codeine or dextropropoxyphene lowers (improves) the NNT of the combination to levels similar to that of 10 mg of intramuscular morphine. At a practical clinical level, combinations of simple analgesics with opioids are considered effective, and are often used as one rung in the ladder of analgesic treatments. The clinical need for the combinations is the fact that a proportion of patients cannot or should not be given NSAIDs or Coxibs, usually because of allergy or gastrointestinal problem. In a young group of study patients this proportion was 17% (Merry et al 2004).

The central argument used against combinations is that a combination of A plus B is no better than A alone. Figure 30.3 illustrates that pooling information from individual trials can provide evidence to deal with this argument in a way that individual trials of conventional size cannot. Clearly, the combinations were better than the individual components alone, and the argument that a combination of A plus B is no better than A alone can be rebutted.

Efficacy in chronic use

Efficacy comparisons of NSAIDs and Coxibs in arthritis are of high quality, large, and of long duration, eclipsing previous studies of NSAIDs in arthritis (Bandolier 2002). What the trials showed was that the Coxibs were more effective than placebo, and as effective as maximum daily doses of standard NSAIDs (ibuprofen 2400 mg, diclofenac 150 mg and naproxen 1000 mg daily). The evidence is strong that, at licensed dose, the Coxibs work as effectively as maximum daily doses of NSAIDs. This fits with the bench science. There is no reason to expect better efficacy, but that level of efficacy is achieved with better gastrointestinal safety. This supposes that there are no other issues that have yet to be revealed. What is still unclear is the optimal dosage of the different Coxibs. Given the better gastrointestinal safety, the clinical temptation has been to use doses that are perhaps bigger than the minimum necessary for efficacy. This takes us back to old territory. Increasing the dose of NSAIDs in single-dose acute pain studies has been known for 50 years to have little impact on the area under the curve of pain relief against time within the study. We now see the same with Coxibs, where bigger doses, just like bigger doses of NSAIDs, increase the duration of pain relief rather than increasing peak relief.

Another way of looking at efficacy in chronic use is to look at the proportion of patients who discontinue the drug because of lack of efficacy. In the arthritis trials, 20% of patients discontinue because of lack of efficacy on placebo by 6 weeks, two-thirds of those who discontinue for any reason. For paracetamol 4 g/day, the lack of efficacy discontinuation rate is similar. For maximum daily dose of NSAIDs or the trial dosages of Coxibs, the lack of efficacy discontinuation rate

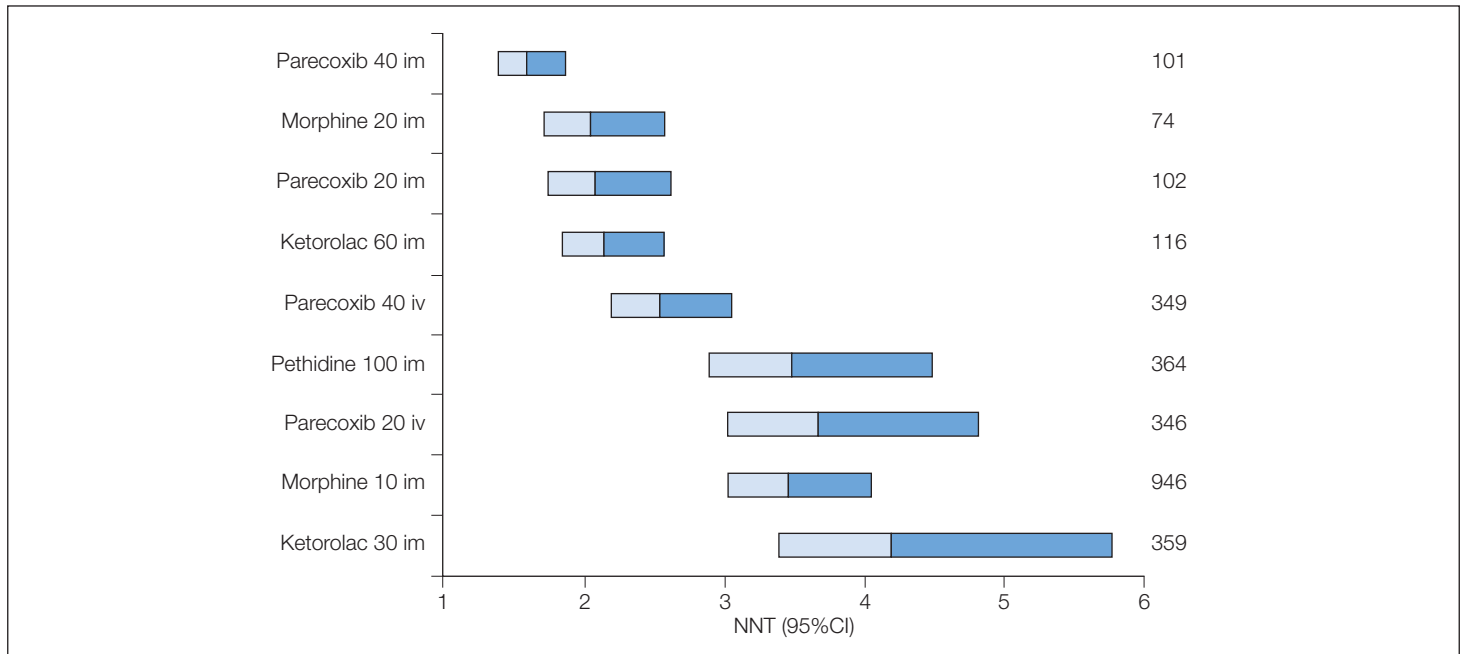


Fig. 30.3 Numbers needed to treat (NNTs) to obtain at least 50% pain relief over 4–6 h: comparison of single-dose combination drugs and their components. Number of patients studied shown on the right.

at 6 weeks is around 6%. At 6 months, the rate is around 14% for both NSAIDs and Coxibs.

Efficacy is not an issue, in the sense that the Coxibs work as effectively as NSAIDs. What we do not have is any analysis to tell us which patients do well on what drugs, and why. We are still left with patients with arthritis whose average pain remains moderate even while on treatment.

Other routes of administration

Topical

Evidence that topical NSAIDs are effective in strains and sprains and in arthritic conditions came from a systematic review of 86 randomized controlled trials involving 10 160 patients (Moore et al 1998). 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 an NNT of 3.9 (3.4–4.4). Analysing by drug (at least three trials), ketoprofen (NNT 2.6), felbinac (3.0), ibuprofen (3.5) and piroxicam (4.2) had significant efficacy. Benzylamine and indomethacin were not distinguished from placebo. In placebo-controlled trials of chronic pain conditions, the NNT for topical NSAIDs was 3.1 (2.7–3.8). This analgesia was not due to rubbing a cream on to the painful area, because both placebo and the topical NSAID were applied in the same way. Although we may not understand the biology of the topical NSAIDs, the limited comparisons of topical and oral formulations show that both work. Topical NSAIDs thus have a place in the armamentarium.

Injected and rectal

A league table of relative analgesic efficacy for injected NSAIDs and Coxibs in postoperative pain is shown in Fig. 30.4, with injected opioid for comparison. As with the oral doses in Fig. 30.1, the best

performers have NNT values between 1 and 2. There are some anomalies, such as the difference in the efficacy of parecoxib between intramuscular and intravenous, and we do not know if this was due to a difference in the trial population or whether this is a true biological difference.

Injected NSAIDs, Coxibs, paracetamol (propacetamol), dipyron and nefopam are all effective analgesics, but it is difficult to establish if they are any more effective than their oral equivalents. Indeed, oral ketorolac 10 mg was equivalent to intramuscular ketorolac 30 mg in one review (Smith et al 2000). If oral and injected formulations are equally effective, then the advantage of the injected route would be restricted to contexts where the patients cannot swallow, or, if injected was faster in onset of action, to contexts where rapid analgesia was required. To prove that injected is better than oral requires that the same drug be compared at the same bioavailable dose across the two routes. A systematic review of randomized controlled trials (2225 analysed patients) published between 1970 and 1996, which examined the difference in analgesic efficacy and adverse effects of NSAIDs given by different routes of administration, found 15 trials that compared the same drug by different routes (Tramèr et al 1998). In just nine of them (35% of all trials) was the same drug compared at the same dose.

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 may make little sense to give that dose by injection instead of by mouth to a patient who can swallow.

Safety

The NSAIDs can cause a number of minor adverse effects at recommended doses, but can also cause major adverse effects at recommended doses. At recommended doses, paracetamol can also cause minor adverse effects but no major adverse effects. It is only in

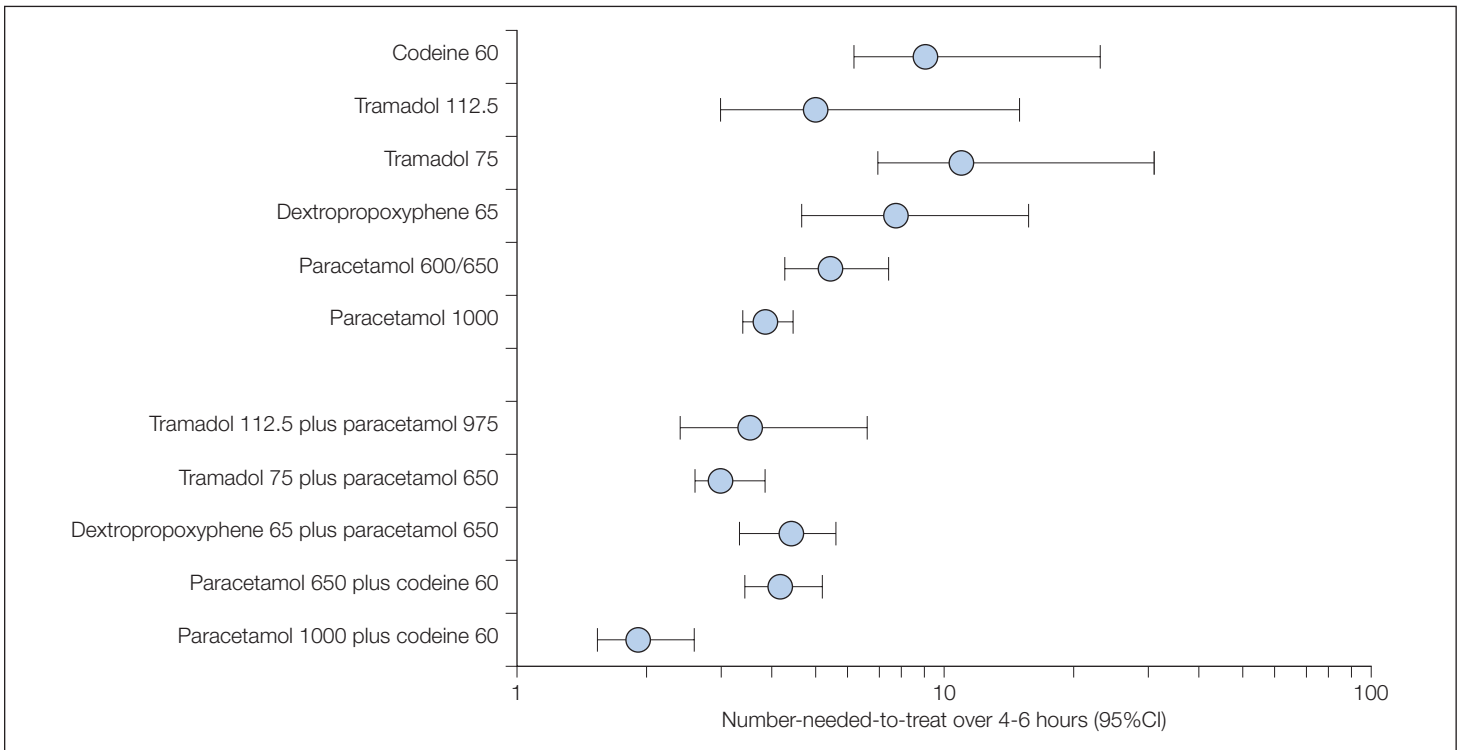


Fig. 30.4 Numbers needed to treat (NNTs) to obtain at least 50% pain relief over 4–6 h: comparison of single-dose injected NSAIDs, Coxibs and opioids.

overdose that paracetamol is dangerous, with the potential to cause hepatic failure. Dipyrrone is not available in many countries because of concerns about agranulocytosis; controversy continues about the incidence of this problem. Dipyrrone was (re)withdrawn from the market in Sweden recently after 6 cases in 10 000 patients exposed. This is a much higher incidence than that encountered in other countries where the drug is used widely.

With the NSAIDs, it is worth recalling the concept that the slope of the dose–response curve for analgesia may not be as steep as that for morphine (Fig. 30.2). The slope of the dose–response curves for adverse effects need not be the same as that for analgesia. If the slope of the dose–response curve for an adverse effect is steeper than that for analgesia, then dose increase to produce greater analgesia may produce proportionately greater increase in the adverse effect.

NSAID safety in acute use

Major problems

In acute pain, the main concerns with NSAIDs are allergic reaction, renal failure, coagulation problems, and impact on healing processes, particularly of bone. Acute renal failure can be precipitated in patients with 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. This raises the possibility that NSAIDs can cause significant increase in blood loss.

A comparison of ketorolac, diclofenac and ketoprofen in over 11 000 patients having major surgery, and given injected then oral doses of one of the three NSAIDs, gave a 1% incidence of increased surgical site bleeding, 0.1% incidence of allergy, 0.1% incidence of acute renal failure, and 0.04% incidence of gastrointestinal bleeding

(Forrest et al 2002). There was no difference between the three NSAIDs.

The paper does not tell us what would happen in the absence of NSAIDs, so that these estimates are in a sense the worst case, using relatively big doses of injected and oral NSAID. The paper shows that the postoperative risk of acute renal failure with NSAIDs is greater than the risk of gastrointestinal bleeding. No clinical renal failure was seen in the tenoxicam study (750 patients) (Merry et al 2004). The risk will be context-dependent. The incidence reported will depend on the definition, biochemical or clinical. Older dehydrated patients will be at greater risk than young fit adults having third molar removal. There would not appear to be any biological reason why the incidence would be any lower with Coxibs than with NSAIDs. If higher doses of Coxibs are used, then the incidence may be greater, although reports of long-duration use of high doses of Coxibs have not yet reported high incidence of renal problems, even in older cohorts.

Surgical site bleeding with NSAIDs after tonsillectomy has been the subject of two systematic reviews (Marret et al 2003, Møiniche et al 2003). The number needed to harm (NNH) for reoperation after NSAID compared with after placebo was about 60. One patient in 60 given an NSAID will require reoperation who would not have needed that reoperation if they had not had an NSAID. A very similar reoperation NNH was reported for coronary artery bypass grafting with aspirin compared with non-aspirin (Ferraris et al 2002). We do not yet know if the Coxibs will have a clinically relevant lower incidence of surgical site bleeding than that of NSAIDs.

The questions of whether or not NSAIDs delay healing to a clinically relevant extent, and whether Coxibs differ from NSAIDs, remain contentious, and particularly so with bone injury. NSAIDs inhibit Coxibs, which are essential for prostaglandin production. Prostaglandins mediate inflammation, influence the balance of bone formation and resorption, and are essential for bone repair. Some animal

studies showed inhibition of fracture-healing by NSAIDs. There is no good clinical evidence that NSAIDs or Coxibs inhibit bone healing, with the possible exception of long-term use. NSAID and Coxib use appears to increase bone density, and does not increase fracture risk. Smoking reduces bone density and significantly impairs healing after surgery or trauma, and is likely to be an important confounder in studies of the effects of NSAIDs and Coxibs on tissue-healing.

Minor problems

Adverse effects from single-dose oral acute pain studies have been examined systematically for paracetamol, ibuprofen and aspirin (Edwards et al 1999). The common adverse effects such as nausea, dizziness or drowsiness were reported more often when diaries were used, and drowsiness was reported more often in dental rather than in other pain models. The incidence of any adverse effect with any single dose of analgesic was low, but for paracetamol and ibuprofen, but not aspirin, was statistically greater than with placebo. Gastric irritation was two to three times more common with aspirin rather than with placebo, with an NNH of 22 (95% confidence interval 22–174) (Edwards et al 2000). For injected and rectal NSAIDs, commonly reported adverse effects independent of the route of administration were nausea, vomiting, dizziness, drowsiness, sedation, anxiety, dyspepsia, indigestion and dry mouth (Tramèr et al 1998). Two studies reported bleeding time changes. In 12 patients with rheumatoid arthritis treated with indomethacin 100–150 mg orally and rectally, respectively, in a crossover design for 2 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 with placebo. Longer-duration use was not associated with gastrointestinal bleeding.

NSAID safety in chronic use

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 106 000 NSAID-related hospital admissions and 16 500 deaths in the USA every year (Singh 1998). Age and sex are the major risk factors for serious gastrointestinal complications with NSAIDs, although a history of previous ulcers and heart disease are also important. Of the different NSAIDs, some are implicated more than others, although case control and cohort studies give somewhat different estimates. 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 UK studies, each on about 1% of the UK population, indicated, first, that 1.9% of NSAID users might be admitted to hospital each year with upper gastrointestinal emergencies (Blower et al 1997, and, second, that one episode of ulcer bleeding in the elderly will be expected for each 2823 prescriptions (Hawkey et al 1997), and this was confirmed by a Canadian study (Mamdani et al 2002). Another way of putting this is that if

oral NSAIDs are taken for at least 2 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 (Tramèr et al 2000). None of these risks is associated with topical NSAIDs, which have much lower plasma concentrations.

Gastrointestinal adverse effects

Epidemiological studies published in the 1990s associating NSAID use and upper gastrointestinal problems have been reviewed and the data pooled to give a much clearer picture of risks (Hernandez-Diaz & Rodriguez 2000). To be included, studies had to be case control or cohort studies on non-aspirin NSAIDs, with data on bleeding, perforation, or other serious upper gastrointestinal tract events resulting in hospital admission or referral to a specialist, and with data to calculate relative risk. Eighteen studies were found, all of which had specific definitions of exposure and outcome, and similar ascertainment for comparison groups. All but two attempted to control for potential confounding factors such as age, sex, history of ulcer, or concomitant medicines.

The main results are summarized in Figs 30.5 and 30.6. Compared with non-users, NSAID users had a higher risk of upper gastrointestinal bleed when they were current NSAID users and used a higher dose. The duration of use was unimportant, but different NSAIDs had different risks, with ibuprofen (especially doses below 2400 mg a day) being least harmful.

The effect of ulcer history and age is shown in Figs 30.7 and 30.8. People with a history of ulcer or with a previous bleed who took NSAIDs were at much greater risk than those with no history of ulcer who took NSAIDs. Older patients who took NSAIDs were at greater risk than under-50s who took NSAIDs.

The advantage of Coxibs over NSAIDs is their reduced potential for causing serious gastrointestinal bleeding. The evidence for this advantage, from both trials (Bombadier et al 2000) and meta-analyses (Goldstein et al 2000, Langman et al 1999), is that serious bleeding is less frequent than with NSAIDs. The cumulative incidence of perforations, ulcers and bleeds over 12 months is about half that with classic NSAIDs. The limited evidence available suggests also that there are fewer dyspeptic symptoms with Coxibs than with NSAID.

Renal failure

The NSAIDs can cause acute renal failure with chronic use, as they can with acute use. In renal dysfunction, the kidneys may depend on extra prostaglandin production just to maintain function. Taking NSAIDs, which reduce the extra prostaglandin production, will then impair function. The risk factors, as with acute NSAID use, include pre-existing heart or kidney disease, use of loop diuretics, or loss of more than 10% of blood volume. An estimate of the risk came from a study conducted among all members of the Tennessee Medicaid programme aged 65 years or more in 1987–1991 and enrolled for at least 1 year (Griffin et al 2000). Those with first admission to hospital for acute renal failure (admission creatinine level of 180 $\mu\text{mol/L}$ or more at admission) were patients with community-acquired acute renal failure. Controls were randomly selected for all persons in the study population. Exclusions were people with end-stage renal disease and those with hospital-acquired acute renal failure. NSAID exposure was ascertained from prescriptions filled in the year before the index date.

There were 1799 patients, with an annual incidence of community-acquired acute renal failure of 4.5 admissions per 1000. The median hospital stay was 8 days. Thirty-six per cent of patients died within

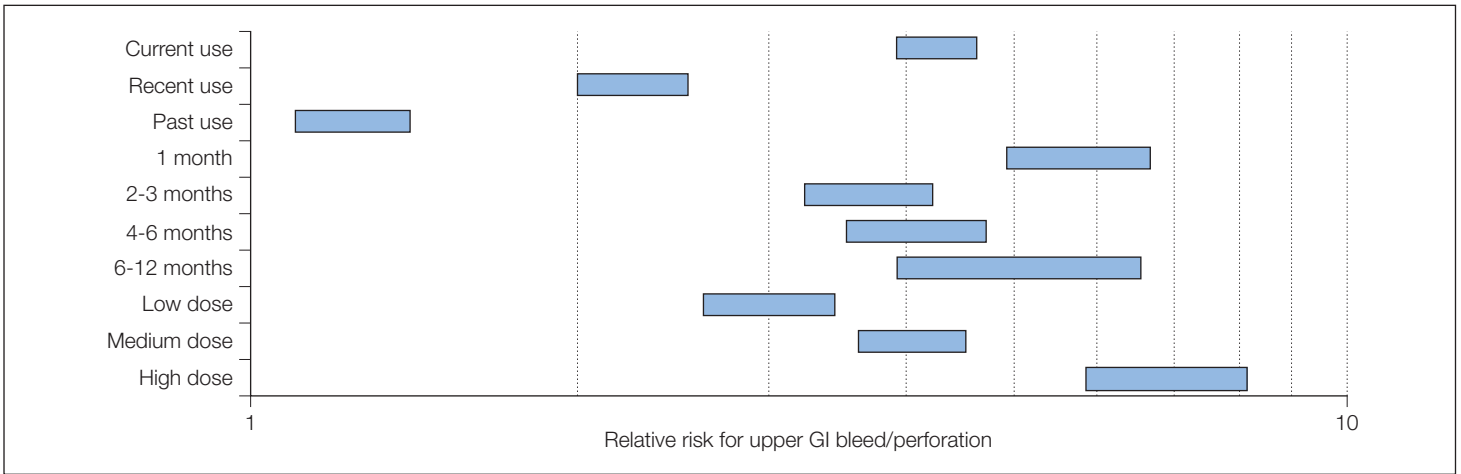


Fig. 30.5 Risk of upper gastrointestinal bleed or perforation for NSAID users compared with risk in non-users. Bars represent 95% confidence interval of relative risk.

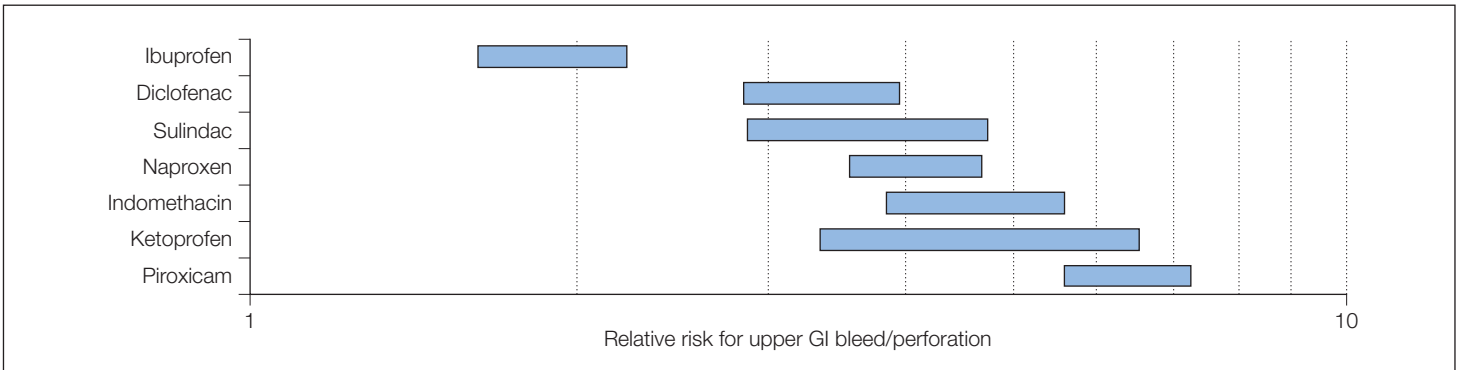


Fig. 30.6 Risk of upper gastrointestinal bleed or perforation for particular NSAID users compared with risk in non-users. Bars represent 95% confidence interval of relative risk.

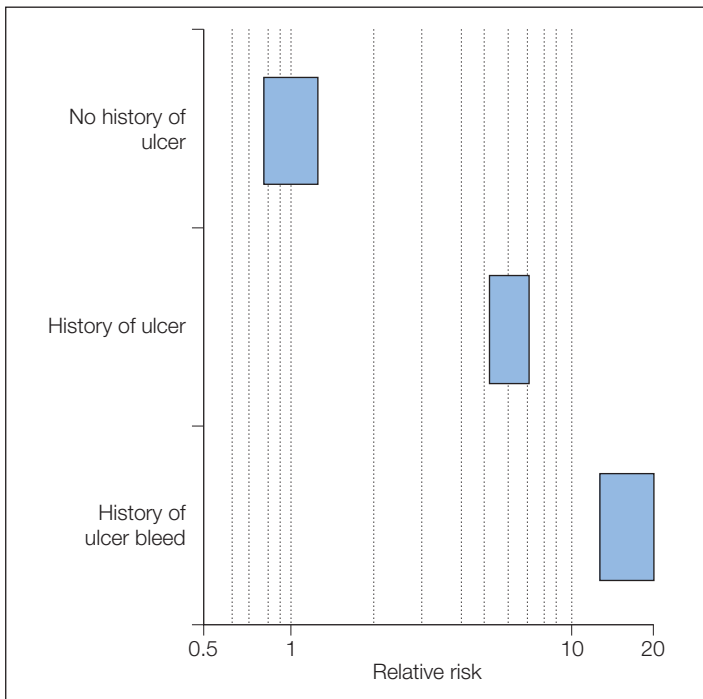


Fig. 30.7 Effect of history of ulcer in users of NSAIDs. Bars represent 95% confidence interval of relative risk.

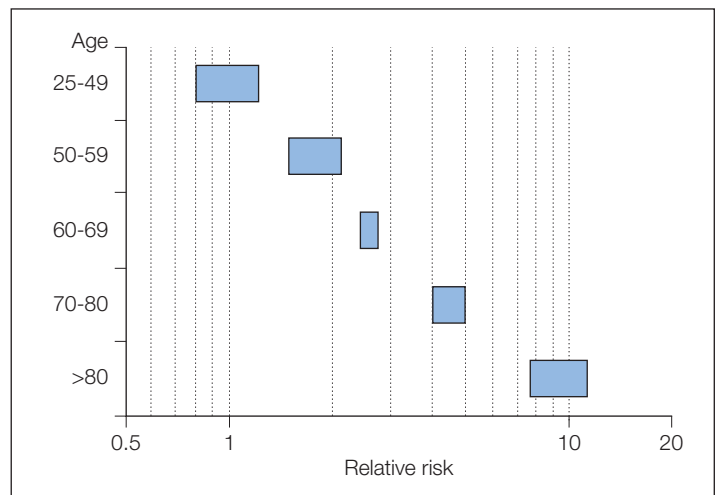


Fig. 30.8 Effect of age in users of NSAIDs. Bars represent 95% confidence interval of relative risk.

30 days. Forty-two per cent were classified as having new renal disease. The remainder were classified as having chronic renal failure with acute exacerbation based on a prior creatinine level above 122 $\mu\text{mol/L}$, a documented history of chronic renal failure, or imaging studies compatible with chronic renal disease. There were 9899 control subjects. Controls were less likely to be nursing home residents or be 85 years or older.

Use of NSAIDs was higher (18%) in the patients with acute renal failure than in control subjects (11%). For current NSAID use, the odds ratio was 1.6 (95% confidence interval 1.3–1.9). Those who had stopped using NSAIDs within the past 30 days had no increased risk of renal failure. For certain NSAIDs where there was sufficient information, ibuprofen and indomethacin, there was a dose-related response for risk. For individual NSAIDs, ibuprofen, piroxicam, fenoprofen and indomethacin had the greatest increased risk, with odds ratios of about 2.

A previous detailed study, although on smaller numbers, indicated that previous renal disease, or gout—but particularly a combined history of gout and previous renal disease—were major risks for renal failure with NSAIDs (Henry et al 1997). Patients using NSAIDs with half-lives of 12 h or more in the previous week had particularly increased risk of renal failure.

There seems to be no biological reason why the risk of renal problems should be lower with Coxibs than with the NSAIDs.

Congestive heart failure

The third in the triad of major problems is congestive heart failure in older people (Page & Henry 2000), and this problem has had a much lower profile than those of gastrointestinal bleeding and renal failure. This low profile may have been inappropriate, because as many hospital admissions may result from NSAID-induced congestive heart failure as from gastrointestinal bleeding.

A study at two hospitals in New South Wales (caring for a population of about 450 000) enrolled as cases consecutive patients between 1993 and 1995 where the medical officer admitting the patient and the attending physician agreed that the primary reason for admission was congestive heart failure (Page & Henry 2000). Patients admitted for other reasons with incidental congestive heart failure were not included. Study nurses ensured that all included cases met Framingham criteria for congestive heart failure. Control subjects (target two per case patient) were patients of the same sex and within 5 years of age, admitted to the same hospital but with no clinical or radiological signs of congestive heart failure.

There were 365 case patients and 658 control subjects, with a mean age of 76 years. Most case patients had moderate or severe congestive heart failure. Use of non-aspirin NSAIDs was 17% in the case patients in the week before admission, compared with 12% in controls. The adjusted odds ratio was 2.1 (5% confidence interval 1.2–3.3) for all cases, and 2.8 (1.5–5.1) for the 272 cases with first admission for congestive heart failure (Table 30.1).

Congestive heart failure was far more likely in those patients with a prior history of heart disease, in which the odds ratio was 26 (5.8–119). Complicated statistical analysis confirmed the effect of pre-existing heart disease, and suggested that NSAIDs with longer half-lives (naproxen, piroxicam and tenoxicam) had much higher risk than those with short half-lives (ibuprofen and diclofenac, for instance), although on small numbers in a subgroup analysis.

The importance of the NSAID precipitation of congestive heart failure was substantiated by a large study from Sweden (Merlo et al 2001). Ecological line regression established an increased relative risk of 1.26 (1.23–1.28) between outpatient NSAID use and hospitalized

Table 30.1 NSAID use and history of heart disease: effect on risk of developing congestive heart failure

Heart disease	NSAID use	Odds ratio (95% confidence interval)
No history	Non-user	1
No history	User	1.6 (0.7–3.7)
History	Non-user	2.5 (1.4–4.3)
History	User	26 (6–119)

heart failure. Starting NSAID therapy doubles the incidence of heart failure in susceptible individuals: those with renal failure, diabetes or hypertension (Garcia Rodriguez & Hernandez-Diaz 2003).

Hypertensive effects of analgesics

The NSAIDs raise blood pressure in some individuals, but with variable extent (Hillis 2002). Hypertensive patients on NSAIDs are more susceptible to blood pressure increases than are normotensive patients, and the mean increase in blood pressure was slightly higher in untreated hypertensive patients than in normotensive patients (Johnson et al 1994). Hypertensive patients receiving antihypertensive therapy experienced a greater mean increase in supine blood pressure as a result of NSAID therapy than that of uncontrolled hypertensive patients (4.7 mm Hg versus 1.8 mmHg), and blood pressure increases were greater in patients receiving β -blockers than in those receiving vasodilators and diuretics (Johnson et al 1994). In normotensive patients, hypertensive effects of conventional NSAIDs appear to be minimal (Johnson et al 1994, Pope et al 1993). Coxib drugs probably have similar effects, but the information is still limited (Hillis 2002).

Comment

The three major NSAID risks—gastrointestinal bleeding, renal failure, and congestive heart failure—are important, particularly because increased age is such an important factor. Putting all this into the perspective of an average primary care grouping of 100 000 (Bandolier 2000), then in this population (3500 over-65s taking NSAIDs), there would be 18 hospital admissions every year for upper gastrointestinal bleeding, 10 for acute renal failure, and 22 for congestive heart failure. The majority of the renal and heart failure cases would be in those aged 75 and over. For both renal failure and congestive heart failure, NSAIDs uncover existing disease problems, and for both there are plausible mechanisms, dose–response relationships, and particular association with NSAIDs with longer half-lives.

What can be done to minimize these risks? The risk of gastrointestinal bleeding with NSAIDs may be reduced by coadministration of proton pump inhibitors or misoprostol. Gastrointestinal adverse effects limit the tolerability of misoprostol. For gastrointestinal bleeding, the Coxibs reduce but do not eliminate the risk. The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95% confidence interval 0.2–0.8). Coxibs, however, do not reduce the risk of renal failure or of congestive heart failure, and for these risks there has to be a clinical balance between the analgesia provided by an NSAID or Coxib and the risk of complication. Over half the patients in the Celecoxib Long-term Arthritis Safety Study (CLASS) of celecoxib

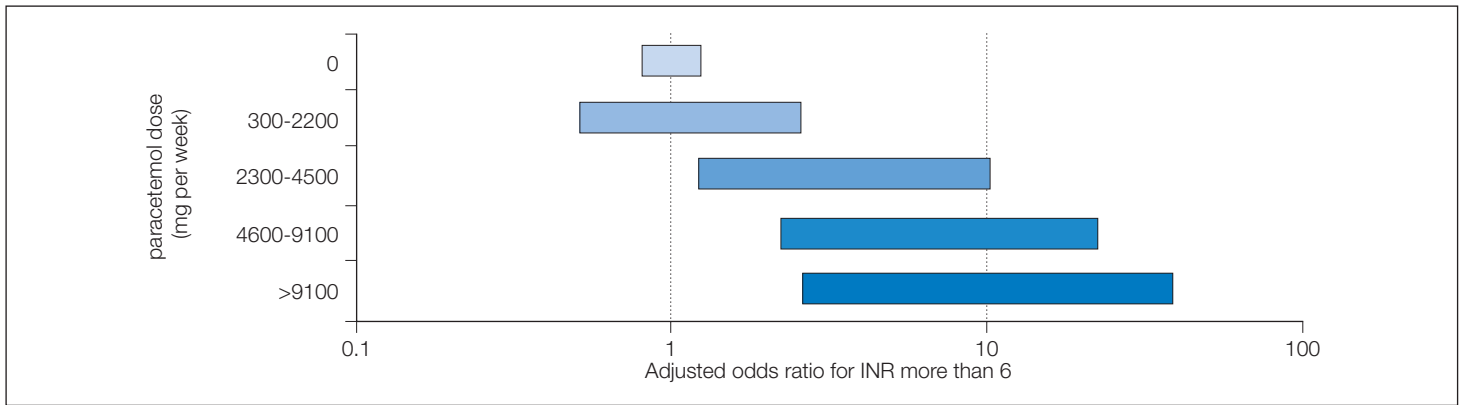


Fig. 30.9 Effect of paracetamol dose on risk of international normalized ratio (INR) above 6.0.

versus NSAIDs in arthritis (US Food and Drug Administration 2002) were on hypertensive treatment, a reminder of the awkward fact that the patients with pain will often be hypertensive and hence at risk. There is no evidence that the risk of congestive heart failure is higher with Coxibs than with NSAIDs, but for rofecoxib there is debate about thrombotic safety (US Food and Drug Administration 2001). Equally, there is no evidence that the risk of renal failure is higher with Coxibs than with NSAIDs. The three risks can only be minimized by sensible assessment and selection, starting at low dose, and titrating.

Contraindications

A history of gastrointestinal bleeding, particularly in the past year, and coadministration of steroids, which also increase the risk of gastrointestinal bleeding, are potential contraindications to NSAID use, as would be the presence of moderate or severe renal problems. In mild renal dysfunction, dose reduction and use of shorter half-life drugs may reduce risk.

Asthma and allergy

The NSAIDs may make asthma worse, and NSAIDs should be avoided in any patient who has had exacerbation of asthma, angio-oedema,

urticaria or rhinitis while taking aspirin or any other NSAID (Jenkins et al 2004). The advice to use paracetamol as the alternative in this circumstance seems sound. Recent publications claiming that paracetamol causes asthma appear to suffer from confounding by indication. Patients with asthma are told not to take NSAIDs but to take paracetamol. Therefore many people taking paracetamol have asthma, but the paracetamol is not causal.

Drug interactions

Warfarin

In a case control study of patients attending the anticoagulant therapy unit (2000 patients) over a single year, who had been on warfarin for at least 1 month, had a target international normalized ratio (INR) of 2.0–3.0, but who had an INR greater than 6.0, paracetamol was a risk factor (Hylek et al 1998). The more that was taken in the week before the test, then the greater the chance of a raised INR (Fig. 30.9). More than nine 500-mg tablets a week gave an odds ratio of 7, and more than 18 tablets a week an odds ratio of 10.

Clearly, again there is a risk of confounding by indication, in that patients on warfarin are advised not to take NSAIDs and may be at risk of the other factors that cause INR changes, such as eating broccoli.

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