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Does Multimodal Analgesia with Acetaminophen, Nonsteroidal Antiinflammatory Drugs, or Selective Cyclooxygenase-2 Inhibitors and Patient-controlled Analgesia Morphine Offer Advantages over Morphine Alone?

Meta-analyses of Randomized Trials

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The authors analyzed data from 52 randomized placebo-controlled trials (4,893 adults) testing acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors given in conjunction with morphine after surgery. The median of the average 24-h morphine consumption in controls was 49 mg (range, 15–117 mg); it was significantly decreased with all regimens by 15–55%. There was evidence of a reduction in pain intensity at 24 h (1 cm on the 0- to 10-cm visual analog scale) only with nonsteroidal antiinflammatory drugs. Nonsteroidal antiinflammatory drugs also significantly reduced the incidence of nausea/vomiting from 28.8% to 22.0% (number needed to treat, 15) and of sedation from 15.4% to 12.7% (number needed to treat, 37) but increased the risk of severe bleeding from 0% to 1.7% (number needed to harm, 59). Selective cyclooxygenase-2 inhibitors increased the risk of renal failure in cardiac patients from 0% to 1.4% (number needed to harm, 73). A decrease in morphine consumption is not a good indicator of the usefulness of a supplemental analgesic. There is evidence that the combination of nonsteroidal antiinflammatory drugs with patient-controlled analgesia morphine offers some advantages over morphine alone.

NONOPIOID analgesics are often used for the treatment of acute, postoperative pain. Systematic review of randomized trials have confirmed the analgesic efficacy of acetaminophen, classic nonsteroidal antiinflammatory drugs (NSAIDs), and selective cyclooxygenase-2 (COX-2) inhibitors after minor surgery.[1–8] They act on peripheral and central sites and interfere with pain mechanisms that are different from the opioid system. They are also frequently used after major surgery, in conjunction with morphine delivered by patient-controlled analgesia (PCA), as part of a multimodal pain treatment. The aim of this approach is to improve analgesia and to decrease the amount of morphine that is needed to achieve pain relief, thus decreasing the incidence of morphine-related adverse effects.

Patients who receive nonopioid analgesics in conjunction with morphine PCA are expected to consume less morphine to achieve satisfactory pain relief as compared with those who receive morphine alone. However, it remains unclear whether there is a clinical benefit when a nonopioid analgesic is added to morphine.[9] In this context, we define a clinical benefit as the evidence of improved analgesia or a reduction in the incidence of morphine-related adverse effects, in the absence of adverse effects that are attributable to the nonopioid analgesic.

The aim of this systematic review is to quantify and to compare the morphine-sparing capacity of acetaminophen, NSAIDs, and COX-2 inhibitors after major surgery and to test the evidence that their use in conjunction with morphine PCA provides a clinically relevant benefit.

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Materials and Methods

Systematic Search

Randomized trials testing acetaminophen, NSAIDs, or COX-2 inhibitors compared with placebo (or no treatment) for pain management after surgery were searched in Medline, Embase, CINHAL, Biosis, Indmed, and the Cochrane Controlled Trials Register. We used the key words *post(-) operative morphine*, *pain treatment* OR *analgesia*, *acetaminophen* OR *paracetamol* OR *propacetamol*, *nonsteroidal antiinflammatory drug* OR *NSAID*, *cox(-)2* OR *coxib**, and individual drug names, without language restriction. Generics that contained the term *coxib* were considered as COX-2 inhibitors. The last electronic search was on July 21, 2004. We identified additional studies from the bibliographies of retrieved reports. We contacted authors of original reports for translation or to obtain additional information.

We considered trials in adults that reported the 24-h cumulative dose of morphine delivered by a PCA device. We excluded trials that used intrathecal opioids or peripheral nerve blocks, and those that included less than 10 patients per group.

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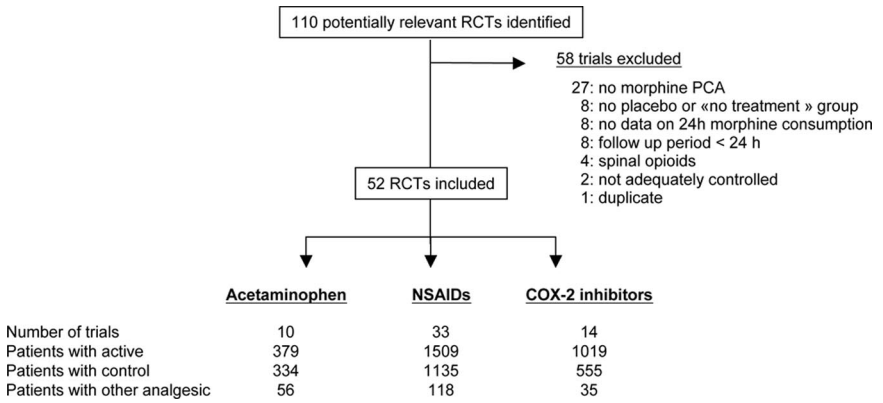

Fig. 1. Flowchart. Numbers of included trials and patients do not add up because five trials tested two classes of analgesics.[16,18,24,32,38] COX-2 inhibitor = selective cyclooxygenase-2 inhibitor; NSAID = nonsteroidal antiinflammatory drug; PCA = patient-controlled analgesia; RCT = randomized controlled trial.

Quality Scoring and Data Extraction

One author (N. E.) screened the abstracts of all retrieved reports and excluded articles that did not meet our inclusion criteria. Two authors (N. E. and C. L.) then independently read all included reports and assessed their methodologic quality using a modified Oxford scale.[10,11] Because there was a previous agreement that we would exclude nonrandomized reports, the minimum score of an included trial was 1, and the maximum was 7. One author (N. E.) extracted information on analgesics, number of analyzed patients, anesthesia, surgery, 24-h cumulative morphine consumption, and pain intensity at 24 h measured with a conventional visual analog scale (VAS) from 0 to 10 cm. She also extracted data on adverse effects that were related to morphine and to the nonopioid analgesics. Definitions of adverse effects were taken as reported in the original trials. A second author (C. L.) checked all extracted data. We resolved discrepancies on quality scores and extracted data by a discussion with the third author.

Statistical Analysis

We calculated weighted mean differences with 95% confidence intervals (CIs) using means, SDs, and SEs as reported in the original trials for 24-h morphine consumption and VAS pain intensity. If the 95% CI included 0, we assumed that the difference between active and control was not statistically significant. If the authors did not report appropriate data, we contacted them. If they did not answer and the data were presented as graphs, we extracted the data from the graphs. If this was not possible, the data were not considered. We summarized dichotomous data on morphine-related adverse effects using relative risks with 95% CIs. We computed Peto odds ratios that deal better with zero cells for rare outcomes (drug-related adverse effects). If the 95% CI around the relative risk or the odds ratio included 1, we assumed that the difference between active and control was not statistically significant. For statistically significant results, we calculated the number needed to treat or harm, the reciprocal of the absolute risk reduction, with 95% CI as an estimate of the clinical impact of a beneficial or a harmful effect.[12]

We performed meta-analyses when the same drug class was tested in at least three trials or in more than 100 patients and when the same outcome was reported. A random effects model was used throughout. Analyses were performed using ReviewManager software (version 4.2; Cochrane Collaboration, Update Software, Oxford, UK) and Excel® (Microsoft Corp. 2004 for Mac, Paris, France). We compared quality scores between classes of analgesics using the nonparametric Kruskal-Wallis test followed by the Dunn post test.

Results

Trials

We identified 110 potentially relevant randomized trials; 58 were subsequently excluded (fig. 1). There was one duplicate cluster;[13] we considered the older report as the main article[14] and excluded the duplicate.[15] We analyzed data from 52 randomized trials that included 4,893 adults.[14,16–66] One trial was in Turkish,[63] and all others were in English. We contacted the main authors of 18 studies and asked for additional information; 10 provided supplemental data that could be used for analyses.[21,23,32,34,43,49,53,56,57,63] One trial was published as an abstract only;[25] we contacted the study sponsor (UPSA Labs, Paris, France), who provided additional information on that trial. This study has now been published in full.[67]

Patients underwent major orthopedic (13 trials), abdominal (12), gynecologic (16), spine (9), or thoracic (2) procedures. Anesthetic techniques included general anesthesia in 43 trials and spinal or epidural in 5, and were not specified in 4.

Ten trials tested acetaminophen (379 patients received the active drug) as multiple-dose regimens. Thirty-three trials (1,509 patients) tested different NSAIDs as single-dose regimens, multiple-dose regimens, or continuous infusions. Fourteen trials (1,019 patients) tested COX-2 inhibitors as single-dose or multiple-dose regimens.

Acetaminophen trials had higher quality scores (median, 6; range, 2–7) compared with NSAID (4; 1–7) or COX-2 inhibitor (4; 1–6) trials, although the differences did not reach statistical significance.

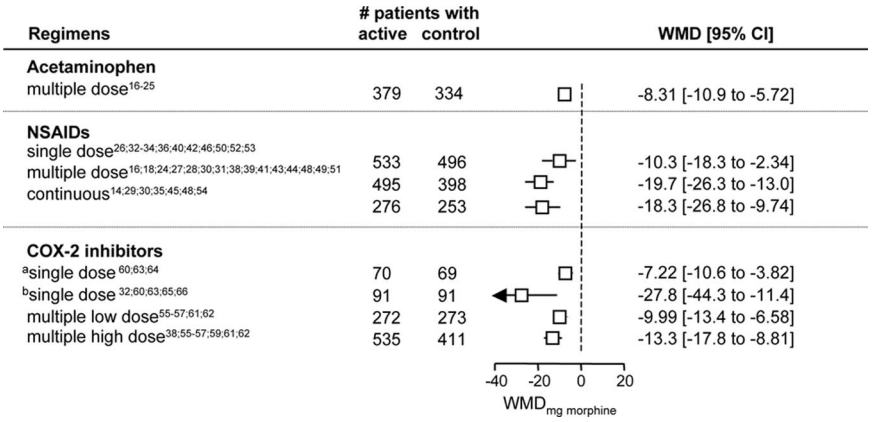

Fig. 2. Twenty-four–hour morphine consumption (in milligrams). A weighted mean difference (WMD) less than 0 indicates less morphine consumption with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant. COX-2 inhibitor = 200 mg celecoxib,[a] 50 mg rofecoxib[b]; multiple high dose = valdecoxib and parecoxib 40 mg/12 h and parecoxib 40 mg/6 h; multiple low dose = valdecoxib and parecoxib 20 mg/12 h; NSAID = nonsteroidal antiinflammatory drug.

Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.‡

24-Hour Morphine Consumption

In control groups, the median of the average 24-h morphine consumption was 49 mg (range, 15–117 mg).

Mean and SD data of morphine consumption were available for all acetaminophen trials.[16–25] When data were combined, 24-h morphine consumption was significantly decreased with acetaminophen, on average by 8.3 mg (fig. 2).

For 31 trials of NSAIDs, mean and SD data of morphine consumption were available.[14,16,18,24,26–36,38–46,48–54] When data were combined, 24-h morphine consumption was significantly decreased with NSAIDs; average reduction was 10.3 mg with single doses, 18.3 mg with continuous infusions, and 19.7 mg with multiple-dose regimens.

Mean and SD data of morphine consumption were available for 13 COX-2 inhibitor trials.[32,38,55–57,59–66] When data were combined, 24-h morphine consumption was significantly decreased with COX-2 inhibitors; average reduction was 7.2 mg with 200 mg celecoxib, 10 mg with multiple low-dose regimens, 13.3 mg with multiple high-dose regimens, and 27.8 mg with single-dose 50 mg rofecoxib. One trial tested 25 mg rofecoxib; in that trial, morphine consumption was significantly decreased by 23 mg.[66]

Analgesia

Most trials that reported on VAS pain intensity did so for pain at rest. Pain intensity on movement was inconsistently reported and was therefore not further analyzed. In control patients, the median of the average pain intensities at 24 h was 2.7 cm (range, 1.5–5.6 cm) on the 0- to 10-cm VAS.

Mean and SD data of VAS pain intensities at 24 h were available for five acetaminophen trials.[18,21–24] None showed a significant reduction with acetaminophen. When data from all five trials were combined, there was still no significant effect; the average reduction in favor of acetaminophen was −0.29 cm (fig. 3). The largest average decrease in pain intensity (−1.2 cm) was in one trial that tested the highest daily dose of oral acetaminophen (6 g).[23]

Mean and SD data of VAS pain intensities at 24 h were available for 20 NSAID trials.[14,18,24,26,27,33–35,37–39,42,43,45,48,50–54] Six reported a significant reduction of pain with NSAIDs.[24,34,35,38,48,52] When data of all 20 trials were combined, there was a statistically significant decrease in pain intensity with continuous- and multiple-dose regimens (average decreases, −0.97 and −1.0 cm, respectively). The effect was not statistically significant with single-dose regimens (average decrease, −0.75 cm).

No similar meta-analysis could be performed for COX-2 inhibitor trials. Four trials reported mean and SD of VAS pain intensities at 24 h. However, they included fewer than 100 patients and tested one of three regimens, 50 mg rofecoxib,[60,65] 200 mg celecoxib,[64] and 40 mg/6 h parecoxib.[38] Four trials did report VAS but not as mean and SD, and the investigators were unable to provide relevant data.[32,58,63,66] The six other trials reported on a multitude of diverse pain outcomes: peak pain intensity difference,[59] maximum daily pain intensity,[61,62] maximum pain relief,[57,62] or mean pain intensity measured on a four-point categorical scale.[55,56]

Morphine-related Adverse Effects

Acetaminophen did not significantly decrease the incidence of respiratory depression, combined nausea and vomiting, urinary retention, or sedation (fig. 4A).

Nonsteroidal antiinflammatory drugs decreased the incidence of nausea or vomiting symptoms from 28.8% to 22.0%. This difference was statistically significant (relative risk, 0.72; 95% CI, 0.61–0.86). The absolute risk reduction (6.8%) indicated that 15 patients need to receive an NSAID in conjunction with morphine PCA for one not to experience nausea or vomiting who would

‡ Supplementary material includes details on drug regimens and included randomized trials. These data are also freely accessible on the author's Web site at http://www.hcuge.ch/anesthesie/data.htm.

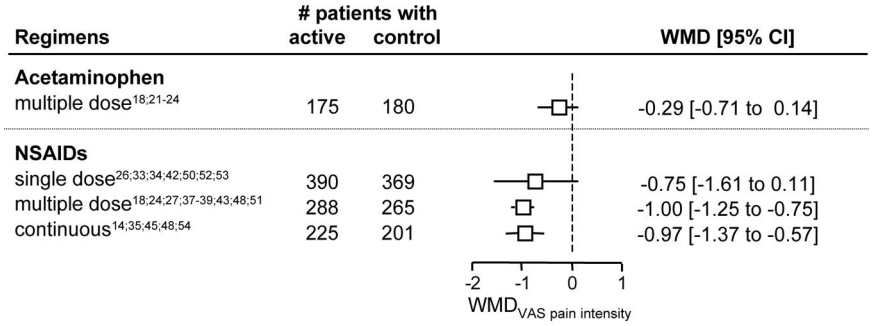

Fig. 3. Visual analog scale (VAS) score for pain intensity at rest at 24 h (0–10 cm). A weighted mean difference (WMD) less than 0 indicates less pain with active compared with control. When the 95% confidence interval (CI) does not include 0, the difference is considered statistically significant. Meta-analyses were performed when data from at least three trials or more than 100 patients could be combined; this was not the case for cyclooxygenase-2 inhibitors. NSAID = nonsteroidal antiinflammatory drug.

have done so had they all received the morphine alone (number needed to treat, 15; 95% CI, 9–47). NSAIDs also decreased the incidence of postoperative sedation from 15.4% to 12.7%. Again, this difference was statistically significant (relative risk, 0.69; 95% CI, 0.54–0.88). The number needed to treat was 37 (95% CI, 15–89) (fig. 4B).

None of the results reached statistical significance with COX-2 inhibitors (fig. 4C). Four of five rofecoxib trials reported on combined nausea or vomiting symptoms.[32,63,65,66] The incidence of nausea or vomiting was not significantly decreased with rofecoxib (relative risk, 0.68; 95% CI, 0.37–1.26).

Safety Analysis

Adverse effect profiles of NSAIDs and COX-2 inhibitors were similar (fig. 5). Renal complications were not consistently defined. In four NSAID studies, renal complications were reported as "renal failures" or were described as an increase in plasma creatinine greater than 2 mg/dl; when data were combined, the odds ratio was 7.03, but the result was not statistically significant.[31,37,42,47] Three COX-2 inhibitors studies reported on renal failure.[57,59,61] In one study, 6 of 311 patients undergoing coronary artery bypass surgery who had received parecoxib and none of 151 with placebo were reported to have an increase in plasma creatinine greater than 2 mg/dl or 0.7 mg/dl above baseline.[59] Reynolds *et al.*[61] reported on one patient with increased baseline blood urea (26 mg/dl) and creatinine values (2 mg/dl) who had development of acute renal failure and metabolic acidosis after two doses of 20 mg valdecoxib, despite fluid replacement therapy. Finally, one COX-2 inhibitor study reported that no cases of renal failure had occurred.[57] When data from these trials were combined, the incidence of renal failure in controls was 0% (0 of 291), and that with COX-2 inhibitors was 1.4% (7 of 512). The

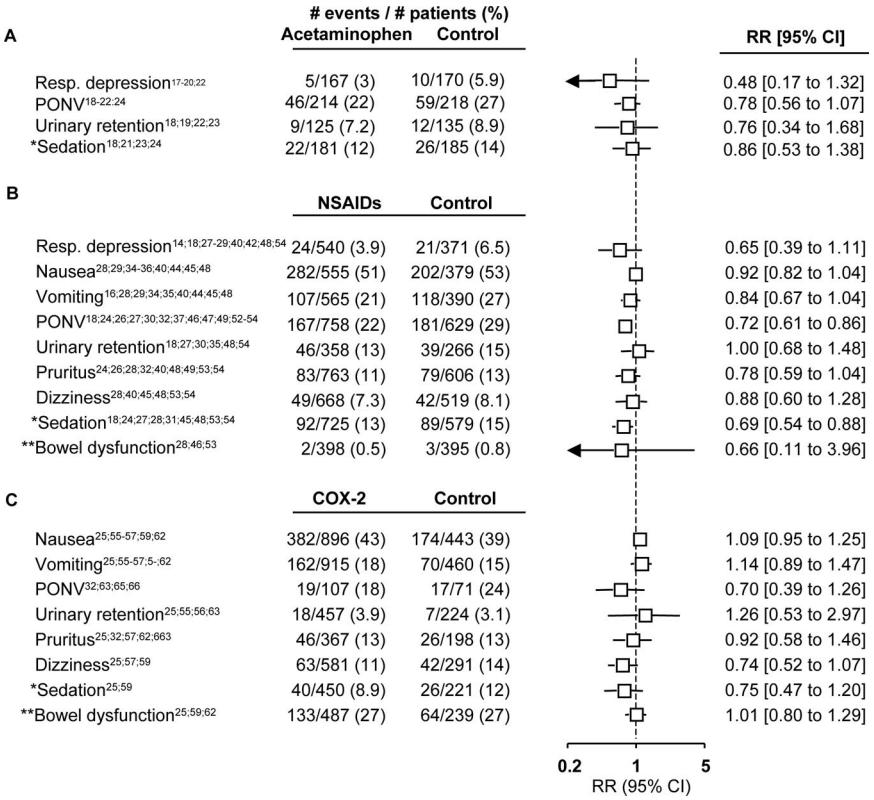

Fig. 4. Morphine-related adverse effects. A relative risk (RR) less than 1 indicates less morphine-related adverse effects with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant. * Sedation or drowsiness or somnolence. ** Ileus or constipation or intestinal obstruction. Meta-analyses were performed when data from at least three trials or 100 patients could be combined. COX-2 = selective cyclooxygenase-2 inhibitor; NSAID = nonsteroidal antiinflammatory drug; PONV = postoperative nausea or vomiting.

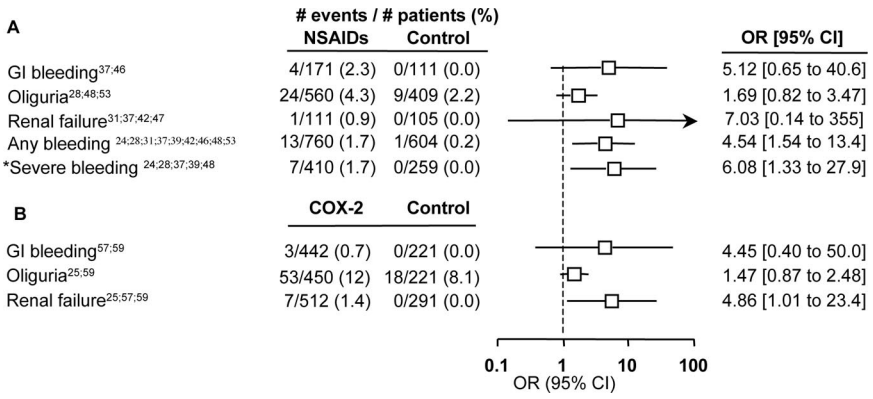

Fig. 5. Adverse effects related to nonsteroidal antiinflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors. An odds ratio (OR) greater than 1 indicates more drug-related adverse effects with active compared with control. When the 95% confidence interval (CI) does not include 1, the difference is considered statistically significant. * Reoperation due to bleeding, transfusion required, severe postoperative hemorrhage. Meta-analyses were performed when data from at least three trials or more than 100 patients could be combined. GI = gastrointestinal.

difference was statistically significant. The odds ratio was 4.86 (95% CI, 1.01–23.4), and the number needed to harm was 73 (95% CI, 42–277). However, 6 of the 7 patients with renal failure with COX-2 inhibitors came from the coronary artery bypass surgery trial.

Nine NSAID studies reported on presence or absence of surgical bleeding complications.[24,28,31,37,39,42,46,48,53] When data from these nine trials were combined, there was an incidence of surgical bleeding of 0.2% (1 of 604) in controls and of 1.7% (13 of 760) with NSAIDs. That difference was statistically significant. The odds ratio was 4.54 (95% CI, 1.54–13.42), and the number needed to harm was 65 (95% CI, 40–176). Five of these nine studies reported that the bleeding was severe and thus clinically relevant: need for blood transfusion,[24,28] need for reoperation,[39,48] or defined by the original investigators as "serious postoperative hemorrhage."[37] NSAIDs tested were ketorolac,[28,48] diclofenac,[24,39] and ketoprofen.[37] When data from these five trials were combined, there was an incidence of severe surgical bleeding of 0% (0 of 259) in controls and of 1.7% (7 of 410) with NSAIDs. Again, the difference was statistically significant; the odds ratio was 6.08 (95% CI, 1.33–27.86), and the number needed to harm was 59 (95% CI, 34–221). No surgical bleeding complications were reported with COX-2 inhibitors.

In the COX-2 inhibitor trial that included patients undergoing coronary artery bypass surgery,[59] life-threatening events resulting in fatality or prolonged hospitalization were reported as "serious adverse events." They included death, cerebrovascular disorder, myocardial infarction, thrombophlebitis, sternal wound infection, renal failure, gastrointestinal hemorrhage, pleural effusion, pneumonia, and cardiac failure. Such events were reported in 19% of patients who had received postoperative parecoxib and in 9.9% of controls. This difference was statistically significant (odds ratio, 1.95; 95% CI, 1.33–3.32); the number needed to harm was 11 (95% CI, 6–39).

Only one acetaminophen trial reported adverse effects: In two patients, transaminase values were increased above 50 U/l; one had received acetaminophen, and one had received placebo.[22]

Discussion

Four main results emerge from these meta-analyses. First, all these nonopioid analgesics are morphine sparing. Second, pain intensity, when measured with a standard VAS scale, is significantly decreased at 24 h with NSAIDs only. Third, there is evidence of a reduction in the incidence of some morphine-related adverse effects with NSAIDs only. Finally, with both NSAIDs and COX-2 inhibitors, there were reports of rare but clinically important adverse effects.

Patient-controlled morphine consumption is a valuable, although indirect, estimate of the efficacy of a concomitant analgesic intervention. An efficient analgesic is expected to decrease the dose of morphine that is needed to achieve satisfactory pain relief. Patients in control groups consumed on average approximately 50 mg morphine during the first 24 h. This amount was decreased by 45–55% by single-dose 25–50 mg rofecoxib. With NSAID regimens, morphine sparing was approximately 40%; with other COX-2 inhibitors, it was approximately 25%; and with acetaminophen, it was below 20%, confirming the results of a recently published meta-analysis on acetaminophen.[68] Two conclusions may be drawn. First, all these nonopioid analgesics are truly analgesic, not only after minor surgery,[1–8] but also after major surgery. Second, the difference in the extent of morphine sparing between drug classes did not reach statistical significance. The question now is whether there is a clinical benefit for the patients when a nonopioid analgesic is added to the morphine PCA.

There was no evidence of a decrease in pain intensity after 24 h with acetaminophen. In control groups, the average VAS was less than 3 cm; therefore, it may be difficult to demonstrate an additional benefit with an analgesic when baseline pain is low.[69] NSAIDs decreased pain intensity from approximately 3 to 2 on the 10-cm VAS. A similar degree of postoperative analgesia has been reported with intraoperative ketamine regimens.[11] Two issues must be considered. First, pain intensity at rest only could be analyzed. Therefore, we do not know to what extent NSAIDs would decrease pain intensity on movement. Second, the net benefit for the patient when

pain intensity decreases from 3 to 2 on a 10-cm scale remains unclear. Unfortunately, no comparison with COX-2 inhibitors was possible because these trials reported on a large variety of alternative pain measurements. The uncritical use of nonvalidated pain measurements has been reported in other pain settings.[11,70]

Clearly, a reduction in morphine-related morbidity would benefit the patient. A recently published meta-analysis suggested a net reduction in nausea or vomiting and sedation when NSAIDs and COX-2 inhibitors were combined with morphine.[71] Our analyses confirm these results for NSAIDs but not for COX-2 inhibitors, and our conclusions are less enthusiastic because the clinical relevance of the effects remains uncertain. For example, with morphine PCA alone, 28.8% of the patients were nauseous or vomited, and the adjunction of NSAIDs decreased that incidence to 22%. This is an impressive 24% relative reduction in the risk of nausea and vomiting, and this difference is statistically significant. However, in absolute terms, the degree of efficacy suggests that of 100 patients who receive morphine PCA with an NSAID, only approximately 7 will not vomit or be nauseous who would have done so had they received the morphine alone (absolute risk reduction, 6.8%; number needed to treat, 15). The protective effect of NSAIDs against morphine-related nausea and vomiting is finite. However, the extent of this effect remains small compared with, for example, the efficacy of truly antiemetic interventions that have numbers needed to treat of approximately 5.[72] Also, it may be overly optimistic to expect that the sole reduction in the postoperative dose of morphine would decrease the risk of nausea and vomiting in a clinically relevant way, because these are of multiple origin.[73] In fact, the correlations between morphine consumption and the risk of nausea or vomiting were recently shown to be weak (for nausea, $r^2 = 0.37$; for vomiting, $r^2 = 0.27$).[71] As with the reduction in nausea and vomiting, the protective effect of NSAIDs against morphine-related sedation was statistically significant. A decrease in the incidence of postoperative sedation from 15.4% to 12.7% will probably remain unnoticed in daily clinical practice but could gain in importance when a larger patient population is considered.

Although the reduction in morphine consumption was significant with all regimens, morphine-related adverse effects were not influenced or were only marginally influenced by this decrease. There may be several reasons for this. First, these trials mainly concentrated on efficacy and did not systematically evaluate and report on adverse effects. This limitation on the reporting of adverse effects has been described in other pain settings.[74] Second, the trials were too small to study adverse reactions that are rare. Finally, the degree of morphine sparing may not have been important enough to decrease the incidence of morphine-related adverse effects. With most COX-2 inhibitors and with acetaminophen, morphine sparing was between 20% and 25%, and there was no decrease in morphine-related adverse effects. With NSAIDs, morphine consumption was decreased by approximately 40%, and there was evidence of a statistically significant beneficial reduction of emesis and sedation, albeit small. With rofecoxib, morphine sparing was even more pronounced; however, in these trials, the decrease in the incidence of nausea and vomiting was not statistically significant, and other morphine-related adverse effects were only inconsistently reported. We still do not know to what extent morphine consumption must be decreased to significantly reduce the incidences of morphine-related adverse effects. Also, not all adverse effects of morphine are equally important. Interestingly, although normal passage is one of the key factors of successful fast-track surgery, bowel dysfunction was inconsistently reported, and definitions varied widely.

When discussing the usefulness of these nonopioid analgesics, we should consider their potential for harm. There were no reports on adverse effects with acetaminophen. We do not know whether none occurred or whether they were not reported. Acetaminophen regimens were 4 g/day, except for one study, where the regimen was 6 g.[23] That trial reported on the largest (although not statistically significant) decrease in pain intensity among all acetaminophen trials. It cannot be ruled out that the tested doses were suboptimal, because there was no beneficial effect and no harm.

With both NSAIDs and COX-2 inhibitors, there were reports of rare but clinically important adverse effects. These results have to be interpreted cautiously. Renal dysfunction was not well defined in these studies. The data on COX-2 inhibitors and renal failure are likely to be skewed because six of seven reports on renal failure came from a single trial of patients undergoing coronary artery bypass grafting.[59] Furthermore, in a recent large randomized trial in patients undergoing coronary surgery, 11 of 1,088 patients (1%) who had received parecoxib and valdecoxib were reported to have postoperative renal dysfunction, compared with only 3 of 538 (0.5%) receiving placebo; that difference, however, was not statistically significant.[75] Also, a previous meta-analysis, including a limited number of patients, suggested that postoperative NSAID-related renal dysfunction was clinically unimportant and transient and that NSAIDs, therefore, should not be withheld from patients with normal preoperative renal function.[76] Data from our analyses do not suggest that renal toxicity for NSAIDs and COX-2 inhibitors is different.

Although NSAIDs increase the risk of surgical bleeding, the incidence of this complication is low. In particular settings, however, that risk may outweigh the benefit.[77] A large randomized trial was unable to show any difference in the risks of surgical site bleeding among ketorolac, diclofenac, and ketoprofen.[78] Trials that tested

COX-2 inhibitors did not report on presence or absence of surgical bleeding.

In the trial including cardiac patients, COX-2 inhibitors increased the risk of rare but serious adverse events.[59] Among those were myocardial infarction and cerebrovascular disorders. Nussmeier *et al.*[75] also reported a significantly higher incidence of combined thromboembolic events among patients who received parecoxib and valdecoxib compared with those who received placebo. No similar data were reported in any of the other (smaller) COX-2 inhibitor trials. The recent withdrawal of rofecoxib challenges the cardiovascular safety of all COX-2 inhibitors.§ This may not be a problem with short-term administration of the drug to patients with normal renal function and without cardiac risk factors, but it may be appropriate to avoid perioperative COX-2 inhibitors in cardiac patients[79] and in those with abnormal renal function.

There are several limitations related to these meta-analyses. First, we included data only from patients undergoing major surgery who consumed morphine postoperatively with a PCA device; in controls, 24-h morphine consumption was considerable. Therefore, these data cannot necessarily be extrapolated to other surgical settings, such as ambulatory surgery, where surgical trauma is less severe and postoperative pain is usually controlled without or with only a minimal amount of opioids. COX-2 inhibitors, for example, have shown adequate analgesic efficacy after minor surgery.[4] Also, a single oral dose of acetaminophen has been demonstrated to have pain-relieving properties after, for example, third molar extraction.[80] Second, we were unable to analyze outcomes beyond 24 h after surgery. Relevant data for longer periods were only inconsistently reported in the original trials. Finally, we restricted our search to trials in adults. The necessary subgroup analyses for children are lacking.

In conclusion, after major surgery, the morphine-sparing effect of acetaminophen, NSAIDs, and COX-2 inhibitors is quantifiable and is, with specific regimens, considerable. Despite this, the combination of a single nonopioid analgesic with morphine PCA offers no (acetaminophen), unclear (COX-2 inhibitors), or only little (NSAIDs) advantage over morphine PCA alone. The combination of several nonopioid analgesics, however, may produce an additive or even synergistic effect. Optimal multimodal postoperative analgesia regimens should be identified in randomized and well-designed, large studies.

Finally, these meta-analyses highlight an important methodologic issue that should be addressed when examining published studies and when designing future trials: Morphine sparing *per se* is not an indicator of the usefulness, and thus the clinical relevance, of a supplemental analgesic. Future trials should be designed to report clinically relevant outcomes important for patients, *e.g.*, decrease in pain intensity at rest and on movement, decrease in morphine-related morbidity (respiratory depression, bowel dysfunction, nausea, vomiting), and absence of drug-induced adverse effects.

§ www.fda.gov/cder/drug/infopage/COX2/default.htm. Accessed August 19, 2005.

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