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Opioids: More to Learn, Improvements to be Made

OPIOIDS are among the most widely used drugs in medicine and are used for the management of acute and chronic pain from a wide variety of disorders. A report in the current issue of ANESTHESIOLOGY by Aubrun *et al.* affords an opportunity to reconsider and reexamine the role of opioids in pain management and also to review the realistic expectations for pain relief and relief of other symptoms for patients receiving opioids for acute pain.

It is worthwhile to begin by defending the uses of these drugs. Opioids are important components of many general anesthetic regimens. They have essential roles in the management of acute pain. For the majority of patients with cancer and sickle cell disease, and for patients in palliative care, opioids are effective in providing pain relief with a tolerable side-effect profile, particularly if mild-to-moderate degrees of sedation are considered acceptable.[1,2] The risk of addiction in hospitalized patients who receive opioids for pain is quite low. Contrary to common belief, opioids also provide analgesia for some patients with neuropathic pain[3] and even for a subgroup of patients with phantom limb pain after amputation.[4]

Aubrun *et al.* examined morphine administration and pain relief in more than 3000 postoperative patients in the PACU, using a standardized titration procedure. Specifically, pain was assessed (using a visual analog scale [VAS] of 0–100) as quickly as possible after arrival in the PACU, and if the reported pain intensity was greater than 30, 3 mg of morphine was given. Assessment and treatment was repeated every 5 min until the reported VAS was 30 or less. Drug administration was stopped before the achievement of adequate pain relief only for respiratory depression (respiratory rate <12 bpm) or other serious events (*e.g.*, hypotension, vomiting). Note that sedation was not considered a serious side effect. These investigators then examined the relationship between the *initial* pain score and amount of morphine required to achieve comfort. They reached several conclusions:

1. Patients with higher initial VAS pain scores required more incremental doses of morphine to reach an acceptable pain score (VAS ≤ 30).
2. There was a marked variation in the number of morphine doses required to produce comfort. The median dose to achieve a VAS of 30 or less was 0.17 mg/kg.
3. In general, VAS scores of 70 or more should be regarded as indicative of severe pain.
4. Most patients with a VAS score of 50 will usually require only one additional dose of morphine to report a VAS of 30 or less.

Aubrun *et al.* are to be commended for an original examination of an everyday occurrence, opioid titration in the PACU, and for examining the results of a standardized titration procedure in a very large number of patients. Some practitioners may adopt the protocol noting the rapid achievement of pain relief (on average, 25 min for most patients). In addition, Aubrun *et al.* examined the quantitative aspects of immediate postoperative pain management and responses to opioids, a process of significant importance to the anesthesiologist, patient, and recovery room nurse.

Several features of the authors' study design suggest caution in interpretation. The patients underwent a diverse group of operative procedures, and, perhaps as a result, the intraoperative administration of opioids and other agents was not standardized (and it would be difficult to do so for such a patient group). Morphine titration in the PACU reflects a complex, non–steady-state situation, with rapidly decreasing effect-site concentrations of general anesthetics, sedatives, and opioids administered intraoperatively, and a rapid stepwise increase of morphine concentrations as the drug is given at 5 min intervals (as dictated by the authors' protocol). This situation is, perhaps unavoidable and certainly reflects common practice. However, it is not clear how well their conclusions can be extrapolated to patients receiving opioids for prolonged period of time or to those with other forms of pain.

It seems problematic to define pain severity based on morphine requirement, especially during the later postoperative stages, because a variety of pharmacokinetic, pharmacodynamic, and psychosocial factors can alter morphine dose–effect relationships. The authors assert that a VAS of 70 or more should be regarded as indicative of severe pain, based on the finding that patients whose initial scores decreased in this range required substantially more morphine than those with initial scores of less than 70. This conclusion concurs with previous work by Collins *et al.*,[5] which incorporated a more direct approach: ask patients to give a VAS score and to

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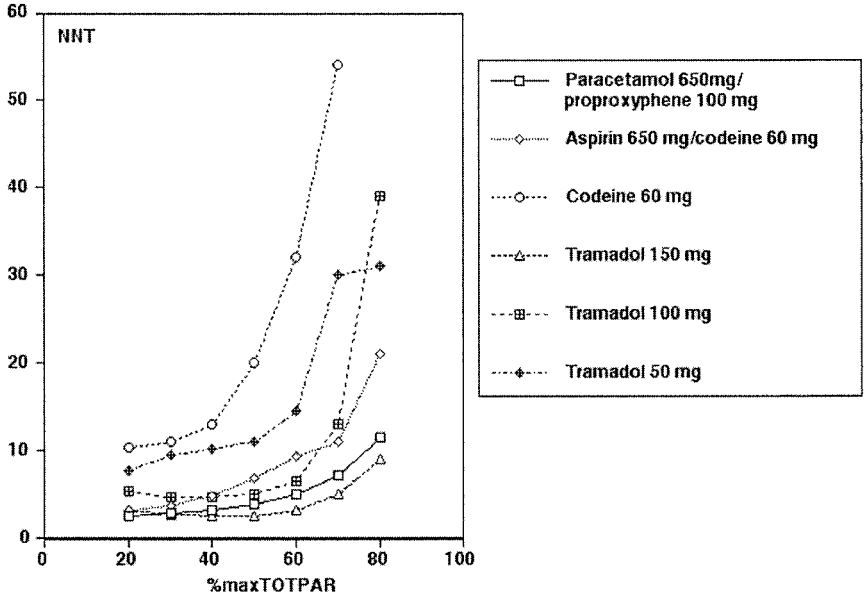

Fig. 1. Effect of percent maximum total pain relief (%max TOTPAR) on NNT, illustrating how much more difficult it is to achieve near-complete pain relief than moderate pain relief. (From McQuay H and Moore A: An Evidence-Based Resource for Pain Relief, London, Oxford Publications, 1998, p 142; used with permission of the publisher.)

simultaneously rate their pain as "mild, moderate or severe." In Collins *et al.*'s study, patients reporting severe pain on a categorical scale had a mean 10 cm VAS score of 7.4, whereas 15% of patients reporting "severe pain" on a categorical scale had VAS scores of less than 5.4.

Aubrun *et al.* conclude that there is a curvilinear relationship between morphine dosing and VAS scores. More specifically, VAS scores changed little with initial incremental doses, and then decreased rapidly to a value of 3 or less with the final incremental dose. McQuay *et al.* depict a different sort of curvilinear relationship between analgesic dosing and effect (fig. 1). A useful indicator of drug effectiveness is the *numbers needed to treat* (NNT). For a given binary endpoint (*e.g.*, success or failure in providing 50% pain relief), NNT expresses how many patients, beyond those who respond to placebo, would have to receive the treatment (*e.g.*, a certain dose of an analgesic) for one patient to have a successful endpoint. In analgesic studies with 50% pain relief as endpoints, NNTs of less than 2 are indicative of a very good effect. When large numbers of diverse clinical trials are analyzed in this way, two significant conclusions emerge:

1. Morphine 10 mg gives NNT values higher than those for maximum recommended doses of nonsteroidal antiinflammatory drugs (NSAIDs). Stated another way, in a diverse group of dental and postoperative trials, morphine 10 mg is less likely to produce 50% pain relief than 800 mg of ibuprofen.
2. With more demanding criteria for effectiveness (*i.e.*, 60, 70, or 80% relief), NNTs for opioids, NSAIDs, and other analgesics increase dramatically. That is, a far smaller percentage of patients treated with a fixed dose of morphine (*e.g.*, 10 mg) achieve 70 or 80% relief compared with the percentage who achieve 50% relief.

The protocol described by Aubrun *et al.* did not measure side effects from morphine administration in the PACU. Morphine administration was stopped if respiratory rate or oxygen saturation reached predefined levels. Few patients (2.4%) were excluded from the analysis for severe morphine-related adverse events (allergy, hypotension, vomiting pruritus, or cutaneous rash). This raises the following question: What is the relationship between opioid dosing and the incidence or frequency of opioid-induced side effects? Does it depend on initial pain scores or extent of pain relief with that dose of opioid? It is widely accepted that more severe pain antagonizes the sedative and respiratory depressant effects of opioids. However, it is less clear how the frequencies of a number of other opioid side effects (*e.g.*, nausea, ileus, itching, urinary retention) vary with both opioid dosing and initial pain severity. An analogous concept to NNT is *numbers needed to harm*, which is a reasonable way to evaluate dose response for side effects. Plots of numbers needed to harm *versus* dose have been used for the assessment of dose-dependence of nausea, vomiting, dizziness, and somnolence in a meta-analysis of studies of tramadol, codeine, and often used combination analgesics.[6]

Opioid side effects exert a major impact on the course of postoperative recovery and limit effective opioid titration in many cases. A variety of strategies have been developed to providing postoperative analgesia while minimizing opioid administration: so-called "opioid-sparing" approaches, including peripheral[7] and neuraxial administration of local anesthetics, oral or intravenous formulations of acetaminophen,[8] NSAIDs[9] or cyclooxygenase-2 inhibitors,[10] systemic or epidural administration of N-methyl-D-aspartate antagonists,[11] and a variety of other approaches. Most of these approaches have mixed success, depending on numerous factors.[12–14] In

some cases the same intervention shows opioid-sparing for some procedures or patient groups but not for others.[15] One interesting report suggested the possibility that, for some patients, apparent morphine-sparing effects of an NSAID could be an artifact of NSAID-induced reductions in renal clearance of morphine-6-glucuronide, which has analgesic activity roughly similar to that of morphine.[16]

Kehlet *et al.* have pioneered studies of approaches to postoperative analgesia and "acute rehabilitation"[17] that emphasize avoidance of parenteral opioids.[18] Major components of this approach include:

1. preoperative education and changes in the "culture" of postoperative care
2. minimally invasive surgical techniques
3. multimodal analgesic approaches with combined use of neuraxial and peripheral regional anesthetic approaches, emphasizing use of local anesthetics
4. NSAIDs, cyclooxygenase-2 inhibitors, or corticosteroids
5. early mobilization, early feeding, early removal of tubes, and supplemental oxygen as needed, particularly during sleep

A major advantage of avoiding opioids in this approach is the ability to minimize postoperative ileus and initiate feeding in the early postoperative period. It should be apparent that any one of these methods of opioid-sparing is useful not as an end in itself, but rather only if it leads to clinically and statistically significant improvements in outcomes, including improved pain scores with rest and with movement, reduced side effects, reduced complications, and improved or accelerated recovery and rehabilitation. Some multimodal interventions produce reductions in opioid use and improved outcomes.[17,19] Several interventions that involve analgesic interventions, but no changes in the overall "acute rehabilitation" approach to postoperative mobilization and nutrition, achieve reduced opioid use but with no change in pain scores, side effects, or recovery parameters.[20]

Recently, the Joint Commission on Accreditation of Healthcare Organizations established standards for pain assessment and treatment in healthcare facilities. This well-intended effort probably will have a positive overall impact in terms of improved standards for pain treatment in many clinical settings. A number of surveys suggest that currently, a high percentage of hospitalized postoperative patients continue to experience moderate-to-severe pain.[21] For example, even when a protocol somewhat similar to that of Aubrun *et al.* was used for patients on surgical wards, the average VAS pain score at rest was still approximately 30 (out of 100), yet the average VAS pain score with activities was 60 after major surgery.[22] However, if hospitals, in an effort to comply with the Joint Commission on Accreditation of Healthcare Organizations, try to generate uniformly low pain scores at rest and with movement (*i.e.*, "all pain scores must be ≤ 3"), using opioids as the sole or predominant method of analgesia, this would likely result in an increased frequency of side effects. Also problematic are surveys that query "the level of the worst pain experienced after surgery." Many patients experience brief, severe episodes of acute pain (*e.g.*, a coughing paroxysm) that cannot be anticipated or well controlled with current opioid regimens. For some patients and some situations, the overall impact on well-being, quality of life, and outcomes may be beneficial. Other patients may prefer moderate pain (*e.g.*, VAS 4–5) to reduce the severity of dizziness, somnolence, or other side effects. Aubrun *et al.*'s study as reported in this issue of the Journal adds to the body of literature that affirms the utility, limitations, and difficulties in titrated dosing of opioids.

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Individual Differences in Pain Sensitivity: Implications for Treatment Decisions

SOME individuals seem to be highly sensitive to pain, whereas others seem to be surprisingly insensitive. A quantitative characterization of an individual's basal pain sensitivity holds the potential to be of significant clinical utility if it could help predict the magnitude of pain that a clinical procedure would evoke in that individual. The current issue of ANESTHESIOLOGY includes an article describing a reasonably strong correlation between a simple preoperative assessment of pain to an experimental stimulus and the amount of pain experienced after a standardized surgery (cesarean section).[1] The purpose of this editorial is to discuss the validity of these preoperative measures and the implications of the authors' observations to further clinical research and, ultimately, clinical practice.

Measurement of Individual Differences in Pain Sensitivity

Historically, pain sensitivity has been defined as the difference between threshold and tolerance,[2] but this definition is problematic.[3] Thresholds are generally insensitive to analgesic manipulations and are subject to significant response biases, whereas tolerance is highly dependent on the motivation of the subject.[3] Magnitude estimates of a single, fixed, supra-threshold stimulus provide a simple, yet straightforward way to characterize pain sensitivity.[4] However, the use of supra-threshold responses as a measure of pain sensitivity has been limited because of inadequate methods of psychophysically assessing the subjective magnitude of pain and the lack of devices capable of delivering supra-threshold noxious stimuli in a well-controlled fashion. Moreover, the interpretation of interindividual differences in magnitude estimates is hampered by questions about differences in the manner in which each individual reports his or her experience or uses the rating scales.[5] Thus, the potential to characterize and subsequently use information about a patient's pain sensitivity to guide treatment decisions has long remained unrealized.

Several factors, however, have currently opened the door for fundamental studies examining the relationship between a patient's basal pain sensitivity and the pain he or she experiences after a clinical manipulation. First, magnitude estimation techniques for assessing pain intensity and pain unpleasantness have slowly but steadily matured over the past 25 years.[6] Visual analog scales, in particular, have been heavily validated and have been shown to produce reproducible, internally consistent, ratio-scale measures of both pain intensity and pain unpleasantness.[6–9] Second, computerized, feedback control thermal stimulators are now commercially available, and some have been approved by the Food and Drug Administration for human use.

Brain imaging studies provide strong evidence that subjective ratings of pain magnitude are closely related to objectively measured neural activity in a number of cerebral cortical and subcortical regions involved in the processing of pain. In *within-individual* studies using either positron emission tomography or functional magnetic resonance imaging, brain regions such as the thalamus, primary somatosensory cortex, secondary somatosensory cortex, anterior cingulate cortex, prefrontal cortex, and insular cortex have been shown to exhibit increasing activation as subjective ratings of pain increase across different intensities of stimulation.[10–12] More important, emerging functional magnetic resonance imaging studies indicate that *interindividual* differences in subjective reports of pain magnitude are closely related to the degree of activation in several brain

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regions important in the processing of pain.[4] Using a visual analog scale, individuals who rate a fixed noxious thermal stimulus as very painful activate the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex more frequently and more significantly than those who report that the same stimulus is only mildly painful. Taken together, these objective correlates of the subjective experience confirm that interindividual differences in subjective pain magnitude ratings do indeed reflect interindividual differences in the pain experience.

The current investigation by Granot *et al.* is on the vanguard of studies examining the clinical implications of interindividual differences in pain sensitivity.[1] In a preoperative session, they assessed both thermal pain thresholds and supra-threshold visual analog scale responses to a fixed set of noxious thermal stimuli in women who were scheduled to undergo elective cesarian section. Postoperative visual analog scale ratings of both resting pain and pain evoked by standing or sitting were significantly correlated with preoperative pain evoked by a supra-threshold 48°C heat stimulus. In contrast, no statistically reliable relationship was detected between preoperative pain thresholds and postoperative pain, consistent with earlier notions that thresholds are of limited utility in defining pain sensitivity.[3]

In identifying this statistically reliable relationship between a preoperative, controlled noxious stimulus and postoperative pain, Granot *et al.* have provided a key piece of evidence that basal pain sensitivity can be related to postoperative pain. It is important to note that this study lacked controls to assess interindividual differences in scale use. Thus, there is a possibility that some individuals would make consistently high ratings or consistently low ratings of any stimulus, and that a nontrivial percentage of the observed relationship between experimental and clinical pain might be attributable to this factor rather than to differences in basal pain sensitivity. However, our own findings examining the neural correlates of interindividual differences in the subjective experience of pain would argue strongly against such an interpretation.[4] Nevertheless, follow-up studies should include magnitude ratings of visual, auditory, or other nonpainful stimuli to explicitly assess this potential confound.

Clinical Implications of Differences in Pain Sensitivity

Differences in pain report to a supra-threshold stimulus are real, are large, reflect differences in brain activation rather than differences in stoicism, and, as noted by Granot *et al.*, correlate with pain after surgery.[1] There remains much left to learn regarding the truth of the above clauses and their implications to clinical research and practice. Why does report to a supra-threshold stimulus, but not the threshold itself, correlate with postoperative pain? Do doses of analgesics or other manipulations that diminish report to supra-threshold stimuli in the normal individual predict doses and efficacy in patients after surgery? Are studies in animals that typically rely on measurement of threshold responses to test analgesics after surgery fundamentally flawed in their ability to predict efficacy in the clinic? These are a few of the obvious questions to be addressed.

More important from a practical standpoint is whether the correlation between report to experimental pain and the subsequent postoperative pain experience equates to an equally impressive correlation with analgesic drug use. Clearly, the many factors that determine individual differences in pain sensitivity may not overlap with those that determine individual differences in sensitivity to the therapeutic and side effects of analgesics. We need several, preferably large, follow-up studies to the current report to determine whether results of preoperative testing can predict analgesic drug consumption postoperatively.

Should there be a strong predictive value in preoperative pain testing and postoperative use of analgesics, several additional questions should be examined. Patient-controlled anesthesia is said to be easily titrated by the patient to effective analgesia, yet small changes in the dose available with each button press results in the inability to achieve analgesia (small incremental dose) or to avoid heavy sedation and respiratory depression.[13] Knowing in advance the rough range of analgesic dose required for treatment of postoperative pain could allow more effective analgesia with patient-controlled anesthesia by personalizing the prescription for dose and perhaps lock out interval. An even bigger improvement in analgesia might be obtained with less frequently titrated methods of providing postoperative analgesia, such as intermittent injections or oral medications.

In summary, Granot *et al.* highlight the real possibility that simple preoperative tests can predict individual differences in pain experience after surgery. The time is ripe for exploiting this observation: we have the tools to quantify individual differences in pain sensitivity with ease, and emerging literature suggests that there are cortical substrates responsible for these differences. Perhaps we are at the beginning of a move toward routine preoperative pain assessment, just as 15 years ago we were at the beginning of a move away from routine preoperative chest radiographs and electrocardiograms.

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