Differential Opioid Tolerance and Opioid-induced Hyperalgesia

A Clinical Reality

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OPIOIDS are highly effective analgesics and as such form the mainstay of pain management after surgery. However, they are associated with a formidable array of side effects, some of them potentially lethal. Also, the opioid signaling system has a remarkable ability—possibly unequalled by any other receptor system in the body—for tolerance development. Although not all patients necessarily develop profound tolerance,1 in many cases doses have to be increased over time to maintain analgesic benefit.

Physicians have not typically been overly concerned about inducing opioid tolerance in the perioperative period. In the first place, it is assumed that the development of tolerance takes time and that the duration of the perioperative period is too short for significant tolerance to develop. In the second place, even if tolerance develops, it can be overcome by administering more opioids, and the drugs are inexpensive. Finally, it is generally assumed that increased tolerance to the analgesic effects of opioids is associated with increased tolerance to side effects as well, and therefore, even if larger doses have to be given, this would not entail any greater risk to the patient.

Unfortunately, these arguments are probably wrong, at least to some degree. The perioperative period may be relatively short, but we now know that opioid tolerance can develop in a shorter time frame, possibly within hours when patients are exposed to high doses (i.e., a phenomenon that classically is referred to as tachyphylaxis). More importantly, many patients are already using opioid drugs for pain control before surgery and, therefore, are tolerant before they even arrive in the operating room. As to the development of tolerance to side effects, we now know that not all opioid targets develop tolerance at the same rate and to the same degree. This differential tolerance can put patients at significant risk.

In addition, recent studies have made it clear that continued exposure to opioids induces more than tolerance. It also induces a degree of hyperalgesia. Whereas, in principle, tolerance can be overcome by increasing opioid dose, hyperalgesia is made worse in the long run by increasing the opioid administration.

In this article, we will describe the clinical concepts of differential opioid tolerance and opioid-induced hyperalgesia (OIH) and discuss the role they may play in our management of patients in the perioperative setting. It should, however, be realized that these issues are relevant not just only to the perioperative period but also to all settings where opioids are administered. We will focus on the clinical setting; a substantial amount of mechanistic information on these processes is available and has been reviewed recently.2,3

Differential Tolerance

The concept of differential tolerance development means that different targets of opioid drugs do not develop tolerance at the same speed and to the same degree. At some level, all anesthesiologists are familiar with this concept. We all know that constipation is a major clinical issue in patients receiving escalating doses of opioids for pain control. Whereas the patients become rapidly tolerant to the analgesic effects of the drugs, tolerance to the gastrointestinal side effects develops slower and to a lesser degree. Although this issue has been insufficiently investigated, particularly in the perioperative setting, it appears that opioid tolerance development is fastest and most profound for the analgesic actions, less for the respiratory depressant effects, and least for the peripheral effects, such as the slowing of gastrointestinal motility.4 The latter has major implications for the postoperative period.
Recovery of bowel function can be delayed by perioperative opioid administration and reducing or eliminating opioids has repeatedly been shown to be associated with faster return of gastrointestinal transit, earlier oral intake, and earlier hospital discharge.3

In the early postoperative setting, differential tolerance development to analgesia and respiratory depression is most relevant. Patients receiving chronic opioids for pain control, especially at high doses, should be assumed to have developed less tolerance to opioid-induced respiratory depression than to analgesia. This means that equianalgesic doses of opioids administered perioperatively will induce more respiratory depression in opioid-tolerant than in opioid-naive patients (note that the dose required to reach this equianalgesic effect will likely be much greater in the opioid-tolerant patient). In other words, contrary to what intuitively would seem to be the case, the opioid-tolerant patient is at an increased risk for respiratory depression when his or her postoperative pain is treated adequately with opioids.

Paronis and Woods6 demonstrated this effect in rhesus monkeys. The animals were studied under four sequential conditions: (1) opioid-free baseline, (2) after being treated with 3.2 mg/kg intramuscular morphine once per day for 4 weeks, (3) after receiving 3.2 mg/kg intramuscular morphine twice per day for 4 weeks (i.e., doubling the dose), and (4) after a drug-free recovery period. The effects of acute administration of morphine on pain (measured by tail withdrawal latency from heated water) and ventilation were determined under each of these conditions (fig. 1). Acute morphine administration predictably induced dose-dependent analgesia. Chronic opioid administration predictably induced dose-dependent tolerance to this effect, and this tolerance was completely reversed after the recovery period (fig. 1A). Acute morphine administration also predictably induced a dose-dependent decrease in minute ventilation. However, no tolerance development to this effect could be demonstrated in the chronically opioid-treated animals. The ventilation curves obtained under the four conditions were virtually identical (fig. 1B). Hence, much more tolerance developed to analgesia than to respiratory depression.

The model used by Paronis and Woods was a chronic opioid administration model, and, if translation to the clinical setting were feasible, would apply primarily to patients receiving chronic opioids, particularly at high doses. However, opioid tolerance develops much faster than is generally realized. Ling et al.7 studied the effects of morphine infusion on analgesia (measured by tail flick latency) and respiratory depression (measured as pCO2) in rats. They found that the infusions initially induced analgesia but that this effect was lost over the course of approximately 8 h. In other words, rats become completely tolerant to the analgesic effects of morphine over a period of time not uncommonly required for a major surgical procedure. In contrast to the effect on pain, there was no tolerance development to the respiratory depressant effects. Even with the greatest dose of morphine (50 μg kg−1 min−1), the initial profound increase in pCO2 was not attenuated over the course of 10 h. Thus, differential tolerance can develop within a matter of hours in animals, and if these data can be translated to humans, patients may potentially be at risk for these issues even when opioid naive preoperatively.

Data confirming these animal results in humans are scarce, but some studies support the differential tolerance development in patients receiving chronic opioids. Stoermer et al.8 studied 25 patients receiving chronic opioid maintenance therapy (16 received heroin and 9 received methadone)
and measured the change in oxygen saturation (SaO₂) after they received their usual maintenance dose. Almost half the patients (11 of 25) had a transient SaO₂ decrease to less than 81%; in all patients, SaO₂ decreased less than 90%. In other words, despite chronic opioid use, the ventilatory response was still highly sensitive to acute opioid administration. Teichtahl et al.9 studied ventilatory responses in patients on stable methadone maintenance therapy. Fifty opioid-dependent patients and 25 matched control subjects were studied; the hypercapnic ventilatory response (HCVR) and hypoxic ventilatory response (HVR) were measured. Patients receiving methadone were normocapnic but showed significantly decreased HCVR and—surprisingly—significantly increased HVR. The decrease in HCVR indicates that these patients exhibited decreased respiratory drive even in the absence of acute opioid administration. In the perioperative setting, this means that a patient receiving chronic methadone who comes to the operating room for a procedure is not, as is commonly thought, tolerant to the respiratory effect of opioids but in fact is at increased risk of respiratory depression when perioperative opioids are administered. The increase in HVR suggests an increased peripheral chemoreceptor response. This could serve as a protective mechanism in the postoperative setting. If sufficient respiratory depression occurred to induce hypoxia, breathing would be stimulated by HVR. Unfortunately, this potential protective effect is negated by the administration of oxygen.

These data show that patients on chronic opioids are highly sensitive to additional opioids and in fact may already exhibit a degree of respiratory depression. Administering opioids perioperatively would therefore be expected to cause further depression. However, these studies are limited in that they did not measure analgesic responses to the opioid. Athanasos et al.10 did measure pain (by cold pressor test and electrical stimulation) and ventilatory responses (by respiratory rate) to a morphine infusion in 18 patients on chronic methadone therapy and in 10 control subjects. In control subjects, morphine-induced analgesia correlated closely with plasma concentration. The response in opioid-tolerant patients was quite different. First, at baseline (i.e., before receiving morphine), they experienced more pain than control subjects did to the same stimulus; this likely reflects OIH. (However, it cannot be ruled out that some of these patients were prone to develop chronic pain and that their increased pain was a reflection of an underlying sensitivity, rather than hyperalgesia.) Second, morphine induced no analgesia in these patients, even at very high plasma concentrations. They did, however, experience a decrease in respiratory rate (although this was only significant for the patients receiving the greatest methadone dose—81 to 115 mg/day).

In other words, the patients were completely tolerant to the analgesic effects of morphine, but only partially tolerant to the respiratory depressant effects of the drug.

Therefore, although more data in humans are required, differential opioid tolerance is appears to be a clinically relevant phenomenon. Patients using chronic opioids are often profoundly tolerant to analgesic actions of the drugs and will require increased doses of opioids to provide adequate postoperative analgesia. However, only limited tolerance to the respiratory side effects of opioids has developed in these patients. They are, therefore, at increased risk for respiratory depression. To prevent adverse outcomes postoperatively, these patients require close monitoring after surgery. Providing supplemental oxygen may prevent hypoxia when ventilation is depressed but also will prevent any protective effect of the HVR, which is increased in patients receiving chronic opioids. Supplemental oxygen will also reduce the usefulness of SaO₂ monitoring.

**Opioid-induced Hyperalgesia**

In addition to the concerns associated with differential tolerance to opioids, clinicians also need to consider the development of OIH in their patients. Although the clinical relevance of this phenomenon during the perioperative period is somewhat controversial, several studies have demonstrated increased opioid requirements and worsened pain scores in patients exposed to high-dose intraoperative opioids.11-15 This suggests that OIH (or acute tolerance) can occur within the perioperative period and it should be considered when opioids are administered during surgery.

The difference between acute opioid tolerance and OIH is conceptually easy to understand, but the two are clinically difficult to separate. OIH is defined as the increased sensitivity to painful stimuli as a result of opioid use. Tolerance is defined as a requirement for increased doses of an opioid to achieve the same analgesic effect. In clinical practice, the development of either of these phenomena will lead to increased pain, with the usual consequence of escalating doses of opioids. Whether the increased opioid requirement is caused by lowering the pain threshold, as in OIH, or by
decreasing the potency of the drug, as in tolerance, the clinical effect is the same. They appear to have a dose–response relation and as such the magnitude of tolerance or OIH in the setting of high-dose opiates is increased.\textsuperscript{16}

**Mechanisms of OIH**

The concept of OIH has been recognized for over 100 yr.\textsuperscript{17} Studies of OIH in humans have been performed in several settings: in volunteers during the short-term opioid infusions, in patients receiving methadone substitution therapy, and in patients with chronic pain and during the perioperative exposure to opioids.\textsuperscript{18} The exact mechanism of this paradoxical response is still unclear but is likely multifactorial. Célèrier \textit{et al.}\textsuperscript{19} describes OIH in terms of the “opponent process theory,” whereby the exogenous central effect of the drug (antinociceptive activity) is counter-balanced by an endogenous response (pronociceptive activity).\textsuperscript{20} The biological mechanisms underlying the pronociceptive activity are presumed to be responsible for OIH. These include activation of adenylate cyclase, N-methyl-D-aspartate (NMDA)-type glutamate receptor activation, and release of pronociceptive peptides such as dynorphin A and neuropeptide FF. According to this theory, the pronociceptive response is delayed or masked by analgesia after administration of an opioid but increases when repeated doses are administered. Hence, one initially expects to see analgesia after administration of an opioid but increases when repeated doses are administered. Thus, if a patient receives repeated high doses or a high-dose continuous infusion of an opioid while under general anesthesia, it is possible that they will have already started to develop an increased “pronociceptive” response by the time they emerge from anesthesia.

Célèrier \textit{et al.}\textsuperscript{21} demonstrated OIH elegantly in a rat model. Six groups of rats were randomized to receive either subcutaneous saline injections or various doses of fentanyl. Their pain threshold was determined at baseline using a paw-pressure vocalization test. They then received saline or fentanyl injections subcutaneously every 15 min for a total of four injections, and the pain threshold tests were repeated over the next few hours until evidence of analgesia disappeared. The examiners then repeated the tests daily for the next 5 days. All rats that received fentanyl developed OIH (meaning that on posttrial day 1, all rats had a decreased pain threshold from baseline.) OIH persisted much longer than the duration of analgesia, with the rats that received the highest dose of fentanyl demonstrating OIH for 5 days. No change in pain tolerance was observed in rats that received saline. This study not only demonstrates robust OIH development after opioid administration but also shows that it can develop within a very short time, comparable to the length of the perioperative period. It is worth noting, however, that the lowest dose of fentanyl was 80 μg/kg, which is higher than the doses commonly used in humans. It is hard to extrapolate these data for human clinical use, but it serves as an illustration of the concept of OIH.

**Evidence of Perioperative OIH in Humans**

Similar findings, however, have been confirmed in humans. As mentioned, separating tolerance and hyperalgesia is difficult in the clinical setting. In addition, the type of pain that is aggravated (wound hyperalgesia vs. spontaneous pain) from opioid use might be different and might have an effect on long-term pain.\textsuperscript{16} As discussed by Angst in his review, spontaneous pain and wound hyperalgesia are not necessarily linked. It has been demonstrated that wound hyperalgesia (the size of the area of hypersensitivity surrounding a wound) specifically has an effect on long-term pain. Salengros \textit{et al.}\textsuperscript{22} randomized patients undergoing thoracotomy to either high-dose remifentanil with an epidural used only at the end of the case or low-dose remifentanil with an epidural used throughout the case. After measuring the area of wound hyperalgesia, he showed that its size was increased by higher doses of IV opioids, and the extent of wound hyperalgesia corresponded to an increased risk of chronic pain at 3, 6, and 9 months.\textsuperscript{22} These findings suggest that interventions addressing wound hyperalgesia, and not just spontaneous pain, could have an impact on long-term outcomes.

Guignard \textit{et al.}\textsuperscript{11} also demonstrated a decreased pain tolerance (either acute tolerance or OIH) in his study of 50 patients undergoing colorectal surgery. Patients were randomized to receive either a high-dose or low-dose remifentanil infusion throughout the procedure; the remainder of the anesthetic was standardized. On average, the patients receiving high-dose remifentanil (receiving on average 0.3 ± 0.2 μg kg\textsuperscript{-1} min\textsuperscript{-1}) consumed almost twice as much morphine over the next 24 h when compared with patients receiving the lower dose, indicating that the higher-dose remifentanil had induced either tachyphylaxis or hyperalgesia. This same phenomenon has been shown with remifentanil in children\textsuperscript{12} and with fentanyl in adults.\textsuperscript{13,14}

Several studies were unable to demonstrate evidence of OIH after intraoperative opioid administration.\textsuperscript{16} There are some important differences between the negative studies and the positive ones. For example, in women undergoing gynecologic surgery, no difference was found in pain scores between groups receiving sevoflurane anesthesia \textit{versus} sevoflurane and a remifentanil infusion.\textsuperscript{23} However, both groups were maintained on 50% nitrous oxide, which is an NMDA antagonist and has been shown to inhibit OIH.\textsuperscript{24} Therefore, it is difficult to interpret the lack of opioid effect in this study because it actively used an OIH prevention strategy. In addition, the average dose of remifentanil was moderate and, therefore, would likely show a lower demonstrable effect of OIH. A recent meta-analysis of postoperative OIH by Fletcher and Martinez\textsuperscript{25} took these negative studies into account and still demonstrated that high-dose (approximately 0.3 μg kg\textsuperscript{-1} min\textsuperscript{-1}) intraoperative remifentanil increased pain at 24 h and increased postoperative morphine consumption. This meta-analysis included 21 randomized, controlled trials of intraoperative remifentanil, most of which were published after 2008. Angst\textsuperscript{16} has
suggested, upon review of the many trials looking for OIH with remifentanil use, that a threshold cumulative dose of 40 μg/kg is needed to produce increased wound hyperalgesia. The meta-analysis also included two studies of fentanyl and one of sufentanil. These opioids did not seem to induce OIH, but obviously the data set is limited. It is reasonable to expect that all opioids would function in the same manner, activating pronociceptive systems, although in recombinant models remifentanil has been suggested to have additional actions, such as direct activation of NMDA receptors.26 It is more likely, however, that it is logistically easier to administer large doses of remifentanil intraoperatively because the context-sensitive half time is so short compared with fentanyl or remifentanil; equivalent doses of fentanyl would likely delay time to extubation. There are also some limited data to suggest that intrathecal opioids can cause OIH27 although much more study is needed to investigate that route of administration.

One study not included in the meta-analysis evaluated the use of remifentanil versus esmolol versus fentanyl during the laparoscopic cholecystectomy.13 Ninety patients were randomized into three groups: (1) remifentanil infusion 0.1 to 0.5 μg kg⁻¹ min⁻¹, (2) fentanyl boluses of 50 μg every 30 min, or (3) esmolol 5 to 15 μg kg⁻¹ min⁻¹. The remifentanil and fentanyl groups showed increased requirement for opioid in the postanesthesia care unit compared with the esmolol group. Postoperative fentanyl requirements were 91.5 ± 42.7 μg (esmolol), 237.8 ± 54.7 μg (remifentanil), and 168.1 ± 96.8 μg (fentanyl) (fig. 2). Patients receiving esmolol also were discharged from postanesthesia care unit earlier than patients receiving opioids. On average, the fentanyl group in this study received 200 μg of the drug intraoperatively, which is well within the standard dose range. Although other explanations are possible (e.g., an antihyperalgesic effect of esmolol), this study does suggest that commonly used doses of intraperative fentanyl might induce a hyperalgesic or acute tolerant state.

The best way to address OIH or acute tolerance will likely be prevention. For this reason, it is prudent to consider alternative opioid-sparing adjuncts when possible, in an effort to reduce the opioid use for patients under general anesthesia. Peripheral nerve blocks and neuraxial anesthesia can reduce the need for opioids and have an opioid-sparing effect. In addition, although usually expensive, drugs such as esmolol28 and dexametomidine29 can approximate the effect of opioids on heart rate, blood pressure control, and volatile anesthetic requirement. However, many patients will still require opioids perioperatively, and occasionally, chronically. Most OIH prevention strategies have focused on the glutaminergic system and NMDA receptor activation, both of which are implicated in the development of central sensitization and OIH. Ketamine, methadone, and nitrous oxide have all been shown to attenuate OIH, whereas drugs such as gabapentinoids and α₂ receptor agonists such as clonidine have been shown to attenuate wound hyperalgesia, although there is not enough evidence to suggest through which mechanism.16

Conclusions

The data available on differential opioid tolerance and OIH, although not absolutely conclusive for the perioperative setting, suggest that it would be prudent to craft an anesthetic that incorporates nonopioid adjuncts and not solely depend on intraoperative opioids for the provision of postoperative pain relief. Patients using very high doses of opioid analgesics preoperatively may not be protected from adverse events by tolerance development, and this group may be at particular risk. Perioperative opioid administration may render subsequent opioid analgesic administration less effective and might lead to OIH or acute tolerance. Still, many patients will undergo surgery of such magnitude that opioids will be required for postoperative pain control. A multimodal approach with a variety of other modalities, including NMDA receptor blockers and regional nerve blockade, can limit the opioid requirements. Overall, reducing the doses of intraoperative opioids should reduce the risk of developing OIH and aggravated wound pain and hopefully improve patient safety.

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Competing Interests

The authors declare no competing interests.

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