Management of Perioperative Pain in Patients Chronically Consuming Opioids

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Background: The prevalence of licit and illicit opioid use is growing, and a greater percentage of chronically opioid-consuming patients are presenting for surgery. These patients can be expected to experience increased postoperative pain, greater postoperative opioid consumption, and prolonged use of healthcare resources for managing their pain.

Methods: Achieving adequate pain control in these patients can be challenging because commonly used strategies for alleviating postoperative pain may have diminished effectiveness. We explore the prevalence and characteristics of opioid use in the United States and discuss its impact on the perioperative management of pain. We examine mechanistically why adequate perioperative pain control in chronically opioid-consuming patients may be difficult.

Conclusions: We present strategies for providing adequate analgesia to these patients that include the optimal use of opioids, adjuvant medications, and regional anesthetic techniques. *Reg Anesth Pain Med 2004;29:576-591.*

Key Words: Pain, Opioids, Tolerance, Hyperalgesia, Addiction, Epidural.

Opioids are the mainstay therapy for alleviating moderate to severe pain. An increasing awareness among patients, healthcare organizations, patient-advocate organizations, and regulatory agencies for adequate pain control has promoted the use of these drugs. Although the treatment of acute pain and cancer pain with opioids is not in dispute, administrating opioids for alleviating chronic nonmalignant pain remains controversial. Most of the controversy surrounds uncertainties as to the long-term analgesic effectiveness of opioids, the ability of physicians to choose appropriate patient candidates, the risk of side effects, and the potential for abuse. Nevertheless, many treatment guidelines for chronic nonmalignant pain list opioids as an option, especially if more traditional treatment modalities have failed.[1-4]

Preoperative Opioid Therapy and Postoperative Pain

Prevalence and Characteristics of Opioid Use for Pain

Opioids are second only to nonsteroidal anti-inflammatory drugs (NSAIDs) in terms of prescription frequency for chronic pain; one study reports that 44% of patients prescribed any analgesic were prescribed an opioid.[5] Despite the commercial success of longer acting opioids such as OxyContin (Purdue Pharma, Stamford, CT) (oxycodone) and guidelines that recommend the use of long-acting opioids on a time-contingent basis, short-acting opioids such as codeine, hydrocodone, and oxycodone are more commonly used for alleviating chronic pain.[5-7] The average daily opioid dose in studies that focus on patients treated in primary care settings was found to be relatively low and corresponded to about 45 mg of oral morphine per day, although a large dose range also was observed in these studies.[5,6] Although the prevalence of chronically opioid-consuming patients who present for surgery is not known, the growing enthusiasm for the use of opioids is likely to increase the number of such patients.

Significance of Postoperative Pain

Despite the long-standing recognition of postoperative pain as both prevalent and undertreated, 20% to 30% of patients continue to experience moderate to severe pain after surgery.[8,9] High levels of postoperative pain are associated with an increased risk of pulmonary and cardiovascular complications, are the most common reason for delayed discharge or for unexpected hospital admission after ambulatory surgery, and are responsible for prolonged convalescence after in-patient surgery.[10-19] High levels of postoperative pain have also been associated with an increased risk of chronic pain as

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a consequence of surgery.[10,16,18-20] Therefore, the aggressive treatment of postoperative pain may be particularly important in chronic-pain patients because they may represent a population that is particularly vulnerable to complications or are at risk for chronic postsurgical pain.

Impact of Chronic Opioid Therapy on Postoperative Pain

Several patient variables predict poorer pain control and increased analgesic requirements in the postoperative period. These variables include demographic factors such as gender and age; psychologic conditions such as depression, anxiety, and neuroticism; preexisting pain conditions; and the preoperative use of opioids.[7,21-27] Some of the psychologic factors, such as depression, are independently associated with an increased likelihood of opioid consumption and aggravated perioperative pain.[6]

Although the existing literature is remarkably sparse, at least 2 studies have examined the association between preoperative opioid use and postoperative pain. de Leon-Casasola et al.[28] studied 116 patients with cancer and reported that subjects who chronically consumed opioids (daily oral morphine dose 90 to 360 mg) required more than 3 times as much morphine given via a continuous epidural infusion and more than 4 times as much morphine given as an intermittent intravenous bolus for breakthrough pain after surgery compared with opioid-naive patients. The severity of postoperative pain in chronically opioid-consuming patients prolonged the need for epidural analgesia by a factor of 3 (9 days versus 3 days). Rapp et al.[7] performed a case-controlled retrospective analysis of 360 patients who experienced malignant or nonmalignant pain also reporting a 3-fold greater postoperative opioid requirement in chronically opioid-consuming patients. The average daily opioid dose before surgery corresponded to 13 mg of intravenous morphine. Chronically opioid-consuming patients experience increased postoperative pain despite the 3-fold greater postoperative opioid consumption. Although available data are quite limited, the management of postoperative pain seems to be more difficult in chronically opioid-consuming patients even when they consume only a modest daily opioid dose.

Opioid Abuse and Postoperative Pain

Prevalence and Characteristics of Opioid Abuse and Addiction

According to the 2002 National Survey on Drug Use and Health, approximately 166,000 people in the United States are active heroin abusers and about 4.4 million people (1.8% of the population) actively abuse opioid analgesics. Abuse of heroin and pain medications is trending upward. For example, approximately 7% of the 18-year-old to 22-year-old group had ever abused pain prescription drugs in 1992, whereas approximately 22% reported having done so in 2002. People who sought treatment for abuse of pain prescription drugs outnumbered those who had sought treatment for heroin abuse in that survey. Because patients undergoing surgery may not admit that they are actively abusing pain medications, difficulties in achieving adequate postoperative pain control may provide a hint to such abuse.

Significance of Postoperative Pain in Opioid Abuse and Addiction

Many of the comments made with respect to chronically opioid-consuming patients also apply to patients who abuse or are addicted to opioids. However, at least 3 important differences exist. First, the daily dose of opioids consumed by opioid-abusing patients before surgery is typically larger and can correspond to many times the daily oral morphine equivalent of 40 to 50 mg used on average by chronically opioid-consuming patients for pain control. Second, opioid-abusing or opioid-addicted patients often suffer from coexisting psychiatric diseases. For example, heroin addicts have an elevated prevalence of depression, anxiety, psychosis, and personality disorders.[29,30] As previously noted, depression and anxiety are independent predictors of aggravated pain after surgery and may complicate the management of postoperative pain. Third, the attitude of healthcare providers toward the use of opioids for controlling pain may be influenced by the abuse history.[31-33] The history of illicit opioid consumption may lead to a tempered use of opioids, which makes these patients particularly vulnerable to inadequate postoperative pain control.

Causes for Increased Postoperative Pain and Opioid Consumption in Patients Chronically Using Opioids

Chronic exposure to opioids may result in a need to increase the dose over time to maintain the desired analgesic effect. The need for escalating the dose is often attributed to the development of tolerance. However, dose escalation can be the result of other factors, such as the progression of the underlying disease that causes the chronic pain. Tolerance is reflected by a right-shift of the opioid dose-versus-response relationship (Fig 1).

More recent evidence points to an alternative

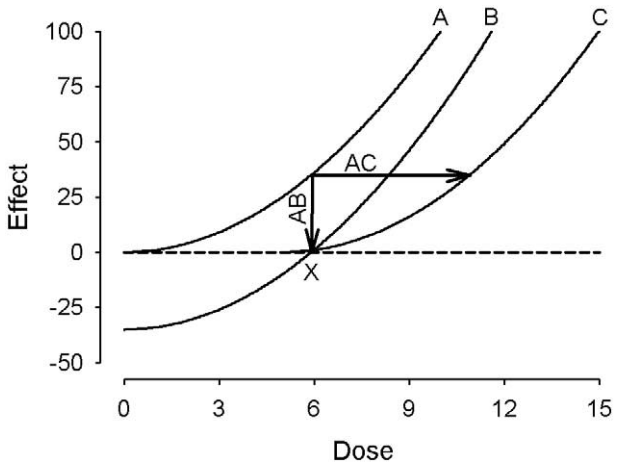

Fig 1. Possible alterations in the opioid dose versus-analgesic effect relationship with chronic opioid administration are depicted. Curve A represents the relationship in opioid naive patients, curve B represents the relationship in patients developing opioid-induced hyperalgesia, and curve C represents the relationship in patients becoming tolerant to opioid analgesia. Arrows AB and AC indicate the shift of the opioid dose-versus-analgesic effect relationship with the occurrence of opioid-induced hyperalgesia and tolerance.

neuropharmacological phenomenon that may explain the need to escalate the opioid dose over time, namely, opioid-induced hyperalgesia (OIH). Somewhat paradoxically, administration of opioids may induce an increased sensitivity to pain (hyperalgesia). OIH can be viewed as a state of facilitated nociceptive signaling. The net result of such facilitation is the downward shift of the opioid dose-versus-response relationship (Fig 1). Further complicating matters, the phenomena of tolerance and hyperalgesia can coexist, at least theoretically. Prospective studies in humans are needed to clarify whether both phenomena develop simultaneously and to determine how they are interrelated.

Opioid Tolerance

In laboratory animals, the development of tolerance is a robust phenomenon that can occur even after a single opioid dose. Many behavioral studies in rodents have characterized the onset, time course, and magnitude of tolerance, and numerous reports have presented potential molecular and cellular mechanisms underlying its development, such as alterations in gene expression, synaptic function, receptor coupling, and activity of neuronal circuits.[34-37] However, prospective and controlled clinical studies that document onset, time course, and extent of opioid tolerance in humans are lacking.

Some human studies that use experimental pain models provide relatively direct evidence for the development of opioid tolerance. Doverty et al.[38] reported that the analgesic effect of an intravenous bolus injection of morphine was significantly reduced in former opioid addicts chronically maintained on methadone when compared with control subjects. Vinik et al.[39] documented analgesic tolerance in human volunteers exposed to a 4-hour remifentanil infusion. However, this study was neither placebo controlled nor double blinded, and other similar studies did not duplicate these findings.[40,41] Whether the divergent results are caused by the use of different experimental pain modalities or are a consequence of study design and data analysis is unclear.

Indirect evidence suggestive of the development of opioid tolerance is provided by studies that report patients who receive a high rather than a low intraoperative systemic opioid dose experienced greater postoperative pain, despite an increased postoperative opioid consumption.[42,43] Cooper et al.[44] replicated these finding in patients who received opioids by the intrathecal rather than by the intravenous route. However, at least 1 study did not detect different postoperative pain scores and cumulative opioid doses among patients who received either a high or a low intraoperative opioid dose.[45] This finding may result from the smaller total intraoperative opioid dose administered to these patients compared with patients enrolled in studies that report positive findings.

Finally, studies that examined the use of oral, transdermal, and intrathecal opioids reported the need for escalating opioid doses during an initial titration period that lasted from weeks to months.[46-49] After this period, the rate the daily opioid dose increased slowed substantially. The initial dose escalation may represent simple titration to effective dose, acute tolerance, or a combination of both. The eventual slowing of dose escalation has sometimes been interpreted to represent the absence of ongoing development of tolerance, although analgesic tolerance was not being directly measured in any available study. Dose escalation over time can be hindered for other reasons, such as financial concerns, intolerable side effects, perceived lack of progress in pain therapy, and concerns on the part of the patient or provider that ever-increasing doses are indicative of drug-seeking behavior and addiction. The need for treatment probably lasts for years in most chronic-pain patients, which makes the months-long period of follow-up in the available studies of limited utility in understanding issues such as tolerance.

In summary, surprisingly little data carefully document opioid tolerance in humans. Clinical obser-

Table 1. Possible Mechanisms Supporting Opioid-Induced Hyperalgesia

Mechanism	Reference
Increased DRG neurotransmitter content	144
Increased primary afferent neurotransmitter release	145
Increased spinal sensitivity to nociceptive neurotransmitters	146
Increased spinal dynorphin activity	147
Enhanced descending facilitation from the rostral ventromedial medulla	50
Activation of NMDA receptors	52,53,148–151
Enhanced monoxide signaling (NO/CO)	52
Activation of protein kinase C	53,152,153
Cytokine activation	154

vations suggest that the controversy regarding opioid tolerance is more about the rate and the extent to which tolerance develops rather than whether it develops at all. Large interindividual differences seem likely. However, the lack of well-controlled prospective studies that examine the development of opioid tolerance in patients by directly determining opioid potency rather than dose escalation likely explains the ongoing debate concerning the significance of opioid tolerance in clinical practice.

OIH

Several animal studies suggest that acute and chronic exposure to opioids can result in increased pain sensitivity (i.e., OIH). In most available animal studies, OIH was generally observed to be maximal during periods of opioid abstinence or in periods between regularly administered opioid doses, although some degree of OIH was observed in a few studies, even during continuous administration.[50-53] Behavioral evidence of opioid withdrawal generally was not observed, even during periods when OIH was robustly demonstrable. These findings were interpreted to imply that the chronic administration of opioids leads to compensatory neurobiological changes that facilitate nociception and, thus, lead to the hyperalgesia that is especially evident between opioid doses. Table 1 summarizes some of the mechanisms proposed to explain the phenomenon of OIH.

In human volunteers, 3 recent studies provided direct evidence for the development of opioid-induced hyperalgesia.[54-56] All studies documented that a skin area already sensitized to pain before an intravenous opioid infusion became significantly larger after stopping the infusion. Responses to mechanical stimuli were more likely to be associated with increased sensitivity after opioid infusion than responses to heat.

Indirect evidence suggestive of the development of opioid-induced hyperalgesia in humans results from 2 different kinds of studies conducted in patients. First, several investigators reported that former opioid addicts maintained on methadone had a lower pain threshold than did former addicts not maintained on opioids and healthy control subjects.[38,57,58] Second, as mentioned previously, several studies documented increased postoperative pain and opioid consumption in patients who received a high rather than a low intraoperative opioid dose. The development of opioid-induced hyperalgesia seems to be as plausible an explanation for this observation as is the development of opioid tolerance.

Optimizing Perioperative Opioid Use in Chronically Opioid-Consuming Patients

The process of optimizing perioperative pain management for chronically opioid-consuming patients is complex. An outline of the steps involved is provided in Table 2.

Preoperative Considerations

Perioperative opioid pain management in chronically opioid-consuming patients needs careful consideration for several reasons. (1) Opioids remain an important component of postoperative pain therapy, even in the case of substantial chronic use. (2) An adequate opioid dose needs to be maintained to prevent opioid withdrawal. (3) The transition back from postoperative to preoperative opioid requirements can be a challenging process. Unfortunately, no data are available that allow predicting individual postoperative opioid requirements on the basis of the opioid dose consumed before surgery.

Identifying chronically opioid-consuming patients is the responsibility of the surgical team, the preoperative clinic staff, and the anesthesia team assigned to the case. Because the minimum daily opioid dose that significantly increases postoperative opioid requirements and pain is not known, all patients should be informed about the potential for aggravated pain and increased opioid requirements during the postoperative period. Patients should be informed about alternative analgesic techniques that complement opioids. The patient and healthcare providers should formulate, at least in general terms, a perioperative pain management plan before surgery. Unfortunately, patients may omit their daily oral opioid dose either because they are told to avoid taking all medications on the day of surgery or because they mistakenly believe they should not take their medication if oral intake of

Table 2. Considerations for Pain Management in Chronically Opioid-Consuming Patients

Time Interval	Considerations
Preoperative	Discussion of the following: Precise opioid use (dose, opioid type, etc.) Potential for increased postoperative pain Patient's fears and expectations related to pain management Effective management strategies after previous procedures Postoperative management options/appropriate regional techniques for complementing opioid analgesia Postoperative pain management plan Initiation of appropriate preoperative medications: Continuation of preoperative opioid regimen on day of surgery (prevent withdrawal, falling behind on opioid requirement) Consideration of acetaminophen 1,000 mg 1 to 2 hours before surgery Consideration of a COX-2 inhibitor such as celecoxib, rofecoxib, or valdecoxib 1 to 2 hours before surgery
Intraoperative	Administration of opioids to meet the following requirements: Chronic Intraoperative surgical Anticipated postoperative Titration of long-acting opiate to respiratory rate 14 to 16 if possible in spontaneously ventilating patient Administration of adjuvant medications: Ketamine 0.5 mg/kg IV bolus followed by 4 μg/kg/min infusion Ketorolac 30 mg IV (if NSAID or COX-2 not started preoperatively) Acetaminophen 1,000 mg PR if not started preoperatively Institution of appropriate regional technique: Continuous techniques preferable Wound lavage or local infiltration with local anesthetic if other technique not possible
Postoperative (acute phase)	Titration of opioids, adjuvant medications, and regional techniques to patient comfort: Expect postoperative opiate requirements to be up to 2 to 4 times the dose required in an opioid naive person. Remember that no individual's requirements can be predicted with confidence. Titrate opioids aggressively to achieve adequate pain control in the postoperative care unit. Start opioid PCA: If oral route is available, start with 1.5 times the preoperative oral opioid dose and PCA for breakthrough pain. If oral route is unavailable, consider basal rate for PCA. In patients undergoing a regional technique, plan to administer at least half of the preoperative opiate requirement systemically. Continue applicable regional techniques. Consider use of high-potency opioids such as fentanyl/sufentanil in place of morphine for epidural management. Continue acetaminophen 1,000 mg every 6 hours, and/or continue acetaminophen, NSAID, or COX-2 inhibitor for several days with attention to renal function and risk of bleeding. Continue ketamine if started in OR, or institute ketamine infusion if pain proves refractory to other measures. Monitoring for oversedation and opioid withdrawal: Chronically opioid-consuming patients are at higher risk for respiratory depression than are opioid naive patients and must be monitored appropriately with regular evaluation of sedation and oxygen saturation.
Postoperative (transition phase)	Transition from regional and parenteral techniques to oral opioids/adjuvants: Use the opioid requirements during the first 24 to 48 hours to determine daily oral opioid dose. Deliver half of estimated oral requirement as a long-acting formulation. Allow PRN use of short-acting opioid every 3 hours in sufficient quantity to provide the remaining required opioid dose. Consider continuing acetaminophen, NSAID, or COX-2 inhibitor during transition phase. Plan taper from postoperative opioid doses toward preoperative doses and discuss with patient or care provider. Determine need for specialty follow-up if regimen is particularly complex.

Abbreviations: IV, intravenous; OR, operating room; PR, per rectum; PRN, as circumstances require.

food and liquids is discouraged. However, chronically opioid-consuming patients should receive their regular opioid dose on the day of surgery, especially if large doses of long-acting opioids are involved, to avoid withdrawal and the need to catch up with the patient's opioid requirement.

Intraoperative and Immediate Postoperative Considerations

During surgery, the required opioid dose is composed of the daily opioid dose taken chronically before surgery and the opioid dose made necessary by surgical stimulation. Long-acting opioids seem best suited for substituting the opioid dose taken chronically because relatively stable opioid plasma concentrations are provided. Often, the use of a continuous infusion of opioid is the best way to provide a steady serum concentration if the oral route is unavailable perioperatively. Although the use of short-acting opioids can be adequate for alleviating short-lasting stimulation caused by the surgical intervention, their sole use in opioid-dependent patients may result in very poorly controlled pain or even opioid withdrawal after surgery. Catching up on the opioid dose in the postoperative period can be problematic because of inevitable delays in obtaining and administering opioids at the bedside, the very high levels of pain that patients may experience, and a possible reluctance of recovery room staff to administer a sufficiently large opioid dose expediently. Although no predictions of opioid requirements can be made for individual patients, one should keep in mind that patients who use even modest opioid doses (<50 mg/day oral morphine equivalent) before surgery will often require their baseline opioid dose plus 2 or more times the amount of opioids typically used for adequate pain control in opioid-naive patients.[7,59]

Regional anesthesia has many benefits and may be particularly useful in chronically opioid-consuming patients, as presented below. However, opioid-dependent patients need their daily systemic opioid dose for the purpose of preventing withdrawal and because their chronic pain may not be affected by the surgical procedure. For example, a patient taking opioids for chronic low-back pain who has a total-knee arthroplasty will require analgesia for both areas postoperatively. Several reports documented opioid withdrawal in the postoperative period when epidural or intrathecal opioids were used solely for perioperative pain control in opioid-dependent patients.[60-62] However, the combined use of epidural opioids and opioids delivered intravenously for breakthrough pain was sufficient for preventing withdrawal in several studies.[28,63,64] In our experience, daily systemic administration of at least half of the preoperative opioid dose is sufficient to prevent withdrawal when regional anesthetic techniques are used.

Administering partial opioid agonists such as buprenorphine or nalbuphine to chronically opioid-consuming patients may induce abrupt opioid withdrawal.[65] Although small doses of partial opioid agonists are useful in opioid-naive patients for alleviating side effects such as pruritus or nausea caused by full agonists, their use in opioid-dependent patients is challenging and requires close monitoring.

Postoperative Transition to an Oral Opioid Regimen

After surgery, the transition from an intravenous or epidural to an oral opioid regimen needs special attention in chronically opioid-consuming patients. These patients require opioids for a prolonged period of time via the intravenous or epidural route when compared with opioid-naive patients.[7,59] However, no broadly accepted guidelines indicate how to switch these patients back to an oral opioid regimen. One approach that has worked well in our institution is to convert the daily postoperative intravenous opioid dose into an oral-dose equivalent and to administer one-half to two-thirds of this dose in the form of a long-acting opioid while allowing the remainder of the requirement to be used as a short-acting opioid as needed. The long-acting opioid provides a steady baseline control of pain, and the short-acting opioid provides control of breakthrough pain. As the surgical pain subsides, cutting back on the breakthrough medication is a simple way by which patients can reduce the total daily opioid dose as needed.

During the early phases of the transition to oral opioids, time will be required for the serum levels of the long-acting opioids to approximate steady state. Therefore, the transition to oral medication should not be unduly delayed, and monitoring of sedation should be maintained during this transition period. Particular caution should be used in titrating very long half-life drugs such as methadone in the postoperative period. The relatively slow accumulation of drug in the setting of resolving pain could lead to overdose. Table 3 provides conversion guidelines for some of the more commonly used opioid analgesics. A recent report describes the conversion process in some detail.[66]

If the oral route is available throughout the postoperative period, providing 1.5 times the preoperative opioid dose by this route and offering intra-

Table 3. Conversion Table for Commonly Used Opioids*

Medication	Intravenous Dose (mg)	Oral Dose (mg)
Morphine	10	30
Codeine	120	200
Fentanyl	0.10	25 μg/h for each 45-mg oral morphine
Hydrocodone	NA	20
Hydromorphone	1.5	7.5
Methadone†	2 (caution)	2–3 (caution)
Meperidine	100	300
Oxycodone	NA	20

Abbreviation: NA, not available.

*Conversion tables are guidelines for approximating dosage equivalence. Substantial interpatient responses should be expected.

†Conversion to methadone is complicated by complex pharmacodynamic and pharmacokinetic issues. As total opioid doses increase, the oral morphine:methadone ratio increases as well and may exceed 10:1.

venous opioids via patient-controlled analgesia (PCA) for breakthrough pain until surgical pain starts resolving has worked well for the majority of our patients. An alternative approach may be offered by the sole use of intravenous opioids via PCA during the first 24 to 48 hours after surgery, the period during which opioid requirements are changing most rapidly. After that period, the total dose delivered intravenously can be converted into a daily oral opioid dose sufficient for alleviating pain as described above.

Use of Adjuvant Systemic Analgesics for Postoperative Pain Control

Many factors make adequate postoperative pain control in chronically opioid-consuming patients more challenging. In these patients, adjuvant analgesic techniques have a particularly useful role. Although many systemic adjuvant agents have been investigated, ketamine and NSAIDs have received the most attention.

Ketamine

Ketamine has many pharmacologic effects, but it is the *N*-methyl-d-aspartate (NMDA) receptor–blocking property that seems to be the best understood, which supports its use as an adjuvant analgesic. The NMDA receptor plays key roles in nociceptive signal transmission as well as in the development of opioid tolerance. Several NMDA receptor antagonists, such as ketamine, dextromethorphan, and amantidine, have been used in the perioperative period. For the purposes of this review, however, we will focus on the intravenous use of ketamine during and after surgery to control pain in chronically opioid-consuming patients because the largest body of data exists for this drug.

Ketamine has been administered as a single low-dose bolus (0.15 to 0.5 mg/kg) or as a low-dose bolus followed by a low-dose infusion (2 to 4 μg/kg/min) in opioid-naive patients undergoing abdominal,[67] inguinal hernia,[14] rectal,[68,69] laparoscopic,[69] and orthopedic[70,71] surgeries. Most of these studies showed reduced postoperative opioid requirements and pain. These effects were most prominent within the first 24 hours after surgery although a study in a small number of patients reported a significant long-term benefit; that is, a reduced incidence of persistent postsurgical pain.[68] Extrapolating from these data, intraoperative administration of ketamine may be a useful adjuvant analgesic technique that simplifies postoperative pain control in chronically opioid-consuming patients. Ketamine may alleviate postoperative pain not only by its direct analgesic effects or by preventing sensitization of nociceptive pathways within the central nervous system but also by reducing or reversing opioid tolerance and opioid-induced hyperalgesia.[72-74]

In the postoperative period, ketamine has been combined with intravenous opioids. Several studies have reported improved postoperative pain control or reduced postoperative opioid requirements when ketamine was used along with opioids.[75-79] However, not all studies demonstrated such a benefit.[71,80,81] Ketamine has been administered as a single bolus (0.25 to 0.5 mg/kg) and as an infusion (1 to 6 μg/kg/min), and it has been directly combined with an opioid for administration via PCA (up to 2 mg per bolus). However, ketamine should not be administered in a fixed-dose ratio with an opioid in chronically opioid-consuming patients because a large or rapidly increasing requirement for opioids may result in an unnecessarily high ketamine dose and cause psychotropic side effects.

The available literature favors the view that ketamine therapy should be initiated intraoperatively as a bolus of 0.25 to 0.5 mg/kg followed by an infusion at a rate of 2 to 4 μg/kg/min that may be continued for a few days in chronically opioid-consuming patients. Whether the combined administration of a benzodiazepine along with ketamine is useful for reducing the incidence of psychotropic side effects in a preemptive manner is unclear. Although precisely which chronically opioid-consuming patients will receive maximum benefit from ketamine is not clear, those who have previously experienced turbulent postoperative pain relief or who are on particularly large doses of opioids may be the best candidates.

NSAIDs and Acetaminophen

NSAIDs and acetaminophen are the most commonly used nonopioid analgesics for the management of pain. Unfortunately, these medications are often omitted from the perioperative analgesic regimen. NSAIDs and acetaminophen have important roles in adequately managing pain in chronically opioid-consuming patients.

The analgesic efficacy of NSAIDs has been documented after various surgeries, and several reviews and meta-analyses support their role in reducing postoperative pain and opioid requirements.[82-88] NSAIDs seem particularly valuable as a component of a multimodal postoperative analgesic regimen in chronically opioid-consuming patients because their mechanism of action is different from that of opioids, and their side-effect profile is favorable, especially for patients without coexisting renal or coagulation disorders. NSAIDs may also provide additional benefits when administered in the perioperative period. A recent study reported that rofecoxib started before and continued for 5 days after joint replacement surgery improved joint function as observed 1 month after surgery.[89]

Specific inhibitors of cyclooxygenase type 2 (COX-2) have enjoyed special attention among NSAIDs for managing perioperative pain because they have a minimal impact on coagulation and provide long-lasting effective plasma concentrations. All 3 oral COX-2 inhibitors presently available in the United States (celecoxib, rofecoxib, and valdecoxib) effectively reduce postoperative pain.[90-95] At least 1 COX-2 inhibitor, parecoxib, is under development for intravenous administration. Parecoxib, administered preoperatively or intraoperatively, reduces postoperative pain and opioid requirements.[96-98] Selective COX-2 inhibitors for intravenous administration will be a welcome addition to the NSAID armamentarium because their administration could be initiated intraoperatively and carried into the postoperative period, perhaps without unduly increasing the risk of gastrointestinal bleeding.[99]

Unfortunately, the use of COX-2 inhibitors is not without hazard in patients undergoing surgery. Patients who are volume depleted or have compromised renal function are at particular risk for acute renal failure when exposed to selective or nonselective COX-2 inhibitors.[100-102] Although specific COX-2 inhibitors produce fewer side effects (bleeding and perforation) than nonselective COX inhibitors, the incidence is not zero.[103-105] Also, nonselective NSAIDs can delay bone healing, although recent evidence suggests that selective COX-2 inhibitors are less likely to interfere with bone growth.[106,107] Finally, some investigators have suggested that selective COX-2 inhibitors may place patients at risk of adverse cardiovascular events.[108,109] Further study will be needed to evaluate the potential for adverse cardiovascular events in patients taking COX-2 inhibitors perioperatively.[108,109]

Acetaminophen does not greatly affect coagulation, renal function, or the gastrointestinal system. In studies, acetaminophen provided perioperative pain control similar if not equal to NSAIDs such as ibuprofen.[86,110,111] Perioperative oral acetaminophen reduces opioid requirements.[112] Although not yet available in the United States, propacetamol, an injectable acetaminophen prodrug, has been shown to reduce postoperative pain in a number of studies.[113-115] Because the mechanisms of action of NSAIDs and acetaminophen are different, both classes of drugs may possibly be administered in the perioperative period.[116] Several studies support the idea that NSAIDs combined with acetaminophen provide postoperative pain control that is superior to either class of drug alone.[86,91,92]

Additional Agents

Although ketamine, NSAIDs, and acetaminophen were discussed in some detail, other agents have been advocated as useful adjunctive analgesic drugs for postoperative pain management. Oral dextromethorphan, an NMDA receptor antagonist, diminished postoperative pain and opioid requirements in several studies when given at doses of 30 to 90 mg before surgery.[117-119] However, not all studies confirmed these findings.[120,121] Gabapentin, an anticonvulsant that provides significant analgesic effects in experimental models of inflammatory pain, reduced postoperative pain in 2 clinical studies when administered preoperatively (1,200 mg) or postoperatively (1,200 mg/day).[122,123]

Dexmedetomidine, an α_2-adrenergic receptor agonist, may reduce postoperative opioid requirements and pain.[124,125] Although unexplored, dexmedetomidine and other α_2-adrenergic receptor agonists such as clonidine may have special value in the treatment of chronically opioid-consuming patients because they alleviate opioid withdrawal symptoms as well as pain.[126]

Not all agents that possess analgesic properties in special situations work well in the postoperative setting. For example, tricyclic antidepressants, long considered the mainstay in the treatment of neuropathic pain, have small or no effects on postoperative pain.[127,128] Although other agents have been explored, and some promising results have been reported, almost all of these agents are at best adjunctive analgesics perioperatively.

Use of Regional Anesthetic Techniques

Regional anesthesia is a particularly attractive choice in chronically opioid-consuming patients because near-complete analgesia can be provided to patients prone to intensified postoperative pain experiences, and certain difficulties inherent to the reduced effectiveness of opioids can be circumvented. Although local anesthetics are the primary class of drugs used for regional anesthesia, opioids are often administered via these techniques and usually cause few systemic side effects.

Unfortunately, a paucity of literature examines regional anesthesia in chronically opioid-consuming patients, with a few notable exceptions. The efficacy of regional anesthesia techniques in chronically opioid-consuming patients might be inferred, however, from studies documenting opioid-sparing effects in opioid-naive patients.[7,28,63]

Infiltration and Wound Lavage

Direct administration of local anesthetics into the surgical wound can reduce postoperative opioid requirements and should be considered whenever other regional techniques are not applicable. Patients undergoing laparoscopic gynecological surgery who received local anesthetics into their intraperitoneal wound by injection and lavage techniques used 4 to 17 times less opioids during the first 24 postoperative hours compared with patients who received saline placebo.[129] Ng et al.[130] confirmed these finding in patients undergoing total abdominal hysterectomy. Gottschalk et al.[131] used temporarily implanted catheters that delivered local anesthetics continuously into the wound in patients undergoing shoulder surgery and reported significant and protracted opioid-sparing effects. The technique used by Gottschalk et al.[131] has recently been reviewed[132] and offers the option of continuing anesthetic administration for days after the surgical procedure. However, a study in patients undergoing microdiscectomy did not detect an opioid-sparing effect when local anesthetics were injected locally.[133] Generally, the success of techniques for administering local anesthetics directly to the surgical wound seems to depend on (1) the type of surgery; (2) the type, amount, and concentration of local anesthetic; and (3) the particular technique used for administering the drug.

Peripheral Nerve Blockade on the Upper Extremity

Opioid-sparing effects have been demonstrated for regional techniques such as the axillary, supraclavicular, and interscalene block. Although most anesthesiologists are familiar with single-bolus techniques for injecting local anesthetics via an inserted needle, the placement of catheters for the prolonged administration of local anesthetics has become more popular. Studies in patients undergoing upper-extremity surgery showed that a continuous axillary or interscalene block provided superior pain control, decreased opioid consumption, and greater patient satisfaction in the postoperative period when compared with patients who received systemic opioids intramuscularly or intravenously via PCA.[134-136]

Although regional techniques that use catheter insertion can provide several days of postoperative pain control, a single-bolus injection may still be useful if the placement of a catheter is not feasible. A number of studies demonstrated opioid-sparing effects of such single-injection techniques for the immediate postoperative period.[135-138] The duration of such benefits is poorly defined but is probably most prominent during the first 24 hours after surgery.

Peripheral Nerve Blockade on the Lower Extremity

Opioid-sparing effects have been shown for a variety of lower-extremity regional techniques that include paravertebral, lumbar plexus, femoral, and sciatic nerve blocks. Techniques that use continuous catheters are particularly appealing for providing continuous postoperative pain control and have been most widely reported for the 3-in-1 and the femoral nerve blocks. For example, a study conducted in 1,338 patients undergoing total-hip arthroplasty reported comparable pain control in patients treated with a continuous 3-in-1 block, opioids via intravenous PCA, and local anesthetics plus opioids via patient-controlled epidural analgesia. Both regional techniques had similar opioid-sparing effects. However, patients treated with a 3-in-1 block had the highest satisfaction scores.[139] The opioid-sparing effects of the 3-in-1 technique were shown for patients having total knee replacement.[80,140] Significant opioid-sparing effects and superior pain control have been shown in patients treated with a continuous femoral nerve block that used bupivacaine while undergoing anterior cruciate ligament repair.[141] Similar results for femoral nerve blockade have been reported for patients undergoing popliteal bypass surgery.[142]

Epidural Anesthesia

In contrast to the regional techniques described above, specific efforts have been made to examine the usefulness of epidural analgesia for postopera-

tive pain control in chronically opioid-consuming patients. As discussed previously, opioid requirements by the epidural route for providing continuous pain control and by the intravenous route for alleviating breakthrough pain are higher in chronically opioid-consuming patients than in opioid-naive patients.[7,28] In chronically opioid-consuming patients, the use of very potent lipophilic opioids seems particularly useful and superior to the use of less potent hydrophilic compounds such as morphine. de Leon-Casasola et al.[63] reported that a cancer pain patient on a high preoperative dose of methadone (1,000 mg/day) suffered from inadequate postoperative pain control despite receiving a high dose of epidural morphine in conjunction with bupivacaine. Satisfactory pain relief was achieved once the patient was switched from morphine to sufentanil, and the authors speculated that sufentanil provided superior pain control because its higher potency allowed analgesic effects to be exerted at a lower receptor occupancy. In a prospective follow-up study in 20 cancer patients, the authors confirmed that epidural sufentanil provided superior postoperative pain control compared with morphine.[64] In agreement with this finding is a study that documents superior postoperative pain control in chronically opioid-consuming patients who received epidural fentanyl rather than epidural morphine.[7] Administration of an epidural opioid, particularly of a very potent lipophilic compound such as sufentanil or fentanyl, in combination with a local anesthetic, is an attractive approach for effectively treating postoperative pain in chronically opioid-consuming patients. However, chronically opioid-consuming patients treated with regional techniques for postoperative pain control should also have access to systemic opioids by the intravenous or oral route for preventing opioid withdrawal.

Adjuvant analgesics have been administered via the epidural route for further improving postoperative pain control in chronically opioid-consuming patients. The use of clonidine or low-dose epinephrine, drugs acting as agonists on the α_2-adrenergic receptor, has been advocated.[59] For example, Niemi and Breivik[143] showed superior postoperative pain control when epinephrine was coadministered with epidural fentanyl and bupivacaine.

Considerations for Discharge

Chronically opioid-consuming patients typically require significantly higher postoperative opioid doses for adequate pain control than they received before surgery for their chronic pain symptoms. Attempting to discharge chronically opioid-consuming patients on the same opioid regimen they adhered to before surgery often results in inadequate pain control. Whatever the final oral dose the chronically opioid-consuming patients are stabilized on at discharge, a slow tapering from this dose toward the preoperative opioid dose over 2 to 4 weeks is often a reasonable goal. Careful communication with patients and surgical teams helps facilitate this process. Tapering patients off their postoperative opioid dose within 4 weeks simplifies matters because it eliminates the need for refilling prescription opioids, particularly schedule II drugs, which require a new written prescription each month, possibly at higher doses than prescribed by the patient's outside physician before the surgery. However, if the patient's postoperative opioid dose has been particularly large, tapering to the preoperative dose in 4 weeks may not be achievable. In this case, a longer-term plan may be formulated that includes responsibility for prescriptions for all the necessary refills or arrangement for a follow-up visit to a pain clinic to facilitate the transition to preoperative opioid doses. If the surgical procedure is expected to reduce the source of the patient's chronic pain, the dose to which the patient is tapered may be lower than the dose required preoperatively.

Conclusions

The use of opioids for licit and illicit purposes is common and growing. The preoperative use of opioids is linked to greater postoperative pain and analgesic requirements. To best address this situation, healthcare providers should (1) identify chronically opioid-consuming patients before surgery, (2) manage opioids optimally in the perioperative period, (3) use adjuvant analgesics and regional anesthetic techniques, and (4) formulate a plan in collaboration with the patient on how to return to the preoperative opioid dose. Future research addressing the perioperative management of chronically opioid-consuming patients should examine in greater detail how adjuvant drug regimens and regional anesthesia techniques could further improve postoperative pain control in these patients.

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