Challenges in Acute Pain Management

Kishor Gandhi, MD, MPH*, James W. Heitz, MD,
Eugene R. Viscusi, MD

KEYWORDS

• Acute pain • Challenging pain patient • Multimodal analgesia
• Analgesic gap

Adequate control of postoperative pain following surgery can be a challenging task.[1,2] Previous studies have shown that more than 50% of patients undergoing surgery report postoperative pain as a major concern, and that a majority of patients have unrelieved postoperative pain.[3] Uncontrolled pain in the postoperative period has been documented to result in several undesirable adverse events including myocardial ischemia and infarction, pulmonary infections, paralytic ileus, urinary retention, thromboembolism, impaired immune functions, and anxiety. In addition, poor pain control can lead to patient dissatisfaction, impaired patient rehabilitation, and prolonged hospitalization.[3] Patients who have well-controlled pain have an improved health-related quality of life, use fewer resources, reduce time lost from work, and have overall greater satisfaction with their experience.[4–8]

Although the benefits of pain control are uniformly recognized, hospitalized patients may not always benefit from optimal pain control because of the unique challenges some patients may present during the course of their hospitalization and surgery. Some difficulties in management can be attributed to patients who present with challenging clinical scenarios (ie, opioid-induced hyperalgesia, chronic pain patients with high tolerance to opioids, sickle cell disease, substance abuse, or metabolic or physical challenges that limit the dosing of pain medications). The clinician may also be unfamiliar with the management of medical problems that may increase the risk of opioid-induced side effects in patients with obstructive sleep apnea, the elderly, and the cognitively impaired. Patients with metabolic and neurologic disease states (such as renal failure, hepatic failure, and multiple sclerosis) have altered metabolism of drugs or unique risks for specific agents or techniques that may complicate the management of pain. Identifying an "ideal" analgesic that is free of undesired side effects and easy to administer may be difficult in such challenging clinical scenarios.[9]

Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, 111 South 11th Street, Suite 8490, Philadelphia, PA 19107, USA
* Corresponding author.
E-mail address: Kishor.gandhi@jefferson.edu

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ACUTE PAIN PROCESSING PATHWAYS

Pain is generated from local inflammation and nerve damage caused by trauma or temperature change (**Fig. 1**). Tissue trauma results in local release of inflammatory mediators such as bradykinins, 5-hydroxytryptamine, leukotrienes, prostaglandins (PGE_2, PGG_2, PGH_2), substance P, and histamine, which serve as activators of primary nociceptors. Receptors in the periphery detect changes of pain and temperature and transmit afferent signals in low-threshold myelinated Aβ fibers or high-threshold unmyelinated Aδ and C fibers. Signals reach the dorsal root ganglion via unmyelinated and myelinated noxious fibers and synapse in the dorsal horn of the spinal cord. The stimulus is then carried by second-order spinal neurons through

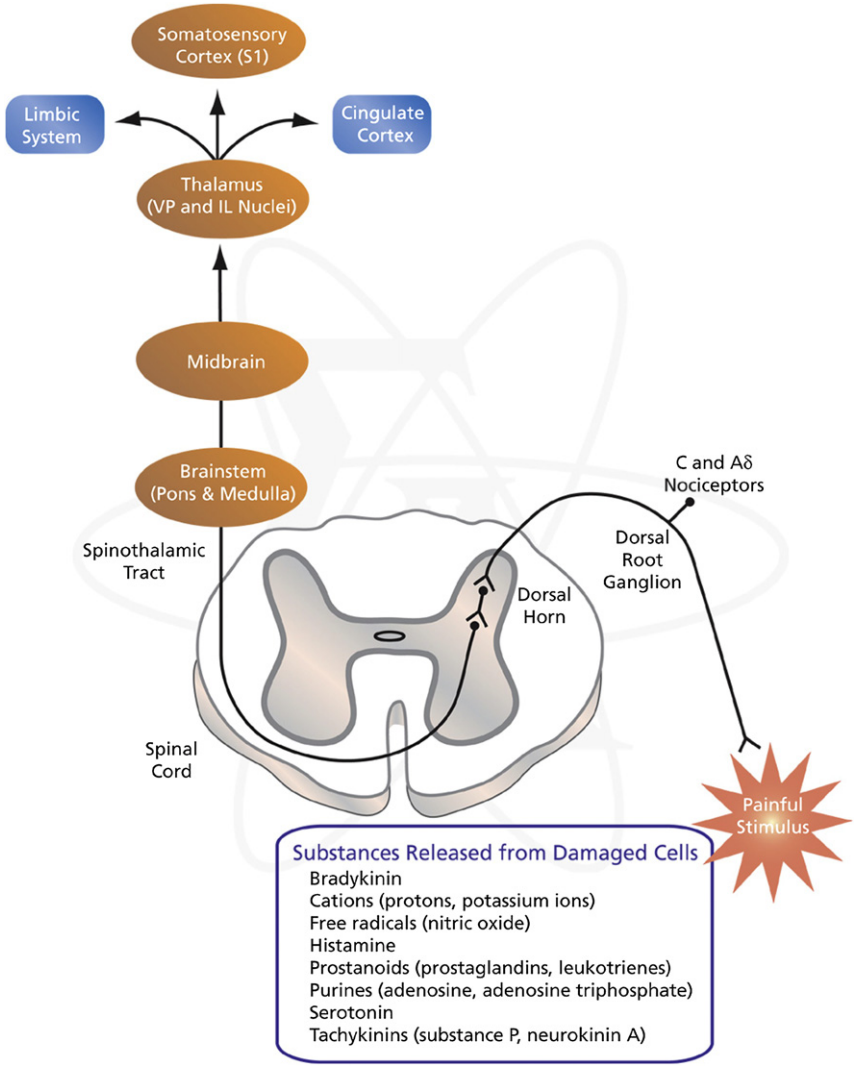

Fig. 1. Acute pain pathway. (*Courtesy of* Sigma-Aldrich, St Louis, MO; with permission. Available at: http://www.sigmaaldrich.com/life-science/cell-biology/learning-center/pathway-slides-and/ascending-pain-pathway.html.)

the neospinothalamic and paleospinothalamic tracts.[4] Modulation of pain transmission can occur at the level of the spinal cord dorsal horn or supraspinally at the brainstem and midbrain. Modulation involves a balance between excitatory effects of glutamine and the inhibitory effects of endogenous analgesics such as enkephalin (ENK), norepinephrine (NE), γ-aminobutyric acid (GABA), opioids, and α-adrenergics that target specific binding sites on 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors.[4] Once modified, noxious stimulus can transmit along axons from dorsal horn to thalamic cells and directly to the somatosensory cortex, which is involved in perception and localization of the stimulus.

OBJECTIVE PAIN ASSESSMENTS IN CHALLENGING PATIENTS

Because the pain experience has a subjective component, validated pain assessment tools are critical in appropriately assessing and treating pain. Because of the importance of pain treatment in the hospital setting, various organizations have created guidelines to assess and appropriately treat acute pain (World Health Organization, Agency for Healthcare Research and Quality, Joint Commission on Accreditation of Health Care Organizations [JCAHO]). The JCAHO has mandated treatment of pain as a basic human right.[10] JCAHO guidelines state that every patient has the right to assessment, treatment, and reassessment of pain.

Unidimensional pain intensity rating scales (Numeric Rating Scale [NRS], Verbal Descriptor Scale, Visual Analog Scale, Faces Pain Scale) can be used for patients who have an obvious cause of pain, but these metrics may not be adequate for more challenging patients (the elderly, and patients with visual/hearing impairment or cognitive impairments). A recent study measuring pain experiences in the elderly showed the NRS captured only part of the pain experience and should be supplemented by other forms of assessments.[11] Furthermore, unidimensional rating scales may not capture functional domains, and can contribute to misleading conclusions about treatment efficacy and recovery.[12] Multidimensional pain assessment tools such as Brief Pain Inventory, Initial Pain Assessment Inventory, and McGill Pain Questionnaire have been shown to be validated for complex pain seen in the perioperative period.[13] These measurement scales may better quantify pain and are reliable across various clinical settings.

PATIENT CHARACTERISTICS INFLUENCING MANAGEMENT

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) is a state in which patients being treated with opioids exhibit diminished pain threshold and enhanced sensitivity to pain. Despite dose escalation of opioids, patients may display reduced benefit from opioid therapy. OIH is considered a separate entity from analgesic tolerance; however, both may be present with dose escalation (**Fig. 2**). With OIH, escalating opioid treatment may paradoxically worsen the patient's pain perception.[14–16] It is difficult to distinguish clinically between tolerance and hyperalgesia.

OIH may result from hypersensitization of pronociceptive pathways in the peripheral or central nervous system (see **Fig. 1**).[17] While the mechanism of OIH is only beginning to be delineated, the process may be multifactorial, involving sensitization of primary and secondary afferents, enhanced release of neurotransmitters, and upregulation of spinal and supraspinal pathways. A critical component of OIH may be the activation of the excitatory NMDA receptor and the central glutamatergic system.[18] The link between NMDA receptors and the glutamatergic system has been shown by reversal

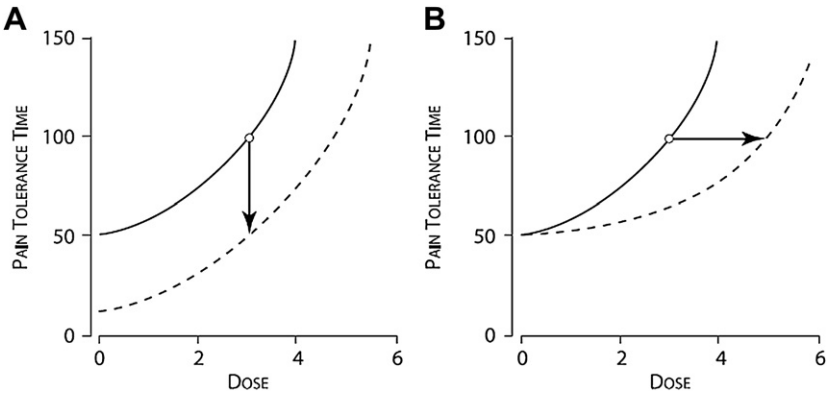

Fig. 2. Opioid dose-response relationship. (*A*) Opioid-induced hyperalgesia. (*B*) Opioid tolerance in chronic pain patients. (*From* Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanism and clinical considerations. Clin J Pain 2008;24:480; with permission.)

of opioid-induced pain sensitivities via inhibition of both systems.[19] However, the glutamatergic system is likely involved in both tolerance and hyperalgesia. OIH has been demonstrated in patients receiving high-dose intraoperative opioids such as fentanyl and remifentanil.[20–22]

A proposed management strategy for OIH involves a multimodal analgesic approach targeting NMDA receptors, α2-agonists, and cyclooxygenase (COX)-2–specific inhibitors[17] (**Fig. 3**). Low-dose intraoperative and postoperative ketamine is an effective antagonist of NMDA receptors. Ketamine has been shown to reduce postoperative pain and opioid consumption. The NMDA receptor antagonism effects of ketamine may reduce postoperative opioid-induced hyperalgesia. Methadone, with its D-isomer acting as an NMDA receptor antagonist, may also reduce hyperalgesia. COX-2–specific inhibitors may attenuate the role of prostaglandin synthesis and NMDA receptor function in the central nervous system (CNS).[23–25] α2-Agonists such as clonidine have also been shown to reduce postoperative hyperalgesia when administered intraoperatively. A multimodal approach is likely beneficial in the management of patients with presumed OIH.

Opioid Tolerance in Chronic Pain Patients

Tolerance (reduced analgesic effects of opioids) occurs in patients with prolonged opioid exposure. The development of tolerance with chronic opioid use results from desensitization of opioid antinociceptive pathways. Unlike opioid-induced hyperalgesia, there is no change in baseline pain perception in opioid tolerance. Opioid tolerance in chronic pain patients can usually be addressed by increasing opioid dose. Chronic opioid consumers may require a twofold to threefold increase in perioperative opioid dosing in comparison with opioid-naïve patients.[26] The molecular basis for opioid tolerance can be attributed to the desensitization of the μ-opioid receptor and second-messenger systems (protein kinase and G-protein) at the cellular level. Furthermore, activation of NMDA receptors and downregulation of glutamate transporter have been recently shown to take part in opioid tolerance.[19]

Appropriate management strategies of patients with opioid tolerance require identification of these patients before surgery. Careful assessment of preoperative opioid requirements is vital. Perioperative management involves use of a multimodal drug

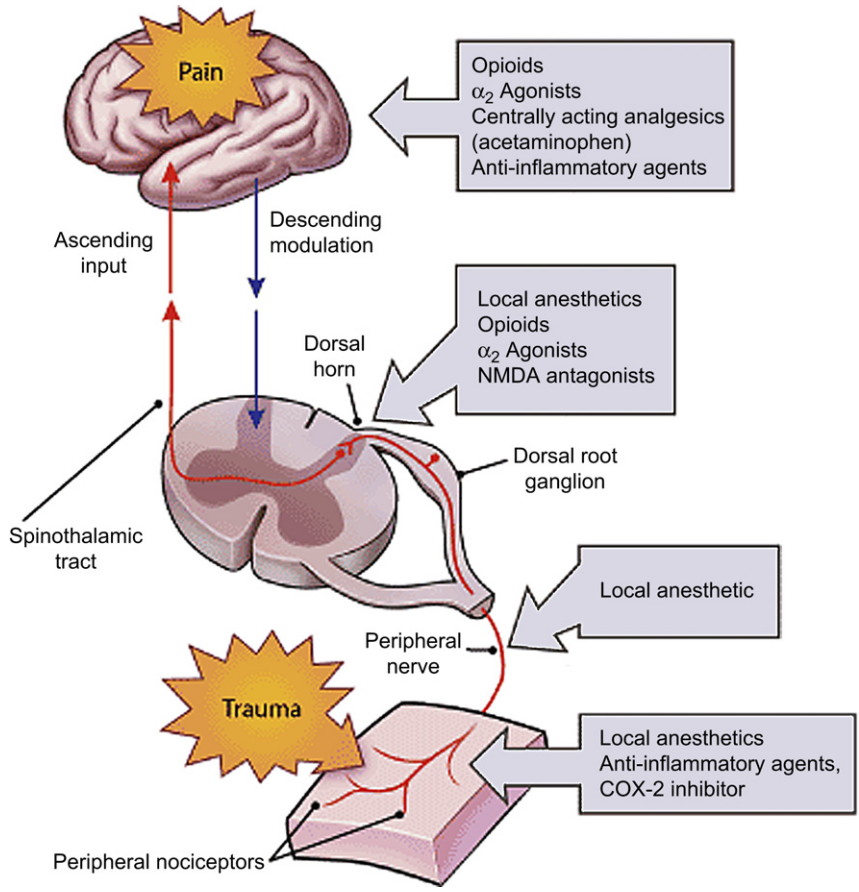

Fig. 3. Multimodal pain treatment. (*Modified from* Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. Am Fam Physician 2001;63:1981; with permission.)

regimen.[27] Prior to surgery, patients may receive acetaminophen, celecoxib, gabapentin, or pregabalin. Both gabapentin and pregabalin act to inhibit $\alpha_2\delta$ subunit on the presynaptic voltage-gated calcium channel and attenuate the neuronal sensitization response. Perioperative use of pregabalin in addition to other nonopioid agents in total knee replacement has been shown to decrease opioid consumption and the incidence of neuropathic pain at 3 and 6 months after surgery.[28,29]

Intraoperative ketamine infusion (0.5 mg/kg bolus followed by 4 μg/kg/min infusion) and long-acting opioids for optimal comfort have demonstrated success. Ketamine, when given preoperatively and intraoperatively during spine surgery, was shown to reduce total morphine consumption and pain intensity for up to 6 weeks after surgery.[30] There were no differences in side effects when compared with placebo. Alternatively, intraoperative single bolus of methadone (0.2 mg/kg) has also shown a 50% reduction in postoperative opioid consumption and pain scores at 48 hours after surgery for complex spine procedures.[31]

Opioid-tolerant patients may see maximal benefits with regional anesthesia techniques using continuous neuraxial and peripheral nerve catheters for certain

orthopedic and vascular procedures. Postoperative management will require supplemental opioid control of breakthrough pain as well as prevention of acute withdrawal from opioids, which best may be met with systemic opioids such as intravenous patient-controlled analgesia (PCA). However, it is helpful to maintain preoperative doses of extended-release opioids during the perioperative course. Postoperative ketamine infusion (up to 4 days) has also proved successful at the authors' institution in decreasing opioid requirements and improving analgesia in chronic pain patients with opioid tolerance.

Substance Abuse and Addiction

The National Survey on Drug Use and Health (NSDUH) estimates that more than 8% of the United States population older than 12 years in 2008 used illicit drugs in the previous month.[32] Patients with a history of opioid abuse and illicit drug addiction present a challenging scenario to the acute pain team. Patients with unrecognized chronic opioid exposure are at risk for opioid withdrawal and severe acute pain following surgery. Such patients may be dependent on polypharmacy through physician shopping or illicit street drugs. Commonly abused illicit drugs include marijuana, cocaine, 3,4-methylenedioxymethamphetamine (Ecstasy), and heroin.[32] Prescription opioid (eg, hydrocodone, oxycodone) abuse and misuse present a significant problem as well. It may be difficult to distinguish the addicted patient from the chronic pain patient or the addicted patient with chronic pain.[33,34] The patient with substance abuse will seek opioids despite effective pain control, while the chronic pain patient will titrate opioids to the degree of pain control. The addicted patient may not follow specific medication plans and may demand specific drugs for treatment, or claim allergies to nonopioids. The nonaddicted patient may display "drug-seeking" behavior if given inadequate doses (pseudoaddiction). Identification of the substance-abusing patient may be challenging and may not be revealed until the postoperative period when drug-seeking behavior is suspected.

Perioperative management of the known substance-abusing patient involves a carefully constructed plan during the preoperative, intraoperative, and postoperative course. The goal of treatment is to choose an appropriate strength of pain medication based on individual patient history.[35] A preoperative drug screen may be helpful to confirm whether the patient is actively using drugs and if so, which drugs are present. These patients should receive their long-acting opioids (methadone, extended-release oxycodone, extended-release morphine, and transdermal fentanyl) on the morning of the surgery to minimize acute opioid withdrawal in the perioperative period.[36] A preoperative dose of pregabalin, acetaminophen, and celecoxib will reduce sensitization of primary and secondary afferents.[17] Neuraxial and peripheral regional anesthesia techniques are recommended for orthopedic and vascular surgeries of upper and lower extremities. These techniques minimize pain and reduce the need for opioids during surgery.[37,38]

Intravenous PCA with morphine, hydromorphone, and fentanyl provide postsurgical analgesia before transition to oral agents alone. PCA has been studied extensively and has proved to be successful in opioid-dependent patients.[39,40] Minimizing postoperative opioid withdrawal is critical. A centrally acting $\alpha 2$-adrenergic agonist such as a clonidine transdermal (0.1–0.2 mg/h) patch is helpful in minimizing side effects and withdrawal in tolerant patients.[41] When appropriate, neuraxial and continuous peripheral nerve blocks can be continued with 0.2% ropivacaine or 0.1% bupivacaine up to 48 hours.[37,38] Opioid coadministration with local anesthetics to epidurals may improve analgesia and limit acute withdrawal symptoms. Continuation of a multimodal

regimen including, acetaminophen, pregabalin, celecoxib, and ketorolac may provide pain relief for inflammatory and neuropathic components of pain.[17]

Sickle Cell Disease

Sickle cell disease is a genetically inherited disorder involving the β-globin chain production of red blood cells (RBCs). When an excess of defective RBCs are in the blood stream, patients develop painful crisis as a result of sickling of the RBCs in the microvasculature, followed by ischemia and activation of inflammatory pathways. Proinflammatory mediators released at the site of ischemia cause the release of vasoconstrictors, which exacerbate the vasoconstriction thus leading to worsening crisis. Local inflammation causes irritation of nerves, creating burning neuropathic-like pain. Crisis events are precipitated by physiologic stresses such as infections, dehydration, cold, or other external stressors. Patients with sickle cell syndrome typically display visceral or bone and joint pain during their "crisis" period, due to release of inflammatory mediators and stimulation of nociceptors.[42] It is common for these patients to display nociceptive as well as central and peripheral neuropathic pain. Often the anatomic location of the pain syndrome will vary by age and the extent of microinfarctions.[43] Differences in patient age and demographics can pose barriers in the reporting of pain during crisis events. Chronic pain syndromes as a result of sickle cell present later in life from avascular necrosis of long bones, leg ulcerations, and joints.[44]

Perioperative management of these patients involves careful planning to minimize any factors that can precipitate a painful crisis. Preparations include prewarming of operating rooms, adequate hydration of the patient before operation, and ample opioids to avoid a sickling event.[45] The first-line treatment for mild to moderate pain in sickle cell patients includes nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, celecoxib, and ketorolac.[43] Studies of patients treated with ketorolac infusion during vaso-occlusive crisis showed improved pain relief and reduced opioid requirements.[46] Tramadol, a synthetic central-acting analgesic, has also been shown to be effective in controlling mild to moderate sickle cell pain.[43] Meperidine is a poor opioid choice in sickle cell patients because of its short half-life (3 hours) and CNS stimulating activity of its metabolite (normeperidine).[47] Normeperidine has a half-life of 18 hours and can cause nervousness, tremors, and seizures. It is poorly excreted in sickle cell patients with kidney disease, leading to accumulation and increased the risk of seizures.

Because these patients often have significant opioid tolerance, they may benefit from PCA with appropriate (larger) patient control doses. Studies comparing opioids by intermittent versus PCA administration in sickle cell patients demonstrate greater satisfaction and pain relief in the PCA group.[48] Some clinicians may advocate the use of a basal infusion to avoid peaks and troughs of a bolus-only PCA program. However, PCA basal infusions should be used with caution because this has been associated with an increased risk of respiratory depression. A randomized trial comparing morphine PCA to a continuous infusion of morphine showed the PCA group to have decreased morphine consumption and reduced side effects.[49] The use of low-dose ketamine infusion has also been shown to reduce pain scores and opioid requirements during hospitalization.[50] Ketamine can be safely administered in low-dose infusion to decrease the amount of opioid consumption in this patient population.

Elderly and Cognitively Impaired Patients

The US Census Bureau estimates that 1 in 5 Americans (20.3%) will be 65 years or older by year 2030.[51] As "baby boomers" continue to age, increasing numbers of

them will require hospitalizations and surgical care. As a consequence of normal physiologic changes of aging, the elderly present with pathophysiologic alterations such as decreased multisystem reserve, decreased cerebral and peripheral nervous system activity (cognitive impairment, delirium), and increased sensitivity to drugs (morphine, scopolamine, diphenhydramine, atropine). Delirium or cognitive impairment is a common postoperative complication seen in the elderly, and is often a worsening of underlying pathology that may have been unrecognized. It is estimated that up to 50% of the elderly population may suffer from postoperative delirium and cognitive dysfunction after orthopedic and cardiac surgeries.[52] The different classifications of cognitive impairment include dementia, mild cognitive impairment, postoperative cognitive dysfunction, delirium, postoperative delirium, and emergence delirium.[52] These cognitive impairments may continue up to 3 months after surgery in a minority of patients.

A careful management of perioperative technique is warranted in this high-risk population. Due to the altered pharmacodynamics of drugs, the elderly are more sensitive to anesthetics. General anesthesia will induce cognitive impairments as well as prolonged recovery times from anesthesia. Most opioids used for pain control have altered volume of distribution and decreased clearance, resulting in increased sensitivities.[53] Perioperative use of regional anesthesia has been shown to be effective in reducing morbidity (pneumonia, pulmonary embolism, myocardial infarction) and superior pain control.[7,54–56] Use of epidurals and peripheral nerve blocks has been shown to improve surgical outcome by decreasing opioid consumption, increasing ambulation and rehabilitative goals, and decreased length of hospital stay.[57] In addition, a multimodal approach with nonopioids such as NSAIDs, acetaminophen, ketorolac, and celecoxib can be used when there is a need to avoid the side-effect profile of opioids. Intravenous PCA may not be effective in patients who exhibit signs of dementia or delirium, due to inherent difficulties of operating the device.

Evaluations of mental status are rarely performed as part of routine preoperative assessments. Baseline deficits are often not recognized. Given the high incidence of perioperative changes of mental status in this age group, some preoperative assessment may be warranted to establish risk stratification and to better target anesthetic and analgesic techniques.

Sleep Apnea

Obstructive sleep apnea (OSA) is a syndrome in which the individual experiences recurrent complete or subtotal airway obstruction during sleep despite intact respiratory effort. The prevalence of OSA among adult Americans has been estimated at 2% of women and 4% of men.[58] However, there is increasing concern that the prevalence of OSA is rising with increasing obesity.

There is a considerable clinical overlap between OSA and central sleep apnea (CSA), and the conditions may present as a spectrum of disease. Individuals afflicted with sleep breathing disturbances may have both central and obstructive components.[59] Sleep apnea is defined as primarily OSA or CSA, depending on the relative proportion of obstructive versus central apneic episodes during a sleep study. In addition, some individuals with OSA develop treatment-emergent CSA after successful treatment. These observations have led to a more comprehensive concept of complex sleep apnea (CompSA). In a recent study of 1286 patients with primary OSA, 6.5% were noted to transiently develop treatment-emergent CSA after initiation of continuous positive airway pressure (CPAP) therapy, with 1% still affected at 8 weeks.[60]

It is important that clinicians maintain a high index of suspicion for OSA, because the majority of these individuals will be undiagnosed at the time they may need acute pain

management. Although obesity is recognized as a marker of OSA, many patients with significant OSA are not obese. A history of loud snoring, daytime somnolence, witnessed apnea during sleep, and concurrent hypertension should alert the clinician to possible OSA.[61] It is estimated that 80% of males and 93% of females with moderate to severe OSA are undiagnosed.[62] Even among bariatric surgery patients, a very high risk group whose concurrent morbid obesity should raise clinical suspicion to possible OSA, the majority of cases of OSA are undiagnosed preoperatively.[63,64] This is unfortunate, because untreated OSA shortens life expectancy by more than 20 years and is linked to significant comorbidities including systemic hypertension, pulmonary hypertension, severe cardiovascular morbidity, and cardiac sudden death.[65–70] Recognition of sleep apnea has significant implications in the treatment of acute pain. Opioids, the most potent and widely used analgesics, can contribute to catastrophic respiratory events. An observed increase in the number of postoperative cardiopulmonary arrests by The Doctors Company in 2002 among patients receiving parenteral opioids later diagnosed with sleep apnea has raised concern about the safety of opioid analgesia in this population.[71]

The effects of opioids on the individual with sleep-disordered breathing have not been well studied. Hence, there is little evidence to guide therapy or craft guidelines. Opioids are known to inhibit the ventilatory response to both hypoxia and hypercapnia in healthy volunteers.[72] Opioids also cause obstructive apnea and hypoxia in the postoperative period in patients not identified with OSA.[73] Chronic opioid therapy with sustained-release opioids has been shown to increase the number of central and obstructive episodes of apnea, and is associated with sustained nocturnal hypoxia.[74] The respiratory depressant effects of opioids demonstrated in healthy individuals raise serious concerns for the consequences of opioids in patients with OSA, CSA, or CompSA.

In a study of volunteers with moderate OSA, opioid-induced apnea was observed during remifentanil infusion during sleep.[75] It is interesting that the number of episodes of obstructive apnea in these individuals decreased during opioid infusion, but this apparent "benefit" was more than offset by an increase in central apnea episodes. This apparent paradox is perhaps explained by the effect of opioids on rapid eye movement (REM) sleep. Opioids are known to decrease REM sleep. Pharyngeal muscle tone reaches a nadir during REM sleep, but REM sleep possibly offers protection against central apnea.[74,76] This finding is consistent with observations that CSA develops in up to 50% of patients on chronic opioid therapy.[77] Opioid-induced suppression of REM sleep is attenuated by prolonged use (REM rebound), so the effect of the remifentanil infusion on the number of obstructive episodes could not be predicted if the infusion had been continued beyond the short duration of the study.[78] Further studies clearly are needed to determine whether individuals with OSA will experience an increase in obstructive apnea as a late effect of opioid infusion, or if this finding can be replicated with other parenteral opioids in patients with sleep apnea.

Based on these findings, minimization of opioids and other sedatives in patients with known or suspected OSA, CSA, or CompSA is prudent. Route of opioid administration (intravenous, intramuscular, intrathecal, epidural) or administration technique (nurse-administered vs patient-controlled analgesia), does not affect the clinical risk.[79] Residual effect of anesthetics and sedatives may contribute to respiratory depression, but the sedating side effects of many adjuvant medications (antiemetics, antihistamines, β-blockers) should not be overlooked. Medications with mild sedating effects have the potential to cause serious adverse events when combined with opioids in patients with OSA.

In 2006, The American Society of Anesthesiologists Task Force of Perioperative Management of Patients with Obstructive Sleep Apnea released practice guidelines that included recommendations for postoperative pain management.[80] Although the task force did not make specific recommendations for analgesia in patients with OSA, they did recommend multimodal analgesic techniques to minimize opioids and to incorporate regional anesthesia and analgesia when possible. Epidural analgesia using only local anesthetics should be considered for postoperative analgesia. Nonpharmacological interventions, including ice and transcutaneous electrical stimulation, may be used when appropriate. The task force was equivocal on whether patient-controlled analgesia was preferable to nurse-controlled analgesia or whether patient-controlled analgesia with a basal infusion is safe. However, basal infusions with intravenous PCA are known to increase the risk of respiratory events.[81] Although CPAP has only been studied in non–perioperative settings, the task force recommended continuing CPAP postoperatively if not contraindicated for surgical reasons, but did not recommend institution of postoperative CPAP for patients not using it before surgery. Furthermore, the task force recommended that patients not be discharged home or to unmonitored settings until they were no longer at risk for postoperative respiratory depression. However, this raises the concern of how to predict when the patient is no longer at risk. While the guidelines clearly are helpful, clinical judgment is essential when guiding treatment decisions.

How best to monitor the sleep apnea patient requiring opioid therapy remains controversial. Although evidence is lacking, there is general agreement that continuous pulse oximetry is recommended for sleep apnea patients receiving opioids. Continuous pulse oximetry may not be available or difficult to manage at many institutions on general hospital floors, because the technology is prone to gaps and artifacts. Moreover, frequent alarms from repeated desaturations or artifacts may place a burden on nurses and be disruptive to the patient being monitored. Effective and accurate continuous pulse oximetry is best achieved in a monitored setting, but this approach considerably increases the cost of caring for these patients and consumes much-needed monitored bed resources. Capnography would also be effective as a monitor of respiration, and is becoming more widely available, but is still challenged by factors similar to pulse oximetry. Capnography may be a more sensitive and an earlier monitor of increasing respiratory difficulty. In a recent prospective cohort study at the Mayo Clinic, a combination of preoperative risk assessment combined with postanesthesia care unit observation for hypoxia was used to triage postoperative patients at risk for sleep apnea to the appropriate level of monitoring.[82] Further validation of this 2-phase screening for sleep apnea may allow for appropriate monitoring of high-risk individuals during opioid therapy for acute pain.

Beyond recommendations to limit opioid doses and general recommendations for monitoring, literature supporting greater safety of specific analgesic techniques or protocols is lacking. A prudent approach would follow the general principles of multimodal analgesia: use local anesthetic or regional anesthetic techniques whenever possible, preferably with a continuous (catheter) delivery, and supplement with nonopioid analgesics (acetaminophen, NSAIDs, or COX-2 inhibitors, antineuropathic pain agents, and ketamine).

OSA raises additional concerns in the ambulatory setting. While there are no hard and fast guidelines, prudence dictates caution. Patients with known severe OSA clearly should be approached with caution or even excluded from outpatient procedures. The use of nonopioids and nonsedating drugs with regional anesthetic and analgesic techniques becomes even more important. Careful and perhaps prolonged observation in the recovery unit may reveal obstructive episodes suggesting that

admission for monitoring is indicated. With the increasing numbers of patients with OSA, the cost of excluding all of these patients from ambulatory surgery would be prohibitive. Many patients remain undiagnosed, complicating this scenario.

Although OSA may be obvious in many patients, the diagnosis remains unclear for many others. This fact, coupled with the lack of specific evidence for analgesic approaches or monitoring or the time period during which patients are at risk, makes for a challenging clinical scenario. For that matter, any patient receiving an opioid analgesic has some risk of respiratory depression. A simple, cost-effective, easy-to-use respiratory monitoring device is needed but remains elusive at this point.

Neurologic Disease

The patient with preexisting neurologic disease who may benefit from neuraxial or regional anesthesia in the treatment of acute pain offers a challenge to the clinician, prompting concerns that are simultaneously medical and medicolegal. Preexisting neurologic disease raises concern that patients may be particularly vulnerable to a second neurologic insult, the so-called double-crush phenomenon,[83] but also raises question of whether a clinician may be inappropriately assigned civil liability for a neurologic deficit that is merely coincidental. Multiple sclerosis, because of its often waxing and waning and unpredictable nature, presents a particularly vexing clinical conundrum.

Several older case reports have implicated spinal anesthesia and epidural anesthesia in contributing to exacerbations of multiple sclerosis.[84,85] More recently, anecdotal case reports have implicated peripheral nerve blocks in exacerbations as well.[86,87] However, anecdotal reports have also been cited as evidence of neuraxial anesthesia preventing exacerbations of multiple sclerosis after surgery.[88]

While there are no randomized controlled trials to guide therapy, several large retrospective studies have failed to show an increased risk of multiple sclerosis exacerbation after neuraxial anesthesia. In a retrospective review of vaginal deliveries at Brigham and Women's Hospital between 1982 and 1988, there was no significant difference in multiple sclerosis exacerbation between parturients receiving epidural anesthesia and those receiving local infiltration.[89] More recently, a review of 139 patients with multiple sclerosis receiving neuraxial anesthesia or analgesia at the Mayo Clinic between 1988 and 2000 did not reveal any exacerbations of the neurologic disease.[90]

While multiple sclerosis should not be considered an absolute contraindication to neuraxial or regional anesthesia, the clinician needs to carefully assess risk versus benefit on an individual basis. Whenever possible, informed consent should include a (documented) candid discussion with the patient about the risks and benefits of the proposed regional anesthetic, and acknowledgment that while the best evidence suggests that regional anesthesia can be used safely for patients with multiple sclerosis, there is no uniformity of opinion or certainty, as our knowledge of the risks is still evolving.[91]

Similar recommendations can be made for performance of regional anesthesia for rare demyelinating disorders such as Guillan-Barré syndrome (GBS) during the perioperative period. Published case reports have described worsening neurologic conditions after performance of epidural analgesia for labor and delivery.[92] However, neuraxial or regional anesthesia may be possible if the patient is treated effectively with intravenous immunoglobulin or plasmapheresis well in advance of surgery.[93] Although there are no published guidelines on the practice of regional anesthesia in GBS, the authors recommend caution in performance of nerve blocks because of

the potential toxic effects of local anesthetic on unmyelinated nerves during the active phase of the illness.

Renal Disease

Acute pain management of the patient with end-stage renal disease (ESRD) presents an increasingly common challenge for the clinician. According the United States Renal Data System, at the conclusion of 2007 there were 526,343 ESRD patients in the United States; 341,264 on chronic hemodialysis, 26,340 on chronic ambulatory peritoneal dialysis, and 158,739 who had received renal transplants.[94] The number of individuals with chronic kidney disease (CKD) is significantly higher and is trending upward by as much as 10% each year, due to an aging population with an increasing incidence of diabetes mellitus and hypertension.[95] Pain is a common comorbidity in this patient population, and as many as one-third of patients with CKD are receiving opioids.[96] Safe use of analgesics in this population requires consideration not only for altered clearance of the parent drug but also altered clearance of metabolites, ability of parent drug and significant metabolites to be removed by hemodialysis in patients with ESRD, and for the potential for renal toxicity in patients with CKD or renal transplantation. Therefore, the clinician should understand not only the pharmacokinetics of the prescribed analgesic but the effect of CKD or hemodialysis on its pharmacokinetics.

Several commonly used opioids display favorable safety profiles with concurrent CKD or ESRD. Fentanyl elimination is greater than 99% hepatic, with transformation to primarily norfentanyl and to a lesser extent desproprionylfentanyl and hydroxyfentanyl.[97] Fentanyl has a long history of safe clinical use in patients with renal failure, as do the closely related alfentanil and sufentanil. This success is despite the fact that as molecules with large molecular weight and high protein binding, poor ability to dialyze these compounds from the blood would be expected. The metabolism of remifentanil is dissimilar, being metabolized by plasma cholinesterases, but it is also believed to be safe in renal failure patients. No increase in respiratory depression from remifentanil infusion was observed in patients with severe CKD.[98] Methadone has a favorable safety record in renal failure, despite having significant renal as well as hepatic elimination. Methadone and its metabolites cannot be dialyzed. However, there is evidence of complete excretion of the parent compound and its metabolites in feces in the setting of concurrent anuria.[99,100] Dose reduction of methadone is only necessary for severe CKD.[101]

Morphine, hydromorphone, and hydrocodone have been administered safely in renal failure patients, but need close monitoring for side effects and appropriate dose reduction because of the accumulation of active metabolites. Morphine undergoes hepatic metabolism, but its metabolites morphine-3-glucuronide, morphine-6-glucuronide, normorphine, and codeine all have renal elimination. Accumulation of morphine-6-glucuronide causes sedation. Although both morphine and morphine-6-glucuronide are effectively removed from the blood by hemodialysis, the slow diffusion of the latter out of the CNS makes elimination by hemodialysis clinically difficult. Hydrocodone is metabolized to hydromorphone by CYP2D6, and individuals lacking this enzyme experience no significant analgesia.[101] Hydromorphone is primarily metabolized to hydromorphine-3-glucuronide, whose accumulation in renal failure is associated with a neuroexcitatory phenomenon. Both hydrocodone and hydromorphone can be administered safely in patients with CKD but, like morphine, require appropriate dose reduction based on creatinine clearance.[100]

Several commonly prescribed analgesics are contraindicated in the presence of CKD. Meperidine, codeine, and propoxyphene are plagued by the accumulation of

toxic metabolites causing unacceptable side-effect profiles.[100] Propoxyphene is particularly troublesome because it is poorly dialyzable and its metabolites are associated with respiratory depression, hypoglycemia, and cardiac conduction disturbances.[102,103] Aspirin and NSAIDs, although not associated with toxic metabolite accumulations, are relatively contraindicated for their ability to adversely affect the underlying CKD.

A unique clinical challenge arises from the need to provide analgesia to the ESRD patient not receiving hemodialysis, as may occur with end-of-life care. Such patients usually receive care via the incremental World Health Organization Analgesic Ladder approach.[104] Whereas Step 1, acetaminophen, may be administered safely in renal failure, there is no clear safe opioid for mild to moderate pain (Step 2). Tramadol may be the safest choice of the Step 2 opioids, but dose reduction is necessary. Good Step 3 opioid choices would include fentanyl or methadone.[105]

Hepatic Disease

The patient with hepatic insufficiency also provides a clinical challenge for analgesia. Unlike renal insufficiency, which can be quantitatively described by glomerular filtration rate or creatinine clearance allowing for dosing of opioids based on measured physiologic function, the severity of hepatic dysfunction is more difficult to measure precisely.

Because most opioids undergo hepatic metabolism, opioid dosing for the patient with hepatic dysfunction may be problematic. Unlike renal dysfunction, which typically results in accumulation of metabolites, hepatic dysfunction can cause accumulation of the parent drug or metabolites. As a general principle, oxidative processes are usually more severely affected than glucuronidation in patients with hepatic impairment.[106] However, the peak plasma concentration and elimination half-life of morphine, which undergoes primarily hepatic glucuronidation, have been demonstrated to be significantly elevated with patients with cirrhosis.[107] Acetaminophen is metabolized in part by glucuronidation. Hence, acetaminophen should be used with caution in the presence of hepatic impairment or known alcoholism.

All opioids must be administered cautiously. Long-acting and sustained-release opioids require extra caution. Codeine, which requires hepatic transformation to morphine for analgesia, should be avoided in severe hepatic dysfunction because its efficacy may be impaired.[108] Remifentanil, with its ultra-short half-life and its unique metabolism, has some attractive pharmacokinetic properties but its clinical utility for the treatment of acute pain is limited.

SUMMARY

The management of acute pain remains challenging, with many patients suffering inadequate pain control following surgery. Certain populations, as discussed in this review, are at unique risk for unrelieved pain. Evidence-based approaches taking into account specific needs and problems of patients will likely substantially improve their perioperative experience. To best serve these at-risk individuals, they must first be identified in the preoperative process. A plan can then be discussed with the patient and integrated into the anesthetic and analgesic strategy. A targeted multimodal approach to pain management should be considered the best clinical practice. Finally, the most challenging patients in acute pain may benefit most from the surveillance of an acute pain service that is able to monitor and coordinate care into the postoperative period.

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