An Update on Nonopioids
Intravenous or Oral Analgesics for Perioperative Pain Management

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- Acute pain
- Multimodal analgesia
- Acetaminophen
- Nonsteroidals
- Gabapentin
- NMDA antagonists
- Ketamine
- Regional anesthesia

KEY POINTS
- Despite an appreciation for many unwanted physiologic effects from inadequate postoperative pain relief, moderate to severe postoperative pain remains commonplace.
- Treatment options have evolved in recent years, including improvement in medications, multimodal regimens, regional anesthetic techniques, and continuous catheters, and the utilization of these agents can reduce acute pain-associated morbidity and mortality.
- This review focuses on the importance of effective postoperative nonopioid analgesic agents, such as acetaminophen, nonsteroidal anti-inflammatory agents, gabapentinoids NMDA antagonists, alpha 2 agonists, and steroids, in opioid sparing and enhancing recovery.
- Using combinations of nonopioid analgesics in a multimodal approach reduces the required dose of each agent, decreasing the risk of toxicity and dose related side effects that are seen when single agents are used alone.

GENERAL INTRODUCTION
In recent years, there has been a significant increase in our comprehension of the nervous system and the consequences of tissue injury, such as surgery, including transmission, modulation, perception, and subsequent responses of the...
body to such injury. Pain management for many years has been largely dominated by pharmacologic interventions and concern for toxicity of these agents, requiring an increasing strategy for a multimodal approach. Treatment strategies in postoperative analgesia are still evolving and recent studies indicate that there is a potential for both morbidity and mortality with many agents, in particular opioid medications. In this regard, the increasing opioid abuse epidemic within the United States implies the need for pain management options that do not involve highly addictive drugs and with favorable safety profiles. Nonopioid analgesics are a class of analgesic agents with a variety of mechanisms that can be used to alleviate or to treat pain and rarely involve abuse with standard dosing regimens. As such, these agents should be the first line of treatment for pain management. It is important that health care providers are familiar with the nonopioid analgesics that are available to treat pain, how they work, and what conditions they should be used to treat. As added benefit, these agents can be used in conjunction with a multimodal approach to better treat patients with pain, maximize pain control, and decrease the prescriptions of opioids.

Equally important, patients undertreated for acute pain can have a variety of untoward systemic effects. Further, long-term pain is highly associated with poorly controlled acute pain. The clinical anesthesiologist or pain provider should be aware that although there are many different treatment modalities, our literature indicates that most patients experience moderate to severe pain in the postoperative period. A dedicated team focused on the evaluation of and modification to analgesic treatment regimens will ultimately best ensure a favorable outcome for patients in the postoperative period. In this article, therefore, we discuss several nonopioid analgesic agents that are useful for analgesia focused, in part, on perioperative pain management. Many of these agents have been recently developed in different preparations, altering pharmacokinetics and utilization strategies. These drugs provide much utility because their effects are mediated or modulated at different levels involved in pain transmission, which is initiated at the peripheral nociceptors and progressed through spinal tracts to the brain. Using combinations of these nonopioid analgesics in a multimodal approach reduces the required dose of each agent, thereby further minimizing the likelihood of toxicity to any individual drug being delivered to a patient.

**ACETAMINOPHEN**

Acetaminophen is used for its analgesic and antipyretic effects and comes in oral, rectal, and intravenous (IV) formulations. It has been approved for use in both pediatric and adult populations for the treatment of mild to moderate pain, fever, and as an adjunct to opioids in the treatment of moderate to severe pain.

The exact mechanism of action is still not completely known. It is believed to exert its effect by inhibition of the cyclooxygenase (COX) enzyme in the central nervous system (CNS) with a preference for COX-2 over COX-1. Inhibition of the COX enzyme results in decreased production of prostaglandins that are involved in sensitization of nociceptors to injurious stimuli. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen has no effects on platelet function and minimal if any anti-inflammatory activity.

Acetaminophen is mostly metabolized by the liver with a very small amount (2%–9%), excreted unchanged. Most of the oral dose is absorbed in the small intestine with very little absorption taking place in the stomach. Intravenous infusion results in a maximum drug concentration ($C_{\text{max}}$) up to 70% higher, but overall exposure is very similar to oral administration. The half-life of a therapeutic dose is 1 to 3 hours, with duration of action of 4 to 6 hours. One systematic review revealed an absence
of strong evidence suggesting that intravenous administration is superior to oral administration in treating postoperative pain when patients have a functioning gastrointestinal tract and can take oral medications. Formulations come as a solo agent or combined with other medications, such as opioids. Oral dosing for adults and adolescents older than 13 is 650 to 1000 mg every 4 to 6 hours with a maximum daily dose of 4000 mg. Dosing for oral extended release is 1300 mg taken every 8 hours for a maximum daily dose of 3900 mg. Rectal dosing is 650 mg every 4 to 6 hours with maximum of 6 doses per day. Intravenous dosing consists of 1000 mg every 4 to 6 hours, again with a maximum dose of 4000 mg. For adults and adolescents 13 years and older weighing less than 50 kg, dosing is as follows: 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours with a maximum dose of 75 mg/kg up to 3750 mg. Acetaminophen should be used judiciously with any other medications that have the potential for hepatic toxicity.

The most common adverse reactions include nausea, vomiting, headache, and insomnia. Major adverse reactions include hepatic injury and allergic/hypersensitivity reactions. Doses exceeding the daily maximum can result in acute liver failure and even death. Dosing should be reduced in those with preexisting liver disease, renal impairment, chronic alcohol abuse, and hypovolemia, as this can increase the risk of hepatotoxicity.

Acetaminophen can be given preoperatively or intraoperative in multimodal analgesia. A Cochrane Review showed that when compared with placebo, the number needed to treat for 1 patient to achieve at least 50% pain relief after a single dose of 1000 mg is 4.6. One dose of IV acetaminophen has shown to reduce pain by 50% in 37% of patients, and those receiving acetaminophen also required 30% and 16% fewer opioids at 4 and 6 hours, respectively.4

NONSTERoidal ANTI-INFLAMMATORY DRUGS

NSAIDs are among the most commonly used medications worldwide, and play a critical role in pain management. The long history of anti-inflammatory treatment dates back thousands of years to the prescription of willow bark extract by Hippocrates. Unknown to him at the time, the active ingredient in willow bark, salicin, was responsible for the anti-inflammatory and analgesic response. Chemically similar, acetylsalicylic acid was first marketed as Aspirin by Bayer in 1899.

Additional NSAIDs were subsequently developed, but it was not until the 1970s that John Vane5 described the disruption of prostaglandin synthesis as a mechanism by which NSAIDs exert their anti-inflammatory and analgesic effects. Further work by Needleman, Simmons and Herschman revealed that different metabolic pathways of arachidonic acid were catalyzed by separate COX subtypes.6 COX-1 and COX-2, as they came to be known, facilitate the production of prostanoids with distinct effects. COX-1 is a nearly ubiquitous enzyme involved in production of prostanoids with numerous beneficial effects, including gastric mucosal protection. In turn, COX-2 is an inducible proinflammatory enzyme.7 Early NSAIDs, including aspirin, act nonselectively inhibiting both COX-1 and COX-2, whereas some newer agents, such as parecoxib act preferentially at COX-2. Most of both specific and nonspecific NSAIDs are readily absorbed after oral administration, strongly bind plasma proteins, and undergo hepatic metabolism followed by renal excretion. Notably, aspirin irreversibly binds COX, leading to antiplatelet effects for up to a week, as platelets are unable to regenerate COX.8

NSAIDs are most commonly used for controlling pain and reducing fever. Additional well-known uses include indomethacin for the closure of patent ductus arteriosus and
aspirin 325 mg for acute coronary syndrome or 81 mg daily for coronary and cerebral vascular event prophylaxis. Numerous studies have examined NSAID use in the perioperative setting. A study by Viscusi and colleagues evaluating postoperative parecoxib use in nearly 500 patients with total hip arthroplasty showed reduced pain with 20 mg once or twice daily after surgery, as well as lower incidence of fever and vomiting. Another study investigated 90 mg/d and 120 mg/d etoricoxib after total abdominal hysterectomy, and both doses showed improved pain control and decreased opioid use compared with placebo. Following postoperative oral surgery, ketorolac 10 or 20 mg and ibuprofen 400 mg provided better pain relief than acetaminophen-codeine 600 to 60 mg. Some suggest ibuprofen dosing of 1600 to 2400 mg daily following dental surgery to optimize the anti-inflammatory capacity. For clinicians who wish to avoid oral administration of medications in the perioperative setting, 800 mg ibuprofen IV has been shown to reduce opioid requirements. For those interested in a COX-2–specific inhibitor, parecoxib is approved for use in Europe, although not the United States.

Although many studies have described the benefits of NSAIDs, others have raised potential concerns. The APPROVe Trial showed that rofecoxib used with hopes of preventing recurrence of adenomatous polyps in patients with a history of colorectal cancer was associated with higher risk of thrombotic cardiovascular events. Another large study evaluated parecoxib after cardiac surgery, and revealed that it too was associated with higher rates of cardiovascular events.

A multimodal approach to perioperative pain management using medications with different mechanisms of action allows for lower dosing of each medication, and by extension, risk of adverse drug reactions for individual medications is decreased. However, each patient must be evaluated individually for appropriateness of NSAID treatment. Evidence suggests that COX-2 inhibitors should be avoided in patients with cardiovascular disease, NSAIDs should be avoided in patients with renal injury, and aspirin is contraindicated in children. There are numerous other instances in which alternative therapies might be preferred, but when used in the correct setting, NSAIDs offer an excellent option in the management of pain.

**N-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS**

N-methyl-D-aspartate, or NMDA, receptors are a group of ionotropic receptors that are involved in transferring electrical signals from neurons of the brain to the spinal column. The NMDA receptor’s pain-processing effect occurs primarily in the dorsal horn of the spinal cord. In response to injury, the dorsal horn releases glutamate, which then binds to the NMDA receptor. After binding, there is an enzymatic cascade and altered gene expression that ultimately leads to central sensitization, opioid tolerance, and opioid-induced hyperalgesia. Increased sensitivity of the spinal neurons leads to hyperalgesia and neuropathic pain, resulting in a heightened level of pain. Drugs that inhibit the NMDA receptor are thought to play a key role in controlling pain through this mechanism. Drugs in this class include ketamine, memantine, amantadine, dextrimethorphan, and magnesium.

**Ketamine**

Since its development in the late 1960s, ketamine has become a useful drug in the medical community. It is commonly administered intramuscularly or IV. There is an oral formulation; however, because it is metabolized by bile acids, there is a low bioavailability and its use is limited. Ketamine is a racemic mixture composed of S (+) and R (−) enantiomers. The S (+) enantiomer has been shown to be up to 4 times
more potent, has a shorter duration of action, and is associated with fewer neuropsychiatric adverse effects.16,19

Ketamine’s analgesic effect is produced by noncompetitively inhibiting the NMDA receptor. When a noxious stimulus is produced, gene expression of proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6, is upregulated in macrophages.20 Ketamine’s antihyperalgesic effects are thought to be due to modulation in the production of these cytokines.21,22 Blocking the NMDA receptor also has been shown to improve efficacy of opioids and reduce chronic pain syndromes.23

Many studies have examined systemically administered ketamine and its ability to control or minimize perioperative pain and the reduce hyperalgesia. Neuraxial administration has not been shown to be an effective route of administration in noncancer pain and can be neurotoxic.24,25 A systematic review done by Laskowski and colleagues23 in 2011 looked at 70 studies using IV ketamine for perioperative analgesia. Using a statistical approach, their review proved that IV ketamine was effective in reducing postoperative opioid consumption, and there was an increased duration until first opioid use.23 Another systematic review done by Elia and Tramer26 in 2005 examined 53 randomized trials of perioperative IV ketamine use in adults and pediatrics. Their results showed a significant reduction in pain scores at 6, 12, 24, and 48 hours in the postoperative period. In the same review, Elia and Tramer26 performed a meta-analysis of 16 trials and showed that administration of IV ketamine (average dose 0.4 mg/kg) before incision reduced pain intensity and morphine consumption in the immediate 24 hours after surgery. A Cochrane Database review of 37 trials looked at ketamine doses of 0.15 to 1.0 mg/kg and found there to be reduced rescue analgesic requirements, decreased pain intensity, and less morphine consumption by patient-controlled analgesia (PCA).27 In chronic opioid users, intraoperative ketamine infusions of 10 μg/kg per minute have been shown to decrease opioid consumption and reduce pain intensity at 1, 2, and 6 days in the postoperative period. Opioid consumption was 71% less compared with placebo.28

Although ketamine has been shown to be an effective modality in perioperative pain control, its use is often limited due to feared adverse neuropsychiatric effects. These effects are dose-dependent and can include vivid dreams, hallucinations, dysphoria, and nightmares. Low-dose ketamine has a much lower incidence of these adverse effects. A meta-analysis of 24 studies revealed in 12 trials, no adverse effects were reported. In 7 of the trials, there was no difference between control and treatment groups. Only 1 study showed an increased number of neuropsychiatric effects in epidural ketamine usage.29

**Memantine**

Memantine is another drug in the class of NMDA receptor antagonists. Because memantine is completely absorbed from the gastrointestinal tract, it can be orally administered. After administration, it is at maximal plasma concentration between 3 and 8 hours and its half-life is 6 to 100 hours. Memantine has been shown to be useful in the treatment of phantom limb pain. In a randomized, double-blind, controlled trial done by Schely and colleagues,30 patients with an amputation were treated with continuous brachial nerve plexus blocks and either daily doses 20 to 30 mg of memantine or placebo. The investigators found a significant decrease in prevalence of phantom limb pain at 4-week and 6-month follow-up appointments in patients receiving memantine.31 Another study done by Lee and colleagues32 showed low-dose memantine decreased methadone dose in opioid-dependent patients undergoing methadone maintenance therapy. Plasma TNF-α, C-reactive protein, IL-6, IL-8, transforming growth factor (TGF)-β1, and brain-derived neurotrophic factor levels...
were measured at scheduled intervals. Patients treated with memantine also had significantly lower plasma TNF-α and significantly higher TGF-β1 levels. Memantine may have a role in the multimodal approach to attenuating perioperative pain; however, more research is necessary.

**Amantadine**

Amantadine is a noncompetitive NMDA receptor antagonist. It is administered orally and is commonly used as an antiviral and as an adjuvant therapy in the treatment of Parkinson disease. There are limited studies supporting its role in anesthesia practices currently. It is hypothesized that amantadine may be useful to decrease pain and analgesic requirements. A randomized, double-blind, placebo-controlled preliminary study done by Snijdelaar and colleagues looked at effects of perioperative oral amantadine on postoperative pain and morphine consumption in patients after radical prostatectomy. The main finding of this study showed a 32% reduction in morphine consumption in patients receiving amantadine compared with the placebo control group within the first 48 hours after surgery. They were unable to prove any further significant differences after the 48-hour period. Although there are several other similar small-powered studies looking at the effects of oral amantadine administration, further trials and studies may demonstrate amantadine to be an effective modality in perioperative pain control.

**Dextromethorphan**

Dextromethorphan is the d-isomer of the codeine analog levorphanol and is most commonly used for its antitussive properties. It noncompetitively inhibits NMDA receptors and has been shown to be an effective modality in perioperative pain modulation. There are multiple formulations for oral administration of dextromethorphan, including a solution, liquid-filled capsule, lozenge, dissolving strip, and a chewable tablet. Numerous studies have been done to prove dextromethorphan efficacy in perioperative pain management. In a study done by Ilkjaer and colleagues, preoperative doses of oral dextromethorphan were given to patients undergoing hysterectomy. There was a 30% reduction the PCA morphine in the first 4 hours after surgery. There was no effect on hyperalgesia near the surgical site, and they were unable to show a significant difference in pain scores 5 to 24 hours after surgery. In 2006, a systemic review of 28 studies was able to demonstrate that patients receiving parental and oral dextromethorphan reported less pain and increased duration until first analgesic use. Unfortunately, the review was unable to determine a recommended dosage or use of dextromethorphan in the postoperative period. A recent meta-analysis done in March 2016 by King and colleagues investigated perioperative dextromethorphan use in multimodal anesthesia and its effect on pain reduction and opioid consumption. They looked at 21 randomized, double-blinded, placebo-controlled trials and concluded that patients receiving dextromethorphan perioperatively had reduced pain scores at 1, 4, 6, and 24 hours after surgery and also decreased opioid consumption 24 to 48 hours after the operation. Common adverse effects encountered with dextromethorphan include drowsiness, blurry vision, nausea and vomiting, unsteadiness, slowed breathing, and difficult urination. Studies have shown that there is no significant difference in adverse effects among dextromethorphan or opioid administrations.

**Magnesium**

Magnesium is another noncompetitive inhibitor of the NMDA receptor. Magnesium is available in multiple formulations, including IV, intramuscular, and oral. It has been
shown to have synergistic effects of other analgesics. The magnesium ion is unable to cross the blood-brain barrier to reach the cerebrospinal fluid. Studies have shown that IV administration of magnesium does not improve pain management. Further studies have not shown any reduction in postoperative pain relief or analgesic requirements with IV magnesium administration. Some studies have been able to prove systemic magnesium as an effective adjunct for pain control. In a systematic review done by Albrecht and colleagues in 2013, the investigators demonstrated that IV magnesium reduced IV morphine consumption by nearly 25% at 24 hours after surgery. More consistency is seen in studies done with intrathecal administration of magnesium sulfate. When administered intrathecally in combination with spinal morphine analgesia, magnesium has been proven to potentiate the analgesia achieved with morphine through its action on spinal NMDA receptors. Although studies have shown limited use of IV magnesium as a pain modulator, multiple studies involving coadministration of ketamine and magnesium have proven a synergistic relationship with increased analgesic effect than either drug used alone. Recommended dose of magnesium for adults is 200 to 400 mg. Higher dosages of magnesium can lead to adverse effects, such as nausea and vomiting, diarrhea, arrhythmias, hypotension, coma, and even death.

GABAPENTIN (NEURONTIN) ORAL CAPSULE, TABLET, SOLUTION

Gabapentin (Neurontin) is used for the management of postherpetic neuralgia (PHN) in adults and adjunctive therapy in the treatment of partial-onset seizures. The precise mechanisms of gabapentin analgesia and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA), although there is no effect on GABA binding, uptake, or degradation. The relationship of binding high affinity to the δ subunit of voltage-activated calcium channels to the therapeutic effects of gabapentin is unknown. Gabapentin dosing starts as a single 300-mg dose on day 1, 300 mg 2 times on day 2, and 300 mg 3 times on day 3. Gabapentin may titrate up (as tolerated for pain relief) to 600 mg 3 times a day. There is no additional benefit of increasing gabapentin doses greater than 1800 mg/d in PHN. The adjustment of the gabapentin dose should correlate with renal function. Gabapentin does not metabolize commonly and will not interfere with the metabolism of other antiepileptic drugs frequently prescribed. The discontinuation of gabapentin treatment needs titration down gradually over a minimum of 1 week or a longer period if needed. Gabapentin bioavailability is not dose proportional. The bioavailability of gabapentin decreases as the dose goes up. When gabapentin was given 900, 1200, 2400, 3600, and 4800 mg/d in 3 divided doses, the bioavailability is approximately 60%, 47%, 34%, 33%, and 27%. The most common adverse reactions associated with gabapentin were dizziness, somnolence, and peripheral edema.

GABAPENTIN (GRALISE) TABLET ORAL ONCE DAILY

Gabapentin (Gralise) is used to treat PHN. Gabapentin (Gralise) is not interchangeable with any other gabapentin preparations related to unique pharmacokinetic profiles and dose intervals between the preparations. The goal is to increase the oral gabapentin (Gralise) dosage up to 1800 mg once daily with an evening meal and to ingest the whole tablet without splitting or crushing the tablet. Gabapentin is absorbed via a saturable L-amino transport system at the proximal small bowel. Gralise, gabapentin in a gastroretentive formulation, with food typically taking at dinner time between 4 and 5 PM, will stay in the stomach for approximately 15 hours compared with...
immediate-release gabapentin, which will stay in the stomach for only approximately 2 hours, thereby reducing rate of release and side effects, such as dizziness and sedation. The bioavailability of gabapentin decreases as the dose goes up. There is a higher Cmax and lower area under the curve at steady state of gabapentin (Gralise) (1800 mg once daily) as compared with gabapentin immediate release (600 mg 3 times a day). The Tmax (time to reach maximal plasma concentration) is 8 hours versus gabapentin immediate release (2–4 hours).

GABAPENTIN ENACARBIL (HORIZANT) EXTENDED-RELEASE ORAL TABLET

Gabapentin enacarbil (Horizant) is used for the management of PHN and the treatment of moderate to severe primary restless legs syndrome (RLS) in adults. The starting dose of gabapentin enacarbil (Horizant) for PHN is 600 mg in the morning for 3 days, then increased to 600 mg twice daily afterward. There is no additional benefit when the dose exceeds 1200 mg. The next dose may continue as scheduled in case of 1 missed dose. The best time to take the daily dose of gabapentin enacarbil (Horizant) 600 mg for RLS is at approximately 5 PM. The gabapentin enacarbil (Horizant) tablet should be taken in the whole form without being split or crushed. There is no additional benefit when the dose exceeds 600 mg. The proton-linked monocarboxylate transporter (MCT-1) facilitates absorption of gabapentin enacarbil. This transporter MCT-1 expresses at high levels in the intestinal tract and will not saturate even with administration of high doses. The Tmax of Horizant is 5.0 hours after administration of 600 mg in fasted subjects and 7.3 hours in fed subjects. Daily dosing of gabapentin enacarbil (Horizant) reaches a steady state in 2 days.

PERIOPERATIVE PAIN MANAGEMENT OF GABAPENTIN

The perioperative use gabapentin is off label and dosages range from 300 to 1200 mg in clinical studies. Preoperative preemptive gabapentin decreased postoperative analgesic consumption during 24 hours after surgery in a systematic review and meta-analysis. A systemic review and meta-analysis of preemptive gabapentin for abdominal hysterectomy resulted in decreasing postoperative pain scores, opioids consumption, and nausea and vomiting. Gabapentin improved postoperative pain control and reduced the opioid requirements after total hip arthroplasty in a meta-analysis of randomized controlled trials. The addition of perioperative gabapentin to multimodal analgesia (ketorolac, acetaminophen, and intravenous PCA with morphine) did not provide significant differences in pain scores, side effects, or range of motion in total hip arthroplasty. Perioperative gabapentin provided no benefit on postoperative morphine consumption, pain scores, patient satisfaction, or length of hospital stay in primary total knee arthroplasty with multimodal analgesia (PCA morphine, oral acetaminophen 1000 mg, and ketorolac 15 mg every 6 hours). There was no additional benefit by a third nonopioid analgesic (such as gabapentin) to double-drug regimens, including IV patient-controlled opioid analgesia after abdominal hysterectomy. It is prudent to be cautious whenever adding gabapentin to perioperative multimodal analgesia.

PREGABALIN (LYRICA)

Pregabalin is used for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN), PHN, fibromyalgia, and spinal cord injury. The mechanism of action is unknown; however, it is a GABA analog that binds to a subunit on voltage-gated calcium ion channels. The dosage of pregabalin begins with...
150 mg/d and titration for all indications. The maximum dose is 600 mg/d for DPN, PHN, and spinal cord injury, and 450 mg/d for fibromyalgia. Pregabalin binds with high affinity to the alpha2-delta subunit of voltage-gated calcium channels in the CNS. The mechanism of action of pregabalin in clinical application is unknown. Binding to the alpha2-delta subunit may correlate with the antinociceptive and antiseizure effects of pregabalin in animal model studies. Pregabalin reduced calcium-dependent release of pronociceptive neurotransmitters in the spinal cord. The interactions of pregabalin with descending noradrenergic and serotonergic pathways originating from the brainstem may also contribute to neuromodulation and analgesia. The peak plasma concentrations occur within 1.5 hours after oral pregabalin under fasting conditions. The oral bioavailability of pregabalin is greater than or equal to 90% and is independent of dose. The steady state can occur within 24 to 48 hours after repeated doses. The pharmacokinetics of pregabalin after multiple doses correlates with the data from a single dose. There is no significant effect on total absorption of pregabalin whether with or without food. Pregabalin does not bind to plasma proteins and commonly excretes unchanged in the urine. There is no interference with pharmacokinetics by other antiepileptic agents through either metabolic interactions or protein-binding displacement. The adverse reactions most frequently leading to discontinuation of pregabalin treatment were dizziness and somnolence; other adverse effects include ataxia, confusion, thinking abnormally, blurred vision, incoordination, and peripheral edema.

PERIOPERATIVE PAIN MANAGEMENT OF PREGABALIN

Perioperative use of pregabalin is off label with dosages ranging from 75 to 600 mg in clinical studies. Perioperative pregabalin reduces preoperative anxiety, postoperative pain scores, and opioid consumption, and improves sleep quality in patients with elective craniotomy. Postoperative pregabalin at 75 mg provides effective analgesia for moderate to severe post-thoracotomy pain with epidural anesthesia. Preemptive pregabalin 150 mg provides effective analgesia and opioid-sparing benefit without significant adverse events after arthroscopic shoulder surgery. A total of 150 mg provided effective analgesia with less opioid consumption and minimal adverse effects in patients who underwent laparoscopic cholecystectomy. Although preemptive pregabalin 600 mg significantly reduced postoperative pain and opioid consumption in cases of laparoscopic cholecystectomy, there was an increased incidence of dizziness reported. Although perioperative pregabalin reduced daily pain scores and opioid consumption in hospital and for 1 week after total hip arthroplasty, there was no improvement in pain control or physical function at 6 weeks or 3 months afterwards. Perioperative pregabalin improved analgesia and reduced neuropathic pain in a systemic review and meta-analysis. The risk of increased sedation and visual disturbances associated with pregabalin certainly warrants precaution, especially in off-label use for perioperative medicine. There was a reduced incidence of chronic neuropathic pain after total knee arthroplasty (TKA) with perioperative pregabalin. Patients reported less opioid requirement and improved range of motion during the first 30 days of rehabilitation. Perioperative pregabalin resulted in a higher risk of sedation and confusion in the early postoperative period. In cases of multimodal analgesia, including femoral nerve block, epidural analgesia, oxycodone-paracetamol, and meloxicam, perioperative pregabalin offered no beneficial effects, but increased sedation and decreased patient satisfaction after TKA. Perioperative pregabalin caused significant sedation in all surgical categories except head and neck, laparoscopic cholecystectomy, and gynecologic procedures. Postoperative nausea and vomiting was
more significantly associated with pregabalin use in various surgical procedures. Clinicians need to take precautions in balancing the analgesia benefit versus adverse effects in different categories of surgeries.62

STEROIDS

**Glucocorticoids**

Corticosteroids are useful for pain management due to their anti-inflammatory and immunosuppressive properties. Corticosteroids diffuse through the fatty cell membranes to bind to a class of cytoplasmic receptors that diffuse into the nucleus.83 They subsequently bind to the DNA to modify transcription and subsequently the production of proteins, which thus elicits a desired effect. The steroids prevent the release of acid hydrolases from leukocytes, prevent leukocyte attachment to vessel endothelium, reduce macrophage accumulation, reduce edema formation through plugging capillary walls, block histamine activity, reduce inflammation from endotoxins, block cytokine release, for example, TNF-α, and they reduce lymphatics and immunoglobulin/complement concentrations.63 Taken together, these can have a potent effect on pain management and reduction of systemic inflammation. The anti-inflammatory action can be directed to the damaged tissue in question by reducing edema through the reduction of tissue pressure and by also limiting pain mediators. They directly block c fiber transmission and stimulate endorphin release. The typical side effects of glucocorticoids involve delayed wound healing due to their immunosuppressive effects, hyperglycemia, gastrointestinal ulcers, restlessness and euphoria, osteoporosis with long-term use, muscle wasting, fat redistribution, and the Cushing effect. There do not appear to be any significant side effects with 1-time dosing in the perioperative setting.64

**Dexamethasone**

Dexamethasone is a potent glucocorticoid that decreases inflammation by decreasing neutrophil migration and reducing capillary permeability. It has a peak serum time of 8 hours. The half-life is 1 to 5 hours with normal renal function and it is typically administered IV or intramuscularly.65 Adults are usually prescribed 0.75 to 9.0 mg/kg per day divided into doses over 6 to 12 hours to treat pain and inflammation. Dexamethasone is contraindicated in patients who have a systemic fungal infection, cerebral malaria, or a previously documented hypersensitivity to the drug. Treatment with this drug can result in adrenal suppression, resulting in hypercorticism or suppression of the hypothalamic-pituitary-adrenal axis, especially in young children. Prolonged use of dexamethasone can increase the incidence of contracting a secondary infection due to immune suppression; therefore, long-term treatment with glucocorticoids is discouraged.

**ALPHA-2 AGONISTS**

**Clonidine**

Clonidine is an alpha-2 agonist that is historically used in the treatment of hypertension, but can also be used as an adjuvant in multimodal analgesia. It can be added to spinal blocks as well as peripheral nerve blocks. It is also thought to reduce opioid consumption, provide anxiolysis, reduce nausea, and can also be used to treat postoperative shivering. Alpha-2 agonism decreases sympathetic outflow and thus the release of norepinephrine in the locus ceruleus and substantia gelatinosa. Clonidine also has some affinity for the alpha-1 receptor. The alpha-2/alpha-1 binding ratio for clonidine is 220:1.
Clonidine can be administered via intrathecal, intravenous, oral, transdermal, intra-nasal, intra-articular, and perineural routes. Intrathecal dosing ranges from 15 to 45 μg. As an adjuvant to peripheral nerve blocks, the dose is 0.5 to 1.0 μg/kg. The transdermal patch comes in 0.1, 0.2, or 0.3 mg per 24 hours and oral dosing for analgesia is 5 μg/kg. Clonidine can increase the effects of CNS depressants, such as benzodiazepines, alcohol, and opioids. As it has sedative effects, administration also will decrease minimum alveolar concentration requirements.

Most common side effects associated with clonidine use are dry mouth, drowsiness, dizziness, constipation, and sedation. Cardiovascular effects of clonidine can include hypotension, bradycardia, congestive heart failure, electrocardiographic abnormalities, and orthostatic symptoms. In the POISE-2 trial, low-dose clonidine administration was shown to increase the risk of clinically significant hypotension and nonfatal cardiac arrest.66

There are many studies looking at the efficacy of clonidine for postoperative analgesia. For instance, addition of 25 to 75 μg clonidine to bupivacaine-morphine spinal provided superior postoperative analgesia than bupivacaine-morphine alone in TKA (total knee arthroplasties).67 When given intrathecally, it can potentiate the sensory and motor block of local anesthetics by 30% to 50%, but may also increase the need for vasopressors.67,68 As an adjuvant to peripheral nerve blocks, clonidine has been shown to increase duration, provide faster onset, and improve postoperative analgesia. This results in a decrease in pain scores and opioid consumption.69,70 A meta-analysis revealed patients receiving clonidine 2 to 5 μg/kg had an approximate 25% dose reduction in morphine at 24 hours.71 However, a subgroup analysis from the POISE-2 trial showed that a preoperative dose of 0.2 mg orally followed by 0.2 mg transdermal patch for 72 hours did not reduce pain scores or opioid consumption in patients undergoing noncardiac surgery.66 Conflicting findings between studies may be related to dose or the route of administration. When administering clonidine for postoperative pain management, clinicians need to take into consideration its potential hemodynamic effects and its role in the multimodal analgesic approach.

**Dexmedetomidine**

Dexmedetomidine is an alpha-2 receptor agonist with a mechanism of action similar to clonidine; however, it has a much higher affinity for the alpha-2 receptor over alpha-1. It is 7 to 8 times more selective for the alpha-2 receptor than clonidine, with a ratio of approximately 1600:1.72 This accentuates its sedative and anxiolytic properties while reducing the hemodynamic effects seen with clonidine. Some of its clinical uses include procedural sedation, sedation in the intensive care unit (ICU), addition to peripheral and neuraxial blocks, and for management of postoperative pain. Dexmedetomidine is not yet approved by the Food and Drug Administration for spinal and epidural anesthesia.20

Following IV administration, there is a rapid distribution phase with a distribution half-life of approximately 6 minutes. The terminal elimination half-life is approximately 2 hours. Dexmedetomidine undergoes almost total biotransformation with very little being excreted unchanged. The drug is mainly metabolized by N-glucuronidation to inactive metabolites and aliphatic hydroxylation.

For sedation in the ICU, a 1 μg/kg dose is given over 10 minutes followed by a maintenance infusion of 0.2 μg/kg per hour. Procedural sedation has a similar loading dose followed by a maintenance dose of 0.6 μg/kg per hour. This is then titrated to effect in a dose range from 0.2 to 1.0 μg/kg per hour. Intrathecal dosing ranges from 3 to 15 μg, whereas perineural dosing can range from 0.75 to 1.0 μg/kg.73
Dry mouth is one of the most common side effects, although hypotension and bradycardia are the most common cardiovascular effects associated with dexmedetomidine use with an incidence of 17% and 26%, respectively. Clinically significant episodes of sinus arrest and bradycardia have been witnessed in young healthy adults with high vagal tone or with rapid IV or bolus administration. As with clonidine, it should be used cautiously in conjunction with beta blockers.

Intraoperative dexmedetomidine administration has been shown to decrease postoperative pain and have an opioid-sparing effect. One systematic review concluded that mean postoperative morphine sparing with dexmedetomidine was 14.5 mg. The use of dexmedetomidine can prolong the duration of both sensory and motor blocks in spinal anesthesia when using longer-acting local anesthetics. Onset of spinal anesthesia is quicker and the time to first analgesic request was longer. Prolongation of postoperative analgesia with the use of dexmedetomidine was approximately 7 hours. Another meta-analysis concluded that dexmedetomidine prolonged motor block, but prolongation of sensory block did not reach statistical significance when used in peripheral nerve block of the brachial plexus. One study showed that both IV and perineural formulations can reduce opioid consumption and prolong analgesic effects of interscalene nerve blocks. Dexmedetomidine can be an effective adjuvant to spinal and peripheral nerve blocks. It also can reduce pain when given IV and its greater affinity for the alpha-2 receptor may make it a more suitable choice as an adjuvant than clonidine.

CONSEQUENCES OF UNDERMANAGED ACUTE PAIN

Secondary to surgical trauma and associated inflammatory reaction and pain pathway signaling, acute postoperative pain is associated with many autonomic, psychological, endocrine-metabolic, and physiologic responses. Inadequate management of postoperative pain can result in numerous consequences involving multiple organ systems, including local, systemic, and reactive effects. Untreated pain also can cause significant psychological symptoms that can play a role in the development of chronic pain syndromes.

SUMMARY

Because many unwanted physiologic effects are related to inadequate pain management in the postoperative period, effective pain treatment strategies can reduce many of these unwanted consequences. In recent years, many treatment options have evolved, including ultrasound-guided regional blocks with catheters and the development of an encapsulated liposomal bupivacaine preparation, Exparel. An appreciation for many of the nonopioid agents described in this article is warranted for the clinical anesthesiologist attempting to reduce postoperative acute pain states. This includes the implementation of multimodal regimen, many involving strategies using these drugs in the perioperative period. Outcomes data indicate that many opioid-focused strategies, unlike nonopioid agents, are associated with significant morbidity and mortality, emphasizing the need for studies that focus on important milestones of recovery, emphasizing pain relief, ambulation, and discharge. An appreciation for pain-mediated pathogenesis, analgesia, toxicity, and important drug-drug interactions can conclude that there are substantial beneficial roles for many of these nonopioid analgesics in our clinical practices.
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