# Chapter 20

# PAIN MEDICATIONS

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## INTRODUCTION

The practice of acute pain medicine in a battlefield environment must take into account injury severity and location-specific capabilities, including continued patient monitoring. Due to austere conditions and possible physiologic instability, an acute pain medicine physician must have a broad command of various multimodal analgesic pathways and options. Various injuries, whether mild or severe, place soldiers at risk for chronic postsurgical pain.[1] Although no analgesic regimen has been shown to significantly impact the prevalence of chronic postsurgical pain following traumatic injury, a multimodal approach aims to mitigate contributing risk factors. Specifically, patients who experience severe preoperative and postoperative pain are noted to have higher incidences of chronic pain.[1,2] A truly preemptive approach is impossible due to the nature of such traumatic injuries; however, a continuous multimodal approach embraces a theoretically preventive strategy.[3] This strategy utilizes both pharmacologic and interventional modalities aimed at various nociceptive mechanisms (inflammatory, neuropathic, etc), with the secondary benefit of minimizing the side effects of any one therapy. The strategy provides a continuous analgesic pathway that extends through numerous preoperative, intraoperative, and postoperative settings.

Various classes of analgesic modalities are available. However, in a battlefield setting, practical issues such as availability, physiologic status of the patient, and the ability to rapidly transport the patient to a tertiary level of care outside the theater of conflict must be considered. Pharmacologic modalities can roughly be separated into two classes, opioids and nonopioid adjuncts. The discussion below of pharmacologic therapies is intended to apply to the first 24 to 48 hours postinjury prior to transfer to a tertiary care site. Interventional modalities will be discussed in Chapter 22, Regional Anesthesia and Coagulopathy of Trauma Shock.

## OPIOIDS

Opioids, particularly morphine, have been the mainstay of analgesic treatment since the 19th century. The range of opioid formulations available makes them versatile for pain control in the setting of limited resources and in patients who may or may not have reliable intravenous access. Although opioids have displayed longstanding utility, overuse accentuates significant limitations in the form of side effects as well as unforeseen effects such as opioid-induced hyperalgesia or acute tolerance. Therefore, acute pain medicine practice on the battlefield has deemphasized the use of opioids as the sole analgesic agent in favor of a multimodal approach. However, opioids still offer the benefit of a diverse array of agents (short or long acting, per os [PO] or intravenous [IV] routes) that can be matched to a variety of injury severities (Table 20-1).

### Per Os Administration

Various formulations of PO opioids of both short- and long-acting duration are available. In general, only short-acting oral opioids are utilized in the acute phase of battlefield pain management for mild and moderate injuries. Patients must be able to tolerate oral intake and cognizant enough to communicate about dosing or hand carry medications that can be self administered during transport. Long-acting agents are often unnecessary because they cannot be titrated and patients are rapidly transferred out of theater.

All short-acting PO opioid formulations can be used with similar efficacy. However, older agents such as codeine-based analgesics require biotransformation into morphine to exert their effects, and up to 10% of the general population lack the necessary enzymes to perform this transformation.[4] Furthermore, synthetic agents such as oxycodone, hydrocodone, or oral hydromorphone exhibit better bioavailability, allowing for a faster onset of action when compared to oral formulations of morphine or codeine.[4,5] Also useful are various short-acting agents available in tablet or liquid form. Almost all short-acting agents share similar clinical onset (15–30 minutes) and duration of action (2–4 hours).

One attribute unique to short-acting PO opioids is that they often come in dual analgesic formulations including either a combination of nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen. Although each of these nonopioid components is useful within a multimodal analgesic regimen, they limit upward titration of their corresponding opioid due to the potential toxicity associated with exceeding daily maximal doses of NSAIDS or acetaminophen. Thus, the opioid component should be administered separately from the NSAID/acetaminophen component.

### Intravenous Administration

IV opioids remain an essential component of battlefield and immediate resuscitation analgesia prior to evacuation. Depending of the severity of injury, intra-

**TABLE 20-1**

**SUGGESTED ACUTE PAIN REGIMEN BASED ON INJURY SEVERITY**

| Medication | Mild Injury, Conscious Patient | Moderate Injury, Conscious Patient | Severe Injury, Patient Extubated | Severe Injury, Patient Intubated |
|---|---|---|---|---|
| | **Examples** | | | |
| | Superficial wounds | Fragmentation wounds, gunshot to extremities, distal amputation | Postoperative exploratory laparotomy, proximal single amputation | Proximal double amputation, significant intrathoracic/abdominal injury |
| Opioids, PO | Oxycodone, hydrocodone, morphine, hydropmorphine, or tramadol | Oxycodone, hydrocodone, morphine, hydropmorphine, or tramadol | Oral opioids as tolerated | Do not use |
| Opioids, IV | Do not use | Morphine/hydromorphone as needed or PCA | Morphine/hydromorphone as needed or PCA, possibly low-dose fentanyl infusion | Opioid infusion (eg, fentanyl) |
| Ketamine | Do not use | Infusion or PCA | Infusion or PCA | Infusion |
| NSAIDs and acetaminophen | Oral acetaminophen + NSAID (eg, celecoxib) | IV or PO acetaminophen + IV NSAID (ketorolac or ibuprofen) or PO NSAID (celecoxib or naproxen) | IV acetaminophen + IV NSAID (ketorolac or ibuprofen) | IV acetaminophen |
| Gabapentanoid | Gabapentin or pregabalin | Gabapentin or pregabalin | As tolerated | As tolerated (unlikely utility in severely injured ventilated patients) |
| Lidocaine infusion | Do not use | Do not use | Consider lidocaine infusion | Consider lidocaine infusion |
| $\alpha$2-Adrenergic agonists | Do not use | Clonidine included in regional anesthetic if applicable | Clonidine included in regional anesthetic if applicable | Clonidine included in regional anesthetic if applicable |

IV: intravenous; NSAID: nonsteroidal antiinflammatory drug; PCA: patient-controlled analgesia; PO: per os

venous opioids can be utilized as a continuous infusion, via a patient-controlled device, or as needed. Mild or moderately injured service members who are awake and alert with pain unrelieved by PO medications are ideal candidates for patient-controlled analgesia (PCA). However, severely injured service members who must remain intubated are often managed with continuous rather than as-needed intravenous opioids, along with continuous monitoring. Patients on PCA who exhibit stable vital signs within a given duration of time do not warrant continuous monitoring during subsequent aeromedical evacuation within or out of theater. Close communication between the transport team and the acute pain service is required to determine appropriate monitoring during transport.

Similar analgesic end points to PO opioids can be achieved with a variety of IV agents. Currently, morphine, hydromorphone, and fentanyl comprise the most common IV opioids used in the battlefield environment. Meperidine use is not recommended because it causes accumulation of detrimental metabolites that may lead to seizures. During the early resuscitative phase (initial operating room visits), fentanyl provides an easily titratable profile and a relatively short duration of action when compared to more hydrophilic agents (morphine or hydromorphone). Notably, it may not be possible to administer IV opioids in severely injured service members until hemodynamic stability is achieved. For postoperative analgesia, either morphine or hydromorphone is appropriate, considering

that morphine may need to be switched to another IV opioid if histamine-related side effects or significant renal impairment occur.

**Adverse Events**

In general, opioid-related adverse events are dose dependent, although some side effects persist regardless of dosing. In the acute postinjury period, when a patient is hemodynamically stable, opioid-related oversedation and respiratory depression are the most pertinent adverse events. These effects have led to numerous in-flight events when injured service members require intubation. Naloxone (suggested dosing: 40-$\mu$g increments up to 400 µg) must be readily available during the acute setting and initial transport to avoid unnecessary hypoxia.

Numerous other adverse events are related to opioids in the acute setting, particularly related to the gastrointestinal system. In mild or moderately injured patients who are awake and alert, nausea, vomiting, and constipation are common occurrences. In addition to deemphasizing opioids via a multimodal approach, rescue modalities such as antiemetics and adequate bowel regimens should be instituted early, if needed. Peripheral opioid antagonists such as methylnaltrexone have received much attention in recent years as an additional adjunct in the setting of opioid-accentuated ileus. However, such agents are probably not necessary within the first 24 to 48 hours of care and can be started if necessary in out-of-theater care centers.

In contrast to the adverse events discussed above, in which opioids detrimentally impact other systems, much attention has been paid to opioid-induced hyperalgesia, when opioids accentuate pronociceptive pathways in the acute setting. While usually not a concern within the first 48 hours postinjury, opioid-induced hyperalgesia serves as an example of how a multimodal strategy may indeed impact analgesic quality at further care sites. Although mechanisms are poorly understood, numerous systems are theorized to be involved: central glutamatergic *N*-methyl-D-aspartate (NMDA) activation, genetic dispositions, descending pathway facilitation, and spinal dynorphins.[6] Recent reports have suggested a role of acute opioid administration with hyperalgesic symptoms in the perioperative setting, especially with the use of remifentanil.[7] While conflicting data exists, a multimodal approach involving NMDA antagonists (noted below) has been indicated as a possible prevention tool for acute opioid-induced hyperalgesia.[6] Opioids cannot be realistically avoided, but the phenomenon of opioid-induced hyperalgesia provides further credence to the utility of multimodal regimens.

## NONOPIOID ANALGESICS

### *N*-methyl-D-aspartate Receptor Antagonists

NMDA receptor antagonists are an evolving treatment option in acute pain control. Through excitatory amino acids, the NMDA receptor is thought to play a significant role in acute pain signaling as well as prolonged central sensitization.[8] Although numerous oral agents are available, ketamine, a noncompetitive IV NMDA antagonist, is the most widely used and practical agent in the initial postinjury stages. A dissociative anesthetic, ketamine has a long history of use in the battlefield setting and is increasingly used in subanesthetic doses to provide excellent pain control postoperatively. Ketamine has numerous routes of administration for acute pain control, including PCA, IV infusion, oral dosing, and IV boluses. Ketamine may be used alone as PCA and can also be combined with morphine into an opioid PCA to decrease overall opioid requirements. Although conflicting data exists about its utility in the perioperative setting, a combined morphine/ketamine PCA has demonstrated benefit in patients undergoing thoracotomy and major abdominal surgery.[9–11] Table 20-2 lists suggested dosing.

Ketamine's side effects include nausea, vomiting, dysphoria, excessive secretions/salivation, hallucinations, hypertension, elevated intracranial pressure, and tachycardia. Pretreatment with a benzodiazepine or addition of transdermal scopolamine will minimize incidence of dysphoria and hallucinations. Episodes of nausea and vomiting can be minimized with prophylactic antiemetics. However, side effects of ketamine when used in low doses are not significantly greater than those associated with opioids.[12] In fact, Subramanian et al, in a metaanalysis of perioperative ketamine, reported that the incidence of side effects such as delirium or sedation is equivalent between groups on a PCA alone and groups on ketamine alone.[13] Compared to opioids, ketamine does not cause respiratory depression and in general has much less of a depressant effect on hemodynamics. As mentioned above, ketamine is also opioid sparing and may help avoid long-term postsurgical pain.[14,15] Recent work has suggested that ketamine may also have favorable effects on the incidence of posttraumatic stress disorder.[16] Ketamine's wide therapeutic window in small doses for acute pain control adds safety benefits, especially in wounded personnel during transport in the field, which often requires larger doses of opioids.

**TABLE 20-2**

**SUGGESTED DOSES OF KETAMINE FOR ACUTE PAIN CONTROL**

| Administration | Steps |
| --- | --- |
| Infusion | 1. Premedicate with benzodiazepine or scopalamine patch.<br>2. Bolus: 0.2–0.5 mg/kg over 30–60 minutes.<br>3. Begin fusion at 0.05–0.3 mg/kg/hr.<br>4. Titrate to clinical effect.<br>5. Observe for side effects (nausea, dysphoria, hallucination, excess secretions) and decrease infusion rate if present. |
| PCA (without opioid) | 1. Initiate PCA at 4–6 mg every 10 minutes<br>2. Adjust bolus and interval as necessary.<br>3. Use caution if doses exceed 0.5 mg/kg/hr due to high incidence of side effects. |

PCA: patient-controlled analgesia

Other agents including magnesium have also been studied in regard to perioperative pain management. Magnesium forms a "plug" within the NMDA receptor, effectively acting as an antagonist. Under physiologic conditions, binding of an agonist and cellular depolarization are required to displace magnesium from the NMDA receptor. IV magnesium has been studied in the setting of abdominal, cardiac, and orthopedic surgery. The data is conflicting, but the predominance of studies demonstrate an improvement in pain scores as well as an opioid-sparing effect.[17] Although rarely used in austere environments, magnesium warrants further study in battlefield-injured service members.

It has been suggested that memantine, an oral NMDA antagonist, may have a significant analgesic benefit in the perioperative period. However, convincing data is scarce, with a lack of strong prospective study designs. Further investigations are indeed warranted into its use in acute pain.

**Nonsteroidal Antiinflammatory Drugs**

NSAIDs are key adjuncts in multimodal acute pain management. NSAIDs are versatile and available in multiple formulations including IV, oral, and topical. Their lack of respiratory and hemodynamic side effects make them valuable for use in the field. Although weak analgesics, NSAIDs add effective synergy to opioids and other classes of analgesics. Unless an absolute contraindication is present, NSAIDS should be administered around the clock for all battlefield-related injuries.

The majority of NSAIDs exert their action by antagonism of cyclooxygenase (COX) 1 and/or 2, affecting prostaglandin synthesis. Older NSAIDs exert nonselective COX inhibition, resulting in possible antithrombotic and gastric side effects. Newer COX-2 inhibitors are more selective, with reduced gastric side effects and no antiplatelet effects. COX inhibitors including ketorolac and ibuprofen are available in IV form that increases their utility in trauma medicine. However, in patients who are awake, alert, and tolerating PO medication, any of the available COX-2 inhibitors or oral ibuprofen or diclofenac are appropriate.

NSAIDs have a long history of success in the perioperative realm, especially in the orthopedic and abdominal surgery literature.[18] These NSAIDs serve as opioid-sparing agents and display no clinically significant increase in bleeding.[19] However, for critically battlefield-injured personnel (bilateral amputation, head trauma, etc), withholding NSAIDs until hemorrhage is adequately controlled and renal concerns are minimal is the best course of treatment.

**Acetaminophen**

Acetaminophen exerts its effects by unknown mechanisms; however, it is suspected to act on both central and peripheral pain pathways. Unlike NSAIDs, acetaminophen is devoid of antithrombotic and gastric side effects. Acetaminophen has a longstanding history of opioid-sparing qualities in the perioperative setting.[20,21] Combination with an NSAID leads to synergistic analgesia when compared to either agent alone. While an IV formulation (paracetamol) has been available in Europe for many years, IV acetaminophen has only recently become available within the United States. While either PO or IV routes are appropriate, IV routes serve as a useful adjunct in severely injured battlefield patients. Unless severe liver dysfunction is present, all patients requiring analgesic therapy should receive a derivative of acetaminophen in the

acute phase of treatment and throughout transport.

Acetaminophen has an excellent safety profile; toxicity is very rare when dosing guidelines are followed. Liver toxicity secondary to the metabolite *N*-acetyl-P-benzoquinine imine (NAPQI) has been associated with large doses. Currently, no more than 4 g per day should be utilized.

## Anticonvulsants

Anticonvulsant agents such as gabapentin and pregabalin have been studied in numerous settings to determine their perioperative analgesic benefit. Both agents act via presynaptic antagonism of the alpha-2-delta subunit of dorsal horn calcium channels, which become excessively active during various levels of nociception.

Numerous trials have demonstrated an analgesic benefit predominantly in the form of opioid sparing and improved pain scores.[22–24] However, there is conflicting data about decreased postoperative nausea and vomiting and opioid side effects with use of these anticonvulsants[25,26]; notably, trials have documented early increased sedation and dizziness with both agents.[24] Further controlled trials are needed to determine the long-term benefit of such agents, although recent investigations in patients undergoing total knee arthroplasty have suggested a lasting effect of decreased neuropathic pain when such agents are extended beyond the immediate postoperative period.[2]

Although both agents have shown some perioperative benefit, pregabalin demonstrates a more favorable pharmacodynamic profile with greater bioavailability, linear pharmacokinetics, and a faster achievement of therapeutic levels. Dosing regimens vary, but in general gabapentin may be administered as a 600-mg preoperative dose followed by 300 mg three times a day. For pregabalin, a 300-mg preoperative dose may be given followed by 150 mg twice a day in the postoperative period. Common side effects include dizziness, sedation, and possibly edema.

In a battlefield setting, gabapentin and pregabalin can be utilized in patients who are tolerating PO intake. Gabapentin can also be administered as a liquid via nasogastric tube in patients who cannot swallow. In mildly and moderately injured patients, either agent can be used preoperatively and continued during transport in awake and alert patients as a means to spare opioid usage. However, in critically injured patients, such agents probably offer little noticeable benefit and can be held until gut function has returned and full resuscitation has occurred.

## $\alpha_2$-Adrenergic Agonists

$\alpha_2$-Adrenergic agonists have a long history of analgesic utility in various perioperative regimens. While the major site of action is via spinal pain modulation, $\alpha_2$ agonists such as clonidine or dexmedetomidine have a complex array of analgesic mechanisms including norepinephrine regulation in the locus cereleus (facilitating descending inhibitory signals), peripheral interaction with afferent neurons, and regulation with nonadrenergic spinal neurotransmitters (acetylcholine, $\gamma$-aminobutyric acid [GABA]) that also modulate pain at the level of the spinal cord.[5]

While clonidine (particularly epidural or intrathecal) and dexmedetomidine have demonstrated opioid sparing qualities, their notable side effects of hypotension and bradycardia severely limit their utility in an austere environment. Even in mildly to moderately injured patients who are hemodynamically stable, their utility probably does not outweigh the risk of their common side effects during forthcoming transport where resources and monitoring is limited. However, peripheral use in the form of extending regional anesthetic blocks is a reasonable use of clonidine.[27] Dexmedetomidine has not been studied in a prospective manner to comment on the safety of its use in peripheral regional anesthetics. Doses for nonopioid analgesics are summarized in Table 20-3.

## LOCAL ANESTHETICS

IV lidocaine has potential as an adjunct in acute pain therapy. Numerous studies have shown additional utility for pain control with lidocaine versus local anesthesia alone. IV lidocaine has demonstrated antiinflammatory, opioid-sparing, and analgesic properties.[28–30] These benefits could be particularly useful in the severely injured casualty, such as a double amputee, whose coagulation status contraindicates regional anesthesia. Side effects, while uncommon, include tongue or perioral numbness, tinnitus, restlessness, vertigo, concentration deficits, slurred speech, muscle twitching, seizures, respiratory depression, and cardiovascular depression. Patients treated with lidocaine infusions should therefore be continuously monitored.

A recommended regimen for a lidocaine infusion is to start with an initial bolus of 1 to 1.5 mg/kg and initiate continuous infusion of 1.25 to 1.5 mg/kg/hr.

**TABLE 20-3**

**NONOPIOID ANALGESICS FOR ACUTE BATTLEFIED PAIN MANAGEMENT**

| Medication | PO | IV | Comments |
|---|---|---|---|
| **Aniline Derivative** | | | |
| Acetaminophen | 1 g every 6 hours | 325 mg–1g every 4–6 hour | Maximum dose: 4 g/24 hours. No gastric or antiplatelet effects. Hepatotoxic in large doses |
| **NSAIDs** | | | |
| Ketorolac | N/A | 30 mg, then 15–30 mg every 6 hours | |
| Ibuprofen | 400–800 mg every 8 hours | 400–800 mg every 6 hours | Maximum dose: 3,200 mg/day |
| Diclofenac | 50 mg three times daily | N/A | Maximum dose: 200 mg/day for first day, then 150 mg/day thereafter |
| Meloxicam | 7.5–15 mg daily | N/A | Maximum dose: 15 mg/day |
| Celecoxib | 100–200 mg daily | N/A | Selective for COX 2 |
| Naproxen | 250–500 mg every 12 hours | N/A | Maximum dose: 1,100 mg/day |
| **Anticonvulsants** | | | |
| Gabapentin | 100–300 mg every 8 hours. Titrate as needed to maximum dose of 1,200 mg three times daily. | N/A | Optional 600 mg loading dose prior to start of therapy |
| Pregabalin | 75–150 mg every 12 hours. Titrate to maximum dose of 300 mg twice daily. | N/A | Optional 300 mg loading dose prior to start of therapy |
| **$\alpha_2$-Adrenergic Agonists** | | | |
| Clonidine | 0.1 mg loading oral dose following by transdermal patch (not applicable within first 24–48 hours postinjury) | 0.3–1 $\mu$g/kg bolus | Severely limited by hypotension and bradycardia in acute battlefield setting. Peripheral nerve block dose: 0.5–1 $\mu$g/kg in local anesthesia |
| Dexmedetomidine | N/A | Load dose: 0.5–1 $\mu$g/kg over 10–20 minutes (if tolerated). Infusion: 0.2–0.7 $\mu$g/kg/h | Limited by bradycardia and hypotension |
| **Local Anesthetics** | | | |
| Lidocaine | N/A | Bolus: 1–1.5 mg/kg followed by infusion of 1.25–1.5 mg/kg/h. | Possible option for noninterventional candidate (lack of access, coagulopathy, etc) |

COX: cyclooxygenase; N/A: not applicable; NSAID: nonsteroidal antiinflammatory drug

**SUMMARY**

A multimodal strategy is essential early in the analgesic treatment of wounded soldiers. Opioids are no longer considered the sole agents of analgesia, as evident in clinically significant adverse events and the possibility that they worsen pain. Each patient's analgesic regimen is stratified based on injury sever-

ity (see Table 20-1), and such a multimodal approach should be continued throughout transport. Although pharmacologic modalities are only a portion of analgesic regimens, expertise in their pharmacokinetics and pharmacodynamics is essential in the setting of polypharmacy. Daily attention is required to monitor for analgesic benefit as well as side effects. However, almost all data about the use of this strategy comes from civilian nontraumatic literature, and further prospective trials are needed among injured service members.

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