Pain management in the intensive care unit

Arunee Motes MD

Abstract

Critically ill patients often experience pain from an underlying illness or injury, a recent surgical or other invasive procedure, or various interventions in the intensive care unit (ICU), e.g., endotracheal intubation, vascular access devices, nasogastric tubes, urinary catheters, mechanical ventilation, and routine nursing care, such as repositioning. Opioids remain the mainstay medication for pain control in the ICU; however, they can have adverse effects, including over-sedation, respiratory depression, opioid-induced constipation, opioid dependence and withdrawal, which result in increased length of ICU/hospital stay, health care costs, morbidity, and mortality. In this review, we summarize the mechanism of action, usual doses, side effects, recent studies of opioids that are frequently used in adult ICUs, and pain assessment tools for monitoring pain in adult ICU patients.

Keywords: analgesia, opioids, intensive care unit, pain assessment tools

Introduction

Continuous intravenous (IV) sedative and analgesic drugs (especially opioids) infusions are often used in critically ill patients. Avoidance of noxious stimuli may not be possible for ICU patients, but adequate pain control can decrease the potential for the development of chronic pain syndromes and control anxiety and agitation, especially in intubated patients.[1]

The primary goal of pain control in the ICU is to provide comfort for patients. This goal is specific to each patient and depends upon the clinical condition, the individual patient's threshold of pain, and adverse effects of analgesic medications. The secondary goals include attenuation of adverse physiologic responses to pain (e.g., hypermetabolism, increased oxygen consumption, hypercoagulability, and alterations in immune function) [2] and prevention of the development of chronic pain syndromes. Inadequate control of acute pain can lead to changes in the central and peripheral nervous systems that result in the subsequent development of chronic pain.[3]

Analgesia should be adjusted to the needs of the individual patient. Underestimation and undertreatment of pain are common in the ICU. It is always challenging to assess pain control in the ICU, particularly in intubated and sedated patients or comatose patients. To optimize analgesic drug use in the ICU, reliable pain assessment tools should be used to monitor pain and titrate analgesia accordingly.[4]

Corresponding author: **Arunee Motes**
Contact Information: Arunee.Motes@ttuhsc.edu
DOI: 10.12746/swrccc.v11i46.1133

Opioids

Mechanisms of Action

Opioids bind to specific receptors located throughout the central nervous system, peripheral nervous systems, gastrointestinal tract, and other tissues. In the central nervous system, opioids have effects in many areas, including the spinal cord. In the peripheral nervous system, the action of opioids in both the myenteric plexus and submucous plexus is responsible for opioid-induced constipation. In peripheral tissues, such as joints, opioids act to reduce inflammation.

Opioid drugs produce analgesic effects by actions at several levels of the nervous system, in particular, inhibition of neurotransmitter release from the primary afferent terminals in the spinal cord and activation of descending inhibitory controls in the midbrain. Three major types of opioid receptor include mu (μ, with subtypes μ1 and μ2), kappa (κ), and delta (δ). All opioid receptors couple to G proteins; the binding of an agonist to an opioid receptor typically causes membrane hyperpolarization. The mechanisms of opioid action probably involve the inhibition of inhibit neurotransmitter release by inhibiting calcium entry, by enhancing outward movement of potassium ions, and by inhibiting adenylate cyclase (AC), the enzyme which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP).

Opioid effects vary based on the duration of exposure, and opioid tolerance leads to changes in opioid responses. Tolerance and dependence are induced by chronic exposure. Tolerance is due primarily to receptor desensitization induced by functional uncoupling of opioid receptors from G-proteins. Dependence usually accompanies tolerance; however, dependence is obscured until the opioid drug is removed from its receptors, either by stopping the drug or by giving an opioid receptor antagonist such as naloxone. A withdrawal response then occurs. Dependence occurs much more rapidly than tolerance, and naloxone-precipitated withdrawal can be seen after a single dose of morphine in humans. Adenylate cyclase has long been implicated in opioid withdrawal and increased adenylate cyclase activity following chronic morphine treatment has been observed in the locus coeruleus, a central noradrenergic cell group that has a major role in opioid withdrawal.[5]

Morphine

Morphine is the prototypical opioid and is the standard against which other opioids are tested. It is used mainly for pain control but is also commonly used recreationally or to make other illicit opioids. Multiple methods are used to administer morphine; these include oral preparations, sublingual preparations, inhaled solutions, injections into muscle and skin, intravenous injection or infusions, injection into the space around the spinal cord, transdermal patches, and rectal suppositories. Morphine provides analgesia with non-CYP metabolism (glucuronidation), which may be an advantage for selected patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. It is an alternative to fentanyl or hydromorphone where preload reduction and myocardial depressive effects are desirable or tolerable. Dose adjustment and gradual titration are needed for patients with renal and/or hepatic impairment. It should be avoided in patients with advanced or decompensated liver disease with renal impairment due to risk of accumulation of neurotoxic metabolites. Infusions are not generally used for sedation or analgesia in the ICU but are more commonly used for palliative purposes. The onset of action is 5 to 10 minutes.

Usual doses

Loading dose is 2 to 10 mg IV; maintenance dose is 2 to 4 mg IV every 1 to 2 hours intermittent and/or 2 to 30 mg/hour infusion.

Side effects

Morphine can accumulate in hepatic or renal dysfunction and prolong effects or increase risk of adverse effects. One of morphine's metabolites, morphone-3-glucuronide can induce myoclonus and seizures at high doses. Histamine release and vagally mediated venodilation, hypotension, and bradycardia can be significant.

Fentanyl

Fentanyl is a synthetic opioid in the phenylpiperidine family. It is a potent analgesic-sedative with immediate onset. Some fentanyl analogues, such as carfentanil, are up to 10,000 times stronger than morphine. Fentanyl causes less hypotension than other opioid analgesic drugs due to relative lack of histamine release. It is a good analgesia for most critically ill patients. It is metabolized hepatically by cytochrome P450-3A4 (CYP3A4) to inactive metabolites. It is highly lipophilic and leads to accumulation in adipose and other tissue with repeated or prolonged

administration. Chest wall rigidity may occur with higher dosing. Onset of action is <1 to 2 minutes.

Usual doses

Loading dose is 1 to 2 mcg/kg IV (25 to 100 mcg); maintenance dose is 0.35 to 0.5 mcg/kg IV every 0.5 to 1 hour intermittent (25 to 50 mcg) and/or 0.7 to 10 mcg/kg/hour infusion (50 to 700 mcg/hour). For most patients, 1 to 3 mcg/kg/hour infusion (50 to 200 mcg/hour) with as-needed intermittent bolus doses is sufficient.

Side effects

The most common side effects of fentanyl include nausea, vomiting, constipation, dry mouth, somnolence, confusion, and asthenia (weakness). Less frequently, fentanyl can cause abdominal pain, headache, fatigue, anorexia and weight loss, dizziness, nervousness, anxiety, depression, flu-like symptoms, dyspepsia, shortness of breath, hypoventilation, apnea, and urinary retention. Compared to morphine, fentanyl tends to cause less nausea, and less histamine-mediated itching.

The most dangerous adverse effect of fentanyl is respiratory depression, i.e., decreased sensitivity to carbon dioxide leading to reduced rate of breathing, which can cause anoxic brain injury or death. This risk is decreased when the airway is secured with an endotracheal tube (as during anesthesia). This risk is higher in specific groups, like patients with obstructive sleep apnea.

Recent studies

A cluster-randomized, cluster-crossover trial between July 2019 and August 2020 in two adult ICUs included 681 ICU patients, compared two continuous infusion regimens (fentanyl versus morphine), and found that among adult patients requiring mechanical ventilation, compared with morphine, fentanyl infusion significantly increased the median number of ventilator-free days at Day 28. The number of ICU-free days was higher, and the length of ICU stay in survivors was shorter.[6]

Hydromorphone

Hydromorphone is a semi-synthetic μ-opioid agonist, also known as dihydromorphinone. It is an analgesic option alternative to fentanyl or morphine used to treat moderate to severe pain. It is available in parenteral, rectal, subcutaneous, and oral formulations, and can also be administered via epidural or intrathecal injection. It also has been administered via nebulization to treat shortness of breath, but it is not used as a route for pain control due to low bioavailability. Transdermal delivery systems are also under consideration to induce local skin analgesia.

On a per milligram basis, hydromorphone is five times more potent than morphine, although the conversion ratio may vary from 4–8 times. Intravenous administration requires small volumes relative to other opioids. Non-CYP metabolism (glucuronidation) may be an advantage for patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. The onset of action for hydromorphone administered intravenously is less than 5 minutes and within 30 minutes of oral administration (immediate release).

In patients with renal impairment, the half-life of hydromorphone may increase to as much as 40 hours. The typical half-life of intravenous hydromorphone is 2.3 hours. Peak plasma levels usually occur between 30 and 60 minutes after oral dosing. Dose adjustment and gradual titration is needed for patients with renal and/or hepatic impairment.

Usual doses

Loading dose is 0.5 to 2 mg IV; maintenance dose is 0.2 to 0.6 mg IV every 1to 2 hours intermittent and/or 0.5 to 3 mg/hour infusion.

Side effects

Common side effects include lightheadedness, dizziness, sedation, itching, constipation, nausea, vomiting, headache, perspiration, and hallucinations. The major adverse effects include dose-related respiratory depression, urinary retention, bronchospasm, and

Figure 1. Visual Analog Scale (VAS).

occasional circulatory depression. Hydromorphone produces potentially neurotoxic metabolites that may accumulate in hepatic and/or renal dysfunction.

Recent studies

In a retrospective cohort study in August 2021, 177 patients were divided according to receipt of fentanyl or hydromorphone as a continuous infusion as a sedative agent. The primary study outcomes were ICU length of stay and time on mechanical ventilation. No statistically significant differences were found in the primary outcomes studied. Patients in the hydromorphone group required more tracheostomies and restraints, and were more likely to have a higher proportion of Critical Care Pain Observation Tool (CPOT) scores >2.[7]

Pain monitoring

According to the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit published in the *Society of Critical Care Medicine 2013,* routine pain monitoring in all adult ICU patients is recommended.[8]

For patients who can communicate, pain assessment tools include the continuous visual analog scale (VAS) (Figure 1), in which the patient makes a mark on a 10 cm line that corresponds to the intensity of pain. The distance from the "no pain" end of the line to the mark is measured and recorded as the score, the numeric rating scale (NRS) (Figure 2) in which the

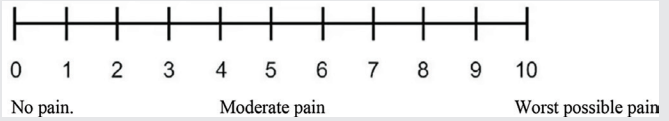

Figure 2. Numeric Rating Scale (NRS).

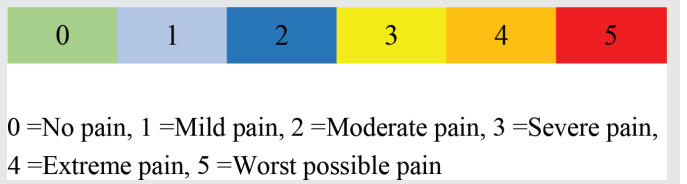

Figure 3. Verbal Rating Scale (VRS).

patient selects a discrete number on the line between 0 and 10, and the verbal rating scale (VRS) (Figure 3) in which the patient can choose a word or phrase describing increasing pain intensity. Each of these scales is valid and generally reliable.[9]

For semiconscious or noncommunicative patients who cannot participate in the assessment, the Behavioral Pain Scale (BPS) (Table 1) and the Critical-Care Pain Observation Tool (CPOT) (Table 2) are the most valid and reliable behavioral pain scales for monitoring pain in medical, postoperative, or trauma (except for brain injury) adult ICU patients who are unable to self-report and in whom motor function is intact and behaviors are observable.[8]

Either enterally administered gabapentin or carbamazepine, in addition to IV opioids, should be

Table 1. Behavioral Pain Scale (BPS)

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with fingers flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting ventilator	3
	Unable to control ventilation	4

Table 2. Critical Care Pain Observation Tool (CPOT)

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2

considered for treatment of neuropathic pain are recommended.

Article citation: Motes A. Pain management in the intensive care unit. The Southwest Respiratory and Critical Care Chronicles 2023;11(46):1–6
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas
Submitted: 11/25/2022
Accepted: 12/12/2022
Conflicts of interest: none

References

1. Barr J, Pandharipande PP. The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. Crit Care Med. 2013;41:S99.
2. Lewis KS, Whipple JK, Michael KA, et al. Effect of analgesic treatment on the physiological consequences of acute pain. Am J Hosp Pharm. 1994;51:1539.
3. Hayhurst CJ, Jackson JC, Archer KR, et al. Pain and its long-term interference of daily life after critical illness. Anesth Analg. 2018;127:690.
4. Gommers D, Bakker J. Medications for analgesia and sedation in the intensive care unit: an overview. Crit Care. 2008; 12(Suppl 3):S4. doi: 10.1186/cc6150.

5. Chahl LA. Opioids-mechanisms of action. Aust Prescr. 1996; 19:63–5. https://doi.org/10.18773/austprescr.1996.063.
6. Casamento AJ, Serpa Neto A, Young M, et al. A phase II cluster-crossover randomized trial of fentanyl versus morphine for analgosedation in mechanically ventilated patients. Am J Respir Crit Care Med. 2021 Dec 1;204(11):1286–1294. doi: 10.1164/rccm.202106-1515OC.
7. Choi H, Radparvar S, Aitken SL, et al. The use of fentanyl compared to hydromorphone. J Crit Care Med (Targu Mures). 2021 Aug 5;7(3):192–198. doi: 10.2478/jccm-2021-0026.
8. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013 Jan;41(1):263–306. doi: 10.1097/CCM.0b013e3182783b72.
9. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46: e825.