

ANALGESIA AND ANESTHESIA OF THE CRITICAL OR EMERGENT PATIENT

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Although we may not be able to prevent all of our patients from dying, we can make sure that we alleviate their pain and suffering. Acute pain may originate from surgical or post-traumatic wounds and injuries, the use of invasive monitoring devices, mechanical ventilation, prolonged immobilization and nursing care procedures. The primary goal is to ensure patient comfort while preventing overmedication and its attendant complications. Unfortunately, pain is often undertreated because of concerns about adverse effects. However, it should be kept in mind that unrelieved pain contributes to patient distress, evokes a stress response, complicates the management of life-saving devices, and may negatively affect outcome. With increasing knowledge of pain physiology and its detrimental influences on the patient (sympathetic stimulation, atelectasis, hypoxemia, immunosuppression, catabolism, arrhythmias, ileus, etc), analgesia therapy should not be considered elective therapy. Adequate analgesia promotes normal respiratory function and allows for appropriate expectoration, modulates the stress response, and promotes hemodynamic stability, these in turn help prevent complications, while reducing the utilization of patient resources.

Pain assessment needs to be performed regularly and consistently in the ICU setting to ensure that the analgesic regimen is adequate and appropriate. This includes evaluation of sympathetic physical manifestations and behavioral changes (see table 1) of the patient. However, critically ill patients may not display overt clinical signs. In addition, these signs are relatively nonspecific in the ICU patient who may have fever, anxiety, or physiologic dysfunction that is unrelated to pain, yet manifests similar signs. Therefore, pain must be assumed if the patient has clinical entities that are associated with pain (inflammation, injuries, organ distension, diagnostics or therapeutic procedures, immobilization or thrombosis). Other variables that are painful in and of themselves, but may potentiate patient stress and possibly pain, include absence of familiar surroundings and companionship, strange odors, loud noises (vacuums, slamming cages doors), and bright lights.

Pain may be difficult to control with use of a single agent, especially if its onset did not lend itself to preemptive treatment, thus necessitating combination therapy. Combination therapy, referred to as multimodal analgesia, allows the clinician to manage pain through more than one of the four major mechanisms (transduction, transmission, modulation and perception) responsible for the sensation of pain. While the term “polypharmacy” often has negative connotations, combining sedatives and analgesics, can be logical and beneficial for the patient.

The administration of analgesics may be provided as a “therapeutic trial” to further identify if clinical signs are related to pain. Analgesics may be administered systemically (intravenous [IV], intramuscular [IM], subcutaneous [SQ], transmucosal, oral, or transdermal), or regionally (epidural, local infiltration, intraperitoneal, or intraarticular). In general, the preferred route for systemic administration in the critically ill is IV, which eliminates the concern for possible altered absorption from a deposit of medication. Secondary routes in order of preference are IM, SQ, transmucosal and lastly transdermal. Obviously each medication has its own limitations based on drug approval, as well as its pharmacokinetics.

OPIOIDS

Opioids are the backbone of analgesic therapy in the moderate to severely painful critically ill patients, however, they are not amnestic agents. Opioids bind to a variable degree with various opioid receptor subtypes (μ , δ , κ) located in the brain, spinal cord and peripheral sites and modulate the transmission (peripheral and spinal receptors) and processing (brain receptors) of nociceptive signals. Opioids are typically classified as pure agonists, partial agonists, agonist-antagonist or full antagonists. Although GI absorption tends to be rapid, the oral bioavailability of many opioids is limited by extensive first-pass hepatic metabolism. Opioids are metabolized by the liver to metabolites with greater (morphine) or lesser activity than the parent compound which are commonly renally excreted, therefore, possibly necessitating dosage adjustment in hepatic or renal patients. However, not all opioids (hydromorphone) have intermediary metabolites. Pure μ -agonists (fentanyl, hydromorphone, meperidine, methadone, morphine, oxycodone) are typically administered with standard dosages and frequency. While intermittent IV injections provide great analgesia, they pose a risk of heavy sedation immediately following the

Table 1. Clinical signs that a painful animal may display

Physical manifestations
Tachycardia
Tachypnea
Mydriasis
Elevated blood pressure
Behavioral changes
Posturing
Protecting, licking or self-mutilating areas
Inactivity or restlessness
Anorexia
Unexplained aggression
Vocalizing
Trembling
Splinting
Lack of grooming
Anxiety
Apprehension

injection and break through pain just before the next dose. The preferred method of intermittent injections is to titrate small incremental dosages until a satisfactory level of analgesia is achieved. Constant or continuous rate infusions (CRIs) minimize these peak and trough effects. Infusion rates may be increased or decreased as needed to achieve the optimal analgesia. An analgesic end-point in cats is the development of mydriasis. Pure μ -agonists are characterized by rapid onset, dose-dependent analgesia, but also dose-dependent side effects (vomiting, respiratory depression, bradycardia, hypotension, ileus, gastroparesis and urine retention). Vomiting and dysphoria are infrequently experienced in dogs that are already painful. The heightened concern of respiratory depression is a reflection of experience in human medicine. This concern has been overstated and has been an infrequently documented complication in the majority of veterinary patients when pure μ -agonists are used at recommended dosages. Respiratory depression is a concern, however, in patients with primary CNS disease. Increases in intracranial pressure may occur secondary to hypoventilation-induced hypercapnia and secondary cerebral vasodilation. Bradycardia is also uncommon unless the patient is predisposed to it already from other drugs or disorders. Bradycardia is readily reversed with the administration of atropine. Hypotension is primarily a concern in patients that are hypovolemic and is typically readily treated with IV fluids. Morphine and meperidine have the added side effects of histamine release, causing a dose-dependent vasodilation, possibly precipitating hypotension. Enteral administration of minimally absorbed opioid antagonists (ie. naloxone) may help prevent opioid-related ileus and constipation. Promising results have been observed with oral naloxone in small preliminary studies. Urine retention occasionally warrants passage of a urinary catheter. Decreased urine production may occur through an increase in ADH release. Hypothermia, after opioid-induced "resetting" of the thermoregulatory center, develops secondary to panting, which may be undesirable. Hyperthermia is more common in other species (cats). Some opioids are centrally acting antitussives (dogs), which may be not desirable in some patients. Reversal of pure μ -agonists side effects is generally performed by slow infusion of dilute naloxone IV. Rapid infusion predisposes the patient to complete reversal, possibly leading to severe onset of pain. Partial reversal may be achieved by the administration of butorphanol. Duration of action of morphine (short-term) and hydromorphone (intermediate acting) is generally 2-4 hours and 4-6 hours, respectively. Although fentanyl has the least negative cardiovascular influences, its ultra-short duration of action (about 20-30 minutes) lends itself to administration via CRI.

The partial μ -agonist, buprenorphine, primarily is used for moderate pain and has a prolonged duration of action (6-12 hours). The duration of action is explained by its high affinity for the μ -receptor, which also prevents it from being readily reversible with naloxone. This high affinity also causes buprenorphine to antagonize the analgesic benefits of pure μ -agonists. Slow onset of action (up to 20 minutes IV and 40 minutes following SQ or IM administration) may limit its use in the acutely painful patient. Variable transmucosal absorption occurs.

Butorphanol is a k -agonist and μ -antagonist (referred to as a mixed agonist/antagonist). Butorphanol is most commonly used to treat mild to moderate pain. It is characterized by a low therapeutic ceiling which limits its therapeutic efficacy, but this also limits its respiratory and cardiovascular side effects. Butorphanol is reversible with naloxone. While common teaching is that butorphanol will antagonize the analgesia provided by pure μ -agonists, others feel that low doses of butorphanol may be used simultaneously with pure μ -agonists to enhance analgesia.

NSAIDS

Non-steroidal anti-inflammatories are commonly used to help manage pain because of the substantial role that inflammation plays in the pain process. However, NSAIDs should be used cautiously in those with existing or recent hypovolemia or hypotension, and those with renal, hepatic or gastrointestinal (GI) disease. Each of the aforementioned conditions places the patient at higher risk for GI ulceration and renal insufficiency. Dosage adjustments are also encouraged in those patients with hypoalbuminemia, due to the high protein binding of all currently approved NSAIDs in veterinary medicine. Some veterinary approved NSAIDs are available in an injectable form and is preferred if GI motility or tolerance is uncertain. Concomitant administration of NSAIDs with food helps reduce the incidence of nausea and possibly gastric ulceration. NSAIDs generally provide analgesia for a more extended duration than most other classes of analgesics and provide a combined therapeutic effect when used simultaneously with opioids. Although post-operative, first dose administration of NSAIDs may not fulfill the theoretical advantages of preemptive analgesia, it does allow one to avoid the added risk that an all too common, anesthesia-induced hypotensive event plays in the critically ill patient. The most common adverse effects include nausea, vomiting, GI bleeding, inhibition of platelet function, and renal insufficiency.

NMDA ANTAGONIST

Ketamine is a dissociative anesthetic that also acts as a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist. Subanesthetic doses of ketamine are typically utilized if the clinician is interested in the NMDA antagonist activity only, and helps prevent wind-up activity and central sensitization. Intermittent bolus doses range

from 0.1 – 1.0 mg/kg IV, but may also be provided by a CRI at 2 ug/kg/min. Ketamine is also absorbed transmucosally for chronic use, primarily utilized to provide pain relief following burn injuries or to provide additional analgesia in orthopedic surgeries. Ketamine increases sympathetic tone in the general population, but may act as a direct myocardial depressant in patients that are sympathetically exhausted. Ketamine maintains laryngeal protective reflexes and produces less ventilatory depression compared to opioids.

LOCAL ANESTHETICS

Local anesthetics commonly used in veterinary medicine are currently limited to lidocaine and bupivacaine. These may be infiltrated into local tissues, or administered regionally through specific nerve or nerve plexus blockade, intraarticularly, intrapleurally or intercostally. A major advantage of these agents is that they provide analgesia without sedation or respiratory depression. These agents are acidic and may cause pain during injection. This pain experienced may be minimized by warming the solution to body temperature prior to administration and by adding 10% of the volume as sodium bicarbonate for lidocaine or 5% of the volume for bupivacaine. Dilution of these agents may limit toxicity while providing an adequate volume to achieve full regional anesthesia. Lidocaine has a more rapid onset of action of < 2 minutes and a short duration of action (1-2 hours) compared to bupivacaine which has an onset of action of about 20 minutes and a longer duration of action of 4-6 hours. Lidocaine may be administered as a CRI at a dose of 1 mg/kg/hr for supplemental analgesia. Intrathoracic bupivacaine administration is contraindicated in the absence of an intact pericardium, as it may cause acute myocardial toxicity.

ALPHA₂-AGONISTS

The α_2 -agonists, xylazine, medetomidine, and dexmedetomidine bind to receptors in the CNS and peripherally to produce profound sedation, analgesia and muscle relaxation. Significant cardiorespiratory depression may occur at clinically recommended doses. Generally, only low dose administration is sparingly utilized in critically ill patients. A decrease in blood pressure (due to severe bradycardia) and hypoventilation are common side effects with these agents. Additional adverse effects include the potential for vomiting, mild diuresis and increased sensitivity to sound.

NONPHARMACOLOGIC INTERVENTIONS

Patient care procedures that should always be tried first to help alleviate pain include proper positioning of the patient with periodic turning and sufficient bedding (towels, bubble wrap, etc), as well as wound stabilization (fractures, etc). Further measures that may help reduce stress include affection, brushing, petting, keeping the patient clean and dry, giving feline patients a place to hide or allowing dogs to feel like they are a part of the activity, in addition to owner visits.

SEDATIVES

Benzodiazepine medications are centrally acting muscle relaxants with minimal cardiorespiratory depression. These agents are short term anxiolytics that do not have direct analgesic benefits, but may help improve the level of analgesia provided by other analgesics. When combined with opioids that produce neuroleptanalgesia or with ketamine to produce short-term general anesthesia. Benzodiazepines decrease the dose necessary to induce or maintain anesthesia and are amnesic. If given alone, may cause aggression or severe dysphoria. These agents are generally highly protein bound. Diazepam is solubilized in 40% propylene glycol and general does not mix well with other drugs. It should only be given IV due to pain during IM or SQ injection. Prolonged administrations (hours to days) may produce a delayed recovery due to active metabolites. Midazolam is water soluble and mixes with other water-soluble drugs (opioids, ketamine). This may be given IV, IM or SQ without substantial pain.

Phenothiazine derivatives cause selective arteriodilation at low doses, which may improve cardiac output in some patients. However, they are best avoided in the critically ill as they may lead to refractory hypotension. Phenothiazines also predispose the patient to epinephrine reversal if the situation arises that epinephrine needs to be administered.

EPIDURALS

Epidural administration of analgesic agents appears to provide equally or more effective analgesia than systemic administration, while limiting the systemic adverse effects (respiratory depression, urine retention, nausea, vomiting). Here too opioid use is common. When opioids are administered, its lipid solubility is directly related to its speed of onset, extent of dermatomal spread and duration of effect. Morphine is highly lipophobic and thus has a long onset of action, extended duration of action, and significant dermatomal spread (cephalad migration). This latter property predisposes to adverse effects such as respiratory depression. Fentanyl with is highly lipophilic, with

a rapid onset and short duration of action, has the tendency to stay localized. This latter property may allow for more focal treatment with the use of an epidural catheter. Critically ill patients may benefit from epidural catheter placement, therefore allowing repeated administration of preservative free agents.

Local anesthetics may be used in the epidural space, but they carry added risk of side effects, specifically, hypotension, motor weakness, and inability to ambulate. Epidural administration is contraindicated in patients with coagulopathies or receiving anticoagulant therapy, patients with systemic infections or skin infection over the injection site, or unstable spinal skeletal fractures.

TRANSDERMALS

Use of transdermal fentanyl is limited in the acutely ill patient due to its prolonged onset of action (≥ 12 -24 hours) and unpredictable absorption and effectiveness. Topical local anesthetic creams such as EMLA (which is made of prilocaine and lidocaine) are very useful in preparing for elective procedures. Generally takes 30-60 minutes for adequate local anesthesia. Lidocaine patches are also available for local analgesia.

ANESTHESIA

Providing anesthesia for the critically ill or emergent patient carries with it all of the same considerations of doing so in a stable patient, but also lends itself to additional challenges for the clinician and greater risk for the patient. This increased level of risk to the patient is due to higher incidence of occult problems and/or an increased susceptibility to side effects in a potentially unstable patient. Patient risk may be minimized through administration of appropriate pre-medications, in combination with appropriate anesthetic agent selection, which is referred to as balanced anesthesia. Pre-oxygenation is always preferred. Utilization of an agent that allows rapid sequence intubation is recommended. Promoting a smooth recovery is also ideal to avoid undue stress and risk of injury to the patient.

Propofol is an alkyl phenol classified as a nonbarbiturate, non-narcotic, sedative-hypnotic. It is rapid onset, short duration of action that is non-cumulative. Propofol does not rely on hepatic or renal metabolism, making ideal both hepatic and renal patients. Propofol is suspended in a lipid emulsion that may or may not have a preservative. In addition to being an anti-convulsant, it reduces intracranial pressure. Low end doses required in unstable patients to limit adverse cardiovascular effects (vasodilation and reduced cardiac output). Rapid bolus or large dose administration may produce apnea. Heinz body anemia may occur in cats with repeated administration or CRIs.

Etomidate is a very short acting, imidazole derivative that is classified as a nonbarbiturate, non-narcotic sedative-hypnotic agent. It causes mild respiratory depression and minimal to no cardiovascular effects, even in hypovolemic patients. May cause pain and phlebitis on intravenous injection. Clonic-*seizure like* activity, thought to be due to disinhibition of subcortical neural activity, is greatly reduced with administration of a benzodiazepine. Unfortunately, profound and potentially long-lasting adrenocortical suppression, even after a single injection, limits its use in critically ill patients. Etomidate is rapidly metabolized in the liver and plasma by non-specific esterases.

Ketamine has good musculoskeletal analgesic properties, weak visceral analgesic properties and poor muscle relaxant properties. A dose dependent respiratory depression occurs in addition to its potent bronchodilation. Sympathetic nervous system stimulation exerts a positive chronotropic and inotropic effect, therefore it is contraindicated in cats with hypertrophic cardiomyopathy. Due to increases in cerebral blood flow, ketamine should also be avoided in patients with increased intracranial pressure and in patients at risk for seizures. Increases in intraocular pressures may also be seen after administration. Although classically considered cardiovascular sparing, ketamine acts as a direct myocardial depressant in patients that are sympathetically exhausted. Ketamine is metabolized in the liver in dogs, but is excreted primarily unchanged in the urine in cats.

Inhalant anesthetics commonly used today in veterinary medicine are isoflurane and sevoflurane. These both cause significant dose-dependent decreases in blood pressure and cardiac output. Mask or tank inductions should be avoided since struggling can increase metabolic oxygen requirements and a deep anesthetic plane may be required before orotracheal intubation is successful. Sevoflurane has gained popularity, because of its low blood gas solubility providing the described advantages of rapid induction and speedy recoveries, however, studies are lacking to support its routine use, over isoflurane, in critically ill patients.

Anticholinergics should not be routinely used in critically ill patients because they increase myocardial oxygen consumption by increasing heart rate, may precipitate cardiac arrhythmias, including lowering the threshold for ventricular fibrillation.

REFERENCES

Available Upon Request