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Prescribing Guidelines for Pennsylvania

GUIDELINES FOR SAFE ADMINISTRATION OF LOW-DOSE KETAMINE

Ketamine has been used as an anesthetic agent for decades. In recent years there has been growing interest in the use of low-dose ketamine for the treatment of a variety of conditions, including treatment of acute pain in opioid-tolerant patients, treatment of chronic noncancer pain, treatment of severe depression (including patients who are experiencing suicidal ideation), and in palliative care. The purpose of this document is to provide guidance on the safe use of low-dose ketamine in any treatment setting. This document is not intended to provide guidance on use of ketamine as an anesthetic or for procedural sedation where higher doses of ketamine are often administered, and for which higher levels of monitoring and support are needed.

Low doses of ketamine are those that are not intended to induce moderate to deep sedation or general anesthesia. Clinicians must be vigilant for the effects of concomitant medications that might increase the depth of sedation when low doses of ketamine are administered. There is wide interpatient variability on response to specific doses, but low ketamine doses would generally be infusions of no more than 1 mg/kg/hour or bolus doses of no more than 0.5 mg/kg.

This is not intended to provide guidance on the administration of ketamine by EMS providers, who must adhere to their scope of practice, medication list, and statewide EMS protocols from the Department of Health.

These guidelines are intended to provide best practices related on the safe use of low-dose ketamine. They are intended to help healthcare providers improve patient outcomes and to supplement, but not replace, the individual provider's clinical judgment.

Treatment location

Intravenous ketamine at low doses may be delivered in the inpatient, outpatient, emergency department, and office-based setting as long as the administration location has the equipment and personnel to safely administer the medication.

Except as noted below, the treatment location should have immediate access to the equipment and supplies that may be necessary to treat potentially serious adverse events related to ketamine administration. These include oxygen, bag-valve-mask devices of sizes appropriate to the patient population served, nasal cannula, non-rebreather face masks, nasopharyngeal airways, oropharyngeal airways, and an automated external defibrillator.

Rarely, ketamine infusion in the home setting as part of palliative care at the end of life may be appropriate. The selection and use of patient monitoring and the availability of resuscitation equipment in this setting should be based on patient and family wishes, and treatment goals.

Treatment team

Administration of low-dose ketamine must occur under the direct supervision of a physician or by a certified registered nurse anesthetist (CRNA) who has adequate training and experience to provide this care. Physicians and CRNAs must be aware of and adhere to the regulations, policies and procedures of any practice setting as it pertains to the scope and practice of ketamine administration. The practitioner should be able to demonstrate competency in understanding the basic pharmacology of ketamine, including proper dosing, proper patient selection (including identifying patients requiring a higher level of monitoring), and proper patient monitoring (including identifying and treating adverse effects that include hypoxia, apnea, hypotension, dysphoria, and dysrhythmia). At least one

member of the treatment team that is immediately available must have skills in advanced airway management.

Ketamine administration (infusion initiation and infusion dose changes) may be provided by any licensed practitioner, such as a registered nurse who has competence in administration of low-dose ketamine, under supervision of a physician or a CRNA. Patient monitoring during infusion is to be completed by a licensed practitioner who is trained and credentialed to provide this care, including immediate treatment of emerging adverse effects. There must be adequately trained health care providers immediately available to monitor and respond to adverse events.

Patient selection

It is important to note that patients with complex or life-threating comorbidities may be best cared for in the inpatient setting. Ambulatory and office-based settings are to establish appropriate patient selection criteria that clearly define which patients are eligible to receive ketamine infusions in that specific setting.

Patients with moderate to severe hepatic dysfunction (cirrhosis), high-risk coronary artery disease and poorly controlled psychosis are at increased risk for adverse events following ketamine infusion, and as a result ketamine infusion outside of palliative care for these patient groups are to be limited to the inpatient setting. Clinical trials that enroll patients with cardiovascular, renal, hepatic, psychiatric or neurological diseases who receive low-dose ketamine are still needed to further delineate the safety profile in these patient populations. Additionally, the long-term effects of low-dose ketamine have not been studied in any patient populations, including those with substance use disorders.

Role of ketamine in palliative care

Ketamine has been included in the World Health Organization's list of essential drugs for the treatment of refractory cancer pain. However, a 2017 Cochrane Review of the use of ketamine as an adjuvant to opioids for the treatment of cancer pain reported that current evidence is insufficient to assess the benefits and harms of ketamine use in this setting. Available evidence is of low quality. A recent multi-center, double-blind randomized clinical trial to evaluate the use of a five-day subcutaneous infusion of titrated ketamine verses placebo documented no difference in pain control between the two study groups, but significantly more toxicity in the ketamine arm. Therefore, it appears that use of ketamine in this setting is not associated with improved patient outcomes.

Administration of short-term low-dose ketamine to improve opioid-tolerant cancer pain may be helpful in select patients, but many patients report adverse effects. There have been reports of generalized hyperalgesia and allodynia following sudden discontinuation of a 3-week ketamine infusion.

Role of ketamine in children

There is growing interest in the use of low-dose ketamine for pain management in hospitalized children. Ketamine infusions have been demonstrated to improve pain control and decrease opioid requirements in children, adolescents, and young adults. Ketamine infusions have been administered to children in a variety of settings, including the emergency department for the treatment of sickle cell-related pain, as well as on the hospital floor and in intensive care units. Based on available data, there are no special precautions for the use of low-dose ketamine in the general pediatric and adolescent populations. However, increased monitoring in the specialty setting should be evaluated when considering ketamine infusions in neonates and congenital heart patients.

Ketamine infusion preparation and dosing

The ketamine infusion must be prepared in conformance with state and federal guidelines and regulations. Improper drug preparation is associated with increased risk of life-threatening adverse events. If drug preparation is outsourced, the facility and provider continue to have a responsibility to ensure that the drug to be administered has been prepared and delivered to the facility in a manner that is in conformance with state and federal guidelines and regulations.

The dosing range that constitutes “low-dose” is not consistently defined in the literature. While the package insert for ketamine states that general anesthesia may be induced with a range of 1-4.5 mg/kg (average dose 2 mg/kg), clinical experience has demonstrated that much lower doses may also alter consciousness and cause psychomimetic adverse effects.

In general, bolus dosing should be avoided to reduce the risk of euphoria and psychomimetic effects, particularly in the ambulatory setting. By way of reference, ketamine doses of 0.2-0.5 mg/kg (most commonly 0.3 mg/kg) infused over 10-15 minutes are appropriate for analgesia in the emergency department setting. Ketamine infusion rates of 0.25-0.5 mg/kg/h will produce sufficient analgesia for most pain indications in the acute pain setting for patients being followed by a pain service or critical care team. Treatment of some chronic pain conditions, such as refractory headache or complex regional pain syndrome, may require higher infusion rates to achieve treatment goals. These rates rarely exceed 1 mg/kg/hr. Patients are to regularly be assessed for sedation and asked about psychomimetic adverse effects. Low-dose ketamine infusion rates do not differ between inpatient and outpatient settings.

When ketamine administration in the home or hospice setting is considered, the most commonly studied treatment method for pain management is through a continuous low-dose intravenous or subcutaneous infusion. Administration rates of 0.05 - 0.5 mg/kg/hour have been reported. Subcutaneous or intramuscular absorption is slower than intravenous, but is still extensive, with a bioavailability of 90%.

Patient Monitoring

Ketamine may result in adverse psychomimetic, cardiovascular, hepatic and gastrointestinal adverse effects from its action on several receptors including NMDA, acetylcholine, opioid, monoamine, and histamine. The minimally recommended monitoring for low-dose ketamine administration includes blood pressure, cardiac monitoring/electrocardiogram (EKG), pulse oximetry, and neurological checks which include assessment for level of consciousness. Monitoring is to occur prior to infusion administration, periodically or continuously throughout the infusion, and should not be discontinued until any adverse effects (respiratory, cardiac, neurologic and/or psychometric symptoms) have resolved. The availability of capnography and pulse oximetry is mandatory in the event of respiratory depression requiring an airway intervention to assure adequacy of respiration. Patients with complex health conditions who are considered to be at increased risk for adverse effects may require more frequent and longer duration of monitoring.

Use of Esketamine

In 2019 the Food and Drug Administration (FDA) approved the S-enantiomer of ketamine, esketamine (Spravato), for treatment-resistant depression. The drug is administered as a nasal spray. Patients must be monitored for at least two hours after administration, which must occur in a medical facility. Esketamine has no other approved indications at this time and clinicians are cautioned to avoid "off-label" use as there are no data available to support safety and efficacy for other uses at this time.

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