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TITLE: PROPOFOL, KETAMINE AND MIDAZOLAM USE FOR PALLIATIVE TREATMENT OF PAIN AND SYMPTOM MANAGEMENT ON 2E (OUTSIDE THE CRITICAL CARE UNIT)

PURPOSE:	To delineate the conditions under which Propofol, Ketamine and Midazolam can be used on Nursing Unit 2E for end of life patients experiencing refractory nausea, pain, and agitation.
SCOPE:	RN, Palliative Care Physician/Nurse Practitioner

POLICY:

Propofol, Ketamine, and Midazolam infusion may be used on Nursing Unit 2E by following the procedures listed below. Outside of the ICU setting, use and prescribing of separate Propofol, Ketamine, and Midazolam infusions as an adjunct to pain and other symptom management is restricted to Pain/Palliative Service Physicians/Nurse Practitioner and to patients on their service. These infusions are to be used in patients at or near end of life who have a documented Life Support Note in place.

DEFINITIONS:

Intractable Pain: Intractable pain is defined as a state in which the cause of the pain cannot be removed or otherwise treated with the consent of the patient and in which, in the generally accepted course of medical practice, no relief or cure of the cause of the pain is possible, or none has been found after reasonable efforts.

SE: Side effects

TID: Three times per day

PRN: As needed

PROCEDURE:

A. Propofol, Ketamine and Midazolam infusions will be run on an Alaris Pump using a lock box received from pharmacy and using palliative care profiles with appropriate guardrails in place.

B. Medications will be picked up from pharmacy by the registered nurse or delivered to the unit by Pharmacy.

C. The medications will be signed in on the unit and placed in the secure refrigerated lock box until ready to administer.

D. The Palliative Care Physician or Nurse practitioner will remain at bedside at initiation of treatment to titrate the medications until a therapeutic effect is achieved. Once treatment has been started, the nurse can adjust the dose on the order of a Palliative Care Prescriber. **(RNs DO NOT Titrate)**.

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E. Propofol Infusion

1. **Contraindications:** Potential contraindications to the use of propofol include an allergy to eggs, soybeans, or sulfites.
   a. Propofol is NOT considered first line therapy; therefore, the patient must have failed one or more of the following therapies;
      1) High dosing of benzodiazepines for agitation/severe anxiety
      2) Multiple antiemetics for nausea/vomiting
      3) Multiple anti-seizure meds for seizures
2. **Reason for:** Patient must be experiencing at least one of the following:
   a. Agitation/severe anxiety
   b. Intractable nausea/vomiting
   c. Uncontrolled seizures
3. **Possible side effects**
   a. Deep sedation
   b. Decreased respiratory rate, loss of respiratory drive, apnea
   c. Metabolic acidosis, respiratory acidosis
   d. Hyperlipidemia
   e. Flushing, fever
   f. Headache, dizziness
   g. Rash, puritis
   h. Local pain at injection site
   i. Myalgia
   j. Twitching, tonic/clonic movements
   k. Anaphylaxis, anaphylactoid reactions
4. **Monitoring Required:**
   a. Respiratory rate every 2 hours
   b. Response to the medication and side effects will be evaluated a minimum of every 2 hours.
   c. Pain will be evaluated every 2 hours, and immediately before and 1 hour after all changes in medication dosage/rate using a developmentally appropriate pain scale.
   d. Patient monitoring in the dying child will be determined by the provider after consultation with the family.
   e. Patients receiving a combination of opioids, benzodiazepines, ketamine, and/or propofol are at increased risk of side effects.
5. **Dose Recommendation**: IV continuous infusion: 0.05-0.5mg/kg/hr.

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a. The Palliative Care Physician or Nurse practitioner will remain at bedside at initiation of treatment to titrate the medications until a therapeutic effect is achieved. Once treatment has been started, the nurse can adjust the dose on the order of a Palliative Care Prescriber. **(RNs DO NOT Titrate)**.

b. If patient is receiving intralipids, the pharmacist will adjust total daily lipids.

F. Ketamine Infusion

1. Contraindications:

a. Intracranial hypertension
b. Poorly controlled systemic hypertension
c. Seizures

2. Reason For:

a. Is reserved for select patients to include the following:

1) Patients having serious and excessive adverse effects from opioids.

2) Patients having inadequate pain control due to opioid tolerance/resistance.

3) Patients with previous history suggestive of significant opioid related inadequate analgesia and/or serious side effects.

b. Neuropathic pain is difficult to treat and often develops into a chronic state of abnormal excitability in neurons. Ketamine is thought to be an NMDA receptor antagonist, thereby blocking the abnormal response. It is thought that there is a synergistic amplification process such that the combination of ketamine and opioid results in a response that exceeds that experienced by the opioid alone.

c. Ketamine may be appropriate for use in children with acute neuropathic pain (e.g. phantom limb pain or complex regional pain syndrome) during the initial phase of titration of a new tricyclic antidepressant or anticonvulsant, which may require several days to weeks to reach peak effect.

3. Possible Side Effects

a. IV site irritation

b. Fatigue, drowsiness, dizziness, vivid dreams, misperceptions or confusion, feeling of inebriation or hallucinations (side effects are most often dose dependent and more frequent when anesthetic doses of ketamine are used).

c. If a patient experiences dysphoria or hallucinations, the dose of ketamine should be reduced or discontinued and the administration of a benzodiazepine may be considered at the discretion of the physician.

d. Long- term use of ketamine leads to elevated hepatic enzyme profiles.

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e. Ketamine is an irritant and will be prepared as a continuous infusion, diluted by pharmacy with 0.9% sodium chloride, in the largest volume possible.

4. **Monitoring: Required**:
   a. Respiratory rate every 2 hours.
   b. Response to the medication and side effects will be evaluated a minimum of every 2 hours.
   c. Pain will be evaluated every 2 hours, and immediately before and 1 hour after all changes in medication dosage/rate using a developmentally appropriate pain scale
   d. Patient monitoring in the dying child will be determined by the provider after consultation with the family.
   e. Patients receiving a combination of opioids, benzodiazepines, ketamine, and/or propofol are at increased risk of side effects.
5. **Dose Recommendation**
   a. The Palliative Care Physician or Nurse practitioner will remain at bedside at initiation of treatment to titrate the medications until a therapeutic effect is achieved. Once treatment has been started, the nurse can adjust the dose on the order of a Palliative Care Prescriber. **(RNs DO NOT Titrate).**
      1) Continuous IV infusion 0.05-0.2 mg/kg/hr
      2) Oral: 0.2-0.4 mg/kg/dose 3-4 times per day (max dose 50 mg TID)

F. Midazolam Infusion

1. **Contraindications:**
   a. Hypersensitivity to midazolam
   b. Intrathecal or epidural injection of parenteral forms containing preservatives (ie, benzyl alcohol);
   c. Acute narrow-angle glaucoma
2. **Reason for:** Reserved for use in patients experiencing refractory agitation and/or terminal delirium
3. **Side Effects:**
   a. Dose dependent side effects may include hypotension, bradycardia, drowsiness, sedation, tonic/clonic movements, and respiratory depression
   b. Prolonged use may cause physical dependence and tolerance. Taper doses slowly with prolonged use to avoid withdrawal signs/symptoms
   c. Paradoxical reactions associated with midazolam use in children (e.g. increased agitation, restlessness, combativeness) have been successfully treated with flumazenil. However,

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decreasing the dose may be the starting point for this limiting side effect

4. **Monitoring required:**
   a. Respiratory rate every 2 hours
   b. Pain will be evaluated every 2 hours, and immediately before and 1 hour after all changes in medication dosage/rate using a developmentally appropriate pain scale
   c. Response to the medication and side effects will be evaluated a minimum of every 2 hours
   d. Patient monitoring in the dying child will be determined by the provider after consultation with the family
   e. Patients receiving a combination of opioids, benzodiazepines, ketamine, and/or propofol are at increased risk of side effects
5. **Dose recommendation:**
   a. The Palliative Care Physician or Nurse practitioner will remain at bedside at initiation of treatment to titrate the medications until a therapeutic effect is achieved. Once treatment has been started, the nurse can adjust the dose on the order of a Palliative Care Prescriber. **(RNs DO NOT Titrate).**
   b. IV continuous infusion: 0.02-0.05mg/kg/hr.

G. Provider Documentation (found in EMR):

1. History and physical exam findings
2. Lab and other diagnostic results
3. Previous therapies used and response (e.g. rotation of opioids, adjuvant therapies, etc)
4. Evaluations and consultations
5. Goal of therapy
6. Discussion of risks and benefits with family to include side effects of medication(s) used
7. Discussion of agreement by the patients/family to the plan of care and consent of patient/family for use of these medications
8. Other strategies recommended for use in combination with the medication choice (e.g. other medications, non-drug strategies, psychosocial support, etc)
9. Plan to evaluate patient response and make necessary adjustments to the treatment plan

H. Nursing Documentation:

1. Pain assessment every 2 hours, and immediately before and 1 hour after all changes in medication dosage/rate.
2. Patient response and any side effects noted (also include vital signs and oxygen saturation if

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applicable).

3. Confirm ordered medication concentration, dosage, and rate on the Medication Administration Record.

PRECAUTIONS:

For each of these infusions, the provider will review with patient and family the benefits, risks, and adverse side effects of the medications, and also place appropriate documentation in the medical record.

SUPPORTIVE DATA:

1. For the purpose of pain and symptom management, use of a propofol, ketamine, or midazolam infusion may be appropriate in patients with intractable pain, refractory agitation and/or nausea/vomiting unresponsive to escalating doses of opioids, anxiolytics, or anti-emetics, or when increasing these medications is precluded by unacceptable effects.
2. Ketamine may be used in combination with opioids to obtain a synergistic effect and to help reduce the development of opioid tolerance. Ketamine has an opioid sparing effect, therefore potentially enabling a decreased dosage of opioid.
3. Propofol, Ketamine and Midazolam may be used in combination with other benzodiazepines, tricyclic antidepressants, and anticonvulsant medications for better control of seizures, pain, nausea/vomiting, and agitation/terminal delirium.

Policy Owner:	Nursing Director - Medical Services
References:	Association of Pediatric Oncology Nurses (Oct 2001). Pain Management for the Child with Cancer in End of Life Care: APON Position Paper. Bell, R.F. (1999). Low-dose Subcutaneous Ketamine Infusion and Morphine Tolerance. *Pain.* 83, 101-103. Children's Hospitals and Clinics of Minnesota (2005, August). Pain and Suffering Management for the Dying Child. Children's Hospitals and Clinics of Minnesota (2008, March) Propofol, Ketamine and Midazolam Use for Pain and Symptom Management Organizational Policies and Procedures Manual, 118.0. Correll, GE, Maleki, J, et al (2004). Sub anesthetic Ketamine Infusion Therapy: A Retrospective Analysis of a Novel Therapeutic Approach to Complex Regional Pain Syndrome. *American Academy of Pain Medicine,* 5(1), 263-275.

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Related Policies:	
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