The Ohio State University Medical Center
Center for Palliative Care
Guideline for Parenteral Opioid Use in End-of-life Care

This protocol is intended only for the guidance of comfort care measures at the end-of-life

PREFACE

This guideline has been developed for use at the Ohio State University Medical Center by individuals from the Center for Palliative Care and the Department of Pharmacy. The intent is to provide guidance for the use of continuous opioid (e.g. morphine, hydromorphone, and fentanyl) infusions for the management of symptoms in end-of-life care.

PHILOSOPHY AND GENERAL INFORMATION

Dying patients may experience distressing symptoms such as pain and dyspnea. The etiologies of these symptoms are multifactorial, often related to progression of and complications from the underlying disease. Opioids are the treatment of choice for both pain and dyspnea in dying patients, however they do not have anxiolytic properties. Opioids can be safely administered in increasing amounts until a sufficient dose provides symptomatic improvement. Titration of opioids is ONLY for symptom relief while death occurs naturally over time, not for the acceleration of the dying process.

The appropriateness of a continuous opioid infusion should be evaluated based on a patient's recent opioid requirement, symptom burden, and available routes of administration. For example, small doses of opioids administered as needed (PRN) are often adequate to relieve symptoms in an opioid naïve patient. However, a patient who has received a scheduled opioid on a chronic basis will continue to need a scheduled opioid to prevent opioid withdrawal and treat symptoms associated with the dying process. Scheduled opioids may be provided as a continuous infusion (SC or IV) or as scheduled boluses (IVP, SC, SL, per PEG, or PR).

The following are principles to follow for safe initiation, monitoring, and titration of an opioid infusion.

Choosing an opioid:

- Avoid morphine if the patient has renal insufficiency, previous adverse reactions to morphine, or an allergy to structurally similar opioids.*
- Avoid hydromorphone if the patient has had previous adverse reactions to hydromorphone or an allergy to structurally similar opioids.* Monitor for opioid toxicity in renal insufficiency and with high doses.
- Avoid a continuous fentanyl infusion in patients with hepatic failure. It is not necessary to switch from a fentanyl infusion to either morphine or hydromorphone in a dying patient, unless they have hepatic failure. Fentanyl is an effective analgesic and anti-dyspnea agent.

Initiation:

- DO NOT write “Morphine continuous infusion 1mg/hr. Titrate to effect.” This is a dangerous and ineffective way to manage symptoms and may hasten death. Reevaluation by the prescriber is necessary prior to increasing the infusion rate.
- For opioid naïve patients:
  - Use IVP or SC opioid boluses for a minimum of 4 hours before starting a continuous infusion opioid. This will help determine if a patient needs an opioid continuous infusion and what starting dose the patient should receive. See Box 1 (Examples #1 and #2).
  - If the patient requires at least 1 IVP/SC bolus per hour for 4 consecutive hours to treat pain or dyspnea, a continuous opioid infusion may be indicated.
  - If it is determined that a continuous opioid infusion is indicated, calculate the initial infusion based on previous opioid use and equianalgesic ratios. See Box 1 (Example #2), Table 1 and/or Opioid Infusion Rate Calculator.
- If a continuous infusion is initiated, utilize IVP or SC breakthrough doses of the same opioid at 100-200% of the hourly continuous rate q15 mins PRN for pain or dyspnea.
- For opioid tolerant patients:
  - Calculate the initial infusion based on previous opioid use and equianalgesic ratios. See Box 1 (Example #3), Table 1 and/or Opioid Infusion Rate Calculator.

*codeine, hydrocodone, oxycodone, oxymorphone, hydromorphone, nalbuphine, or butorphanol
• Utilize IVP or SC breakthrough doses of the same opioid at 100-200% of the hourly continuous rate q15 mins PRN pain or dyspnea

Assessment:
• Consider giving the patient an IVP opioid bolus if the patient displays signs of pain or dyspnea, such as:
  o **Facial Expression**: Tension or furrow in the eyebrow that does not dissipate, grimacing, biting on OT tube
  o **Body Movement**: Flexed/tense/rigid or restless (random movements, pulling, picking)
    • If this symptom does not resolve with an IVP dose of opioid, consider addition of anxiolytic or antipsychotic as these signs may be more indicative of delirium/agitation - also assess for soiled linens, bowel impaction or urinary retention.
  o **Respiratory**:
    • Compliance with Vent - continued cough, fighting ventilator, unable to control ventilator
    • Non-ventilated patient - flared nostrils, use of accessory breathing muscles, retractions (indicate increased work of breathing)
  o **Other**:
    • Diaphoresis
    • Persistent tachypnea (>25) OR persistent tachycardia (>120) combined with tachypnea
      • To treat the work of breathing, not the number of respirations - numbers may not change
• Opioids are NOT the treatment of choice for:
  o Agonal breathing or apnea - these are expected changes in a dying patient
  o Delirium - disrobing, picking at sheets, restlessness
• **Reassess** pain/dyspnea 15 minutes after an IVP opioid dose. Peak effects (adverse effects and therapeutic effects) are reached approximately 15 minutes after an opioid is administered IVP. If pain/dyspnea persists, the patient can be safely re-dosed at that time.

Monitoring:
• Monitor for increased sedation and respiratory depression. Note that these symptoms may be related to the medication or patient decline.
  o If over-sedation without significant respiratory depression occurs secondary to opioids, decrease the continuous infusion by 25-50%.
  o If significant respiratory depression (RR <8 per min) occurs secondary to opioids, consider administering naloxone 0.04 mg q60 seconds until adequate response.
• If there is no improvement in symptoms after four hours or for general questions regarding end-of-life care, contact Palliative Care.

Titration:
• If symptoms do not improve after two IVP boluses (separated by 15 minutes), consider increasing the IVP **breakthrough** dose 25-50% for moderate pain/dyspnea or 50-100% for severe pain/dyspnea.
• With a continuous infusion of hydromorphone or morphine, steady state is not reached for 8-12 hours (4-6 hours for continuous infusion fentanyl). Do **NOT** increase the continuous infusion rate more frequently than every eight hours for morphine or hydromorphone and every 4 hours for fentanyl.
• Use the number of breakthrough doses from the previous four to eight hours as a guide for infusion titration. Do not increase the continuous infusion by more than 100% at any one time. See Box 1 for example.

*codeine, hydrocodone, oxycodone, oxymorphone, hydromorphone, nalbuphine, or butorphanol*
Box 1: Example Opioid Calculations

Patient Example #1: Opioid-Naive Patient
MA is a 55 yo male with a history of heart failure. He has been transferred to comfort care and is actively dying. His current medications include metoprolol, furosemide, and lisinopril. He has been having increasing pain in his legs. Morphine 2 mg IVP q2h prn has been relieving his pain for approximately 4 hours without causing sedation. He has used 2 doses in the last eight hours. What dose of morphine infusion would you start? What would be your IVP bolus dose?

As this case illustrates, a morphine continuous infusion is not necessary for all dying patients. Morphine 2 mg IVP is an adequate dose for this patient. Continue with Morphine 2-4 mg IVP q15 mins prn pain or dyspnea.

Patient Example #2: Opioid-Naive Patient
Mr. K has end-stage renal disease. He was admitted with a GI bleed and is actively dying. Prior to admission, Mr. K did not use opioids daily. He has received hydromorphone 1 mg IVP 2 times per hour for the last 6 hours for abdominal pain. What dose of continuous infusion hydromorphone should be started? What would be your IVP breakthrough dose?

12 doses of hydromorphone IV in 6 hours = 2 mg hydromorphone/hour continuous infusion.

What PRN bolus dose?
Hydromorphone 2-4 mg IVP q15 mins prn pain or dyspnea. (100-200% of the hourly continuous infusion rate)

Patient Example #3: Opioid-Tolerant Patient
Ms. X has metastatic breast cancer and is using OxyContin® (Oxycodone SR) 120 mg orally q8h ATC and oxycodone IR 30 mg orally q3h prn pain. She has been using 8 doses of her breakthrough medication daily because her pain has not been well controlled. She is actively dying and cannot swallow her medications. What dose of hydromorphone continuous infusion would you start?

OxyContin® (Oxycodone SR) 120 mg q8h + 8 doses of Oxycodone 30 mg IR =600 mg oxycodone/24hours= 30 mg IV hydromorphone/24hours=1.2 mg IV hydromorphone/hour continuous infusion

What IVP breakthrough dose?
Hydromorphone 1 – 2 mg IV/SC q15 mins prn pain or dyspnea. (100-200% of the hourly continuous infusion rate)

<table>
<thead>
<tr>
<th>Drug</th>
<th>SQ/IV Dose</th>
<th>Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>6-7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>-----</td>
<td>20-30</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>-----</td>
<td>10</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>-----</td>
<td>30</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 mg (100 mcg)</td>
<td>Not established</td>
</tr>
</tbody>
</table>

General Considerations in End-of-Life Care:
- Review and discontinue any medications which may be precipitating symptoms of discomfort (SQ heparin, insulin/finger stick assessment, fluids aggravating edema and/or pulmonary congestion, nebulizer treatments)
- Remove any physical items that may be uncomfortable (SCD boots, restraints, NG tubes, telemetry, O2 cannulas/masks or other devices requiring patient to be in restraints).

POLICY STATEMENTS
1. All patients should have their recent/previous opioid usage evaluated to determine exposure (naïve vs. tolerant).
2. For opioid naïve patients, use PRN bolus doses for a minimum of 4 hours before starting a continuous opioid infusion.
3. “Titrate to comfort” instructions and dosing ranges are not permitted when ordering a continuous opioid infusion. Range orders are only appropriate for PRN doses.
4. A PRN opioid (IVP, SC, per PEG, SL, or PR) should always be available to treat breakthrough pain and dyspnea in patients who are receiving a continuous opioid infusion.
5. Continuous morphine and hydromorphone infusion rates should not be increased more frequently than every eight hours. A continuous fentanyl infusion rate should not be increased more frequently than every four hours.
6. Opioids should not be used to accelerate the dying process, but rather provide patients with adequate comfort measures as death occurs naturally over time.

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