Concise Review for Clinicians

Use of Opioids in the Treatment of Severe Pain in Terminally Ill Patients—Dying Should Not Be Painful

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Pain is a common symptom at the end of life. The vast majority of pain can be readily managed if simple principles of practice are followed. Chronic pain requires continuous analgesia, and severe pain requires use of strong analgesics, most commonly the opioids. In addition to drugs administered continually, short-acting medications must be available for “breakthrough” pain. This article reviews the principles of pain management in terminally ill patients, using a case-based demonstration.

ILLUSTRATIVE CASE

Mr C is a 54-year-old man who presents to the emergency department with severe abdominal pain of several days’ duration. Computed tomography of the abdomen reveals a 5-cm mass in the head of the pancreas and the presence of hepatic metastases. The patient is in severe pain (rated a score of 9 on a scale of 0 to 10 in which 10 is the worst pain imaginable) (Table 1) and has been taking only over-the-counter analgesics, which are not relieving his pain.

INITIATION OF ANALGESIA

Although there is no tissue confirmation, there is a strong suspicion that this patient has metastatic pancreatic cancer, an ultimately terminal disease. Regardless of the diagnosis, he is in severe pain and requires strong medication for relief. Analgesia should not be delayed while the evaluation is being pursued. Immediate management calls for use of a strong opioid. Although many strong opioids are available, morphine is the prototypic drug, and no other drug is more effective for pain relief. A typical initial dose for an opioid-naive man in severe pain (score of 8) is 1 to 5 mg given as an intravenous bolus. The time to peak effect of an intravenous bolus dose of morphine is 6 to 15 minutes. The time to peak effect is crucial for proper dosing and analgesic control. It is essential to wait at least until the peak effect has been achieved before determining the effectiveness of the last administered dose. If the patient remains in severe pain, doses should be repeated at that same interval until relief is obtained. Using pain scores (selecting a pain scale appropriate for each patient) is an effective guide (Table 1). The pain score should be evaluated at the time of presentation and after each intervention during titration of analgesic medications. It should also be monitored routinely in all patients as part of assessing vital signs.

Mr C is given 4 mg of morphine sulfate as an intravenous bolus. Fifteen minutes later, he notes that his pain level has decreased substantially, but he rates it a 6. A second dose of 4 mg of morphine is administered, and 15 minutes later he rates his pain a 4 and reports that he is more comfortable. After an hour, the patient rates his pain a 4 and is pleased with the progress being made in controlling his pain.

Dosing

Rapid titration of analgesia to relieve pain is possible by using frequent dosing at appropriate intervals determined by time to peak effect. In patients whose pain is likely to persist, a continual supply of drug is necessary to maintain analgesia; however, the required opioid doses must first be determined. The patient should continue to receive doses as needed until the pain is relatively well controlled and a steady state is reached; typically, this takes 12 to 24 hours of dosing. The easiest way to provide this is with a patient-controlled analgesia (PCA) pump (Table 2).
Table 1. Scales to Evaluate Pain

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal numerical rating</td>
<td>On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain</td>
<td>Most adults respond well, elderly adults may not respond as well,</td>
</tr>
<tr>
<td></td>
<td>imaginable, rate your current pain level</td>
<td>young children or those in whom a language barrier exists do better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with other scales</td>
</tr>
<tr>
<td>Visual linear analogue</td>
<td>Line with 0 to 10, may be numerical or colored, ranging from blue (no pain)</td>
<td>Good for elderly adults, patients in whom a language barrier exists;</td>
</tr>
<tr>
<td></td>
<td>to red (maximal pain)</td>
<td>use with caution in those who are color blind</td>
</tr>
<tr>
<td>Faces</td>
<td>Series of pictures of faces, from smiling to severe frown with tears</td>
<td>Best for children or those in whom a language barrier exists</td>
</tr>
</tbody>
</table>

A PCA pump is used with a bolus dose of 4 mg, at a lockout interval of 15 minutes. No basal rate is given until the opioid requirement is known. A 4-hour limit on the total amount of drug delivered may be set.

Physicians are often reluctant to use strong opioids to treat pain because of a fear of oversedation or causing respiratory depression. One of the main advantages to using a PCA pump is that, if the patient becomes sedated, he or she is unable to press the button to receive more drug. Thus, it is critical to instruct family members and nurses to not administer doses.

Mr C continues using his PCA pump, receiving doses of 4 mg every 15 minutes as needed. After 12 hours, he has received 6 additional bolus doses. He currently rates his pain a 2 or 3 and is satisfied with the pain relief. The morphine regimen used is as follows: 8 mg in the first hour, 6 doses at 4 mg each equals 24 mg in 11 hours; total morphine used in the past 12 hours is 32 mg.

When treating pain that is expected to continue, the physician must provide for continuous analgesia based on each individual’s opioid requirements to achieve pain control. Once adequate analgesia is attained, the total number of milligrams of opioid given over the preceding interval, excluding initial loading doses (these are determined by the volume of distribution, not the steady-state pharmacokinetics), should be used to determine the patient’s continuous infusion rate. Of importance, the physician must remember to readjust the breakthrough dose schedule and the lockout rate.

Even though continuous analgesia is required, it is imperative to provide for breakthrough pain. No firm guidelines exist for the exact dose of opioid needed for breakthrough pain, although many investigators recommend using 10% to 15% of the total daily dose. This dose should be administered at a frequency determined by the time to peak effect for the drug and route. For intravenous administration, the time to peak effect is about 15 minutes. For oral administration of immediate-release morphine, the time to peak effect is 1 hour. Such titration of the dose is safe, especially in patients with pain or those who have previously been taking opioids.

The 24 mg of morphine used during the past 11 hours equals 2.2 mg/h of continuous infusion. The as-needed bolus dose is adjusted to 2.2 mg/h for 24 h × 0.10, equaling 5.2 mg. The prescription is a 5-mg bolus dose every 15 minutes as needed.

Eight hours after admission, Mr C is somnolent but arousable. He reports a pain score of 0. His vital signs are unremarkable, and his pupils, although constricted, are reactive. The physician believes the patient is somewhat narcotized. His dose of opioids is reduced by 50% but still continued. The new infusion rate is now 1 mg/h, and the new bolus rate is 2 mg every 15 minutes as needed.

Follow-up

Careful follow-up and frequent reassessment of the patient are the most important aspects of analgesic management. At times, administration of opioids may be excessive, even when administered by an expert. This does not mean that these medications are unsafe; they are safe as long as the patient is monitored appropriately. Among the greatest challenges faced by clinicians in this setting is trying to determine whether the patient’s somnolence is due to excessive analgesic doses or to drowsiness because this is the first substantial pain-free interval the patient has experienced since development of his or her illness. Pain creates sleep deprivation, and if analgesia is obtained, one of the first natural responses in a sleep-deprived individual is to sleep. If vital signs are stable, the patient is easily arousable, and the respiratory rate is sufficient, a dose reduction, or even continuation of the same dose and continued close observation, is appropriate. The use of naloxone in patients with a severe underlying pain source should almost always be avoided. In rare instances when immedi-
Table 2. Patient-Controlled Analgesia Pump

<table>
<thead>
<tr>
<th>Analgesic drug</th>
<th>Name of drug and concentration in milligram/milliliter</th>
<th>Loading dose</th>
<th>Initial dose to be given only once</th>
<th>4-mg intravenous loading dose 1 time only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent patient-controlled dose</td>
<td>Dose patient is able to self-administer as needed</td>
<td>2 mg of intravenous morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lockout interval</td>
<td>Minutes between doses, should be based on time to peak effect of drug</td>
<td>Lockout interval 10 min (typically should be 6-15 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal rate</td>
<td>Amount of drug to be infused continuously; do not begin infusion until opioid requirements are known</td>
<td>3 mg of morphine per hour in a continuous infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-h limit</td>
<td>Maximum dose patient may receive in any 4-h interval, regardless of how often button is pushed</td>
<td>4-h lockout is 36 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain rating</td>
<td>Monitor every 15-30 min when treating severe, acute pain; after severe pain controlled, monitor every 2-4 h</td>
<td>Record pain score every 15 min; notify physician if pain score &gt;6 (on a scale of 0-10, with 0 being no pain and 10 being the greatest pain imaginable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring of adverse effects</td>
<td>Especially respiratory rate and sensorium</td>
<td>Monitor respiratory rate every 1 h; if &lt;10/min, notify physician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Patient should be the only one allowed to administer the drug; if sedation occurs, patient will be unable to administer more doses, preventing oversedation</td>
<td>Family members and nurses are not allowed to administer drug</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Opioid reversal of opioid overdosing is thought to be necessary because of respiratory depression, naloxone can be administered judiciously after 50% dilution. The patient should be monitored closely, and the least amount of naloxone needed to reverse the respiratory depression should be used. Of note, the half-life of naloxone is short, and repeated doses may be necessary. The opioid infusion should be discontinued until respiratory depression is reversed, then resumed at a lower dose (eg, a 50% reduction).

This patient’s pain is now controlled, and the diagnosis, evaluation, and management of his metastatic pancreatic cancer have been addressed. He is preparing to be discharged to his home. Although portable PCA infusion pumps are available, oral therapy is more convenient and less expensive. Conversion to oral therapy should be based on the amount of narcotic required to control his pain in the preceding 24 hours.

Mr C’s average pain score over the previous 24 hours is rated a 1 or 2. During the past 24 hours, his regimen has been as follows: 1 mg/h for 24 hours equals 24 mg, 5 bolus doses at 2 mg/bolus equals 10 mg, and total morphine administered intravenously in the past 24 hours is 34 mg. Dose conversion from intravenous to oral therapy is 1:3; therefore, 100 mg of oral morphine per day is required. A regimen of 30 mg of continuous-release morphine every 8 hours is initiated. (Continuous-release morphine is available in 15-, 30-, 60-, and 100-mg tablets.) Breakthrough medication is also supplied with use of immediate-release morphine: 100 mg/d × 0.10 equals 10 mg of immediate-release oral morphine every 1 hour as needed. The time to peak effect for oral immediate-release morphine is 1 hour.

CONVERSION TO ORAL THERAPY

When converting from intravenous to oral morphine, the intravenous morphine must be discontinued at some time. Given the kinetics of the sustained-release preparations of opioids, it typically takes 4 to 6 hours to achieve adequate blood levels and up to 3 half-lives to achieve steady-state levels. The current recommendation is to stop the continuous intravenous infusion approximately 4 to 6 hours after the first oral dose of continuous-release medication, keeping the as-needed bolus doses available for coverage.

Three weeks later, Mr C presents with persistent nausea and vomiting. Evaluation reveals a fixed small-bowel obstruction secondary to tumor progression. His pain had been controlled with 150 mg of morphine per day. Because he is no longer able to tolerate oral medications, a new route of administration is required.

ROUTES OF DRUG ADMINISTRATION

Fortunately, multiple routes of administration are available for opioids, including oral, rectal, transdermal, intravenous, subcutaneous, epidural, intrathecal, and intramuscu-
lar. Because of erratic absorption and pain, the intramuscular route is generally discouraged. The epidural or intrathecal route requires placement of a catheter, and, although this approach can be effective for pain management, catheters are typically used only in special circumstances. Intravenous opioid administration works well but can be cumbersome for a patient to use at home and requires continuous intravenous access, pumps, and equipment. The subcutaneous route is somewhat more convenient; a 25-gauge butterfly needle is placed under the skin. The needle should be changed every 3 days, but the procedure is relatively simple. However, caution should be used in patients who become dehydrated because this may hamper systemic absorption and decrease analgesic efficacy. Rectal administration is often uncomfortable for the caregiver and the patient but can be effective; both immediate-release and sustained-release preparations can be used. However, the duration of action may be shortened with rectal administration.

The transdermal route of opioid delivery is often the simplest and most convenient for patients who are unable to take oral medications. Fentanyl patches are the preferred choice for transdermal administration. They are labeled on the basis of the administered dose they provide, in terms of micrograms per hour. The dose conversion from oral morphine to transdermal fentanyl is as follows: 1 mg/h equals 2 mg/d of oral morphine. When switching from one opioid to another, most experts recommend a 20% to 25% decrease in the dose of the new opioid because of incomplete cross-tolerance.

Mr C’s pain has been well controlled with 150 mg of oral morphine per day; conversion to transdermal fentanyl is as follows: 150 mg/d of oral morphine × 1 µg/h of fentanyl divided by 2 mg of oral morphine per day equals 75 µg in a fentanyl patch; this dose should then be reduced by 25% for incomplete cross-tolerance. A 75-µg/h patch × 0.75 equals 56 µg/h. Therefore, a 50-µg patch is ordered with plans to change it every 72 hours.

TREATMENT OF BREAKTHROUGH PAIN

The strategy for treatment of breakthrough pain should be determined. Because the patient is having difficulty taking oral medication, the parenteral routes, intravenous and subcutaneous, can be used. However, a more convenient approach is to use an oral high-concentration morphine solution such as Roxanol, which contains 20 mg of morphine per milliliter. One or 2 milliliters of the solution can be placed between the patient’s cheek and gum. A rapid “burst” is absorbed by the buccal mucosa, with the rest being swallowed and absorbed slowly through the gastrointestinal tract. Such small volumes are often well tolerated.

Another choice is to use an oral fentanyl lozenge. This should be placed in the patient’s mouth until pain relief is obtained, and then it should be removed. Fentanyl is rapidly absorbed with this method and can be effective. Care must be taken to not allow the patient to fall asleep with the lozenge in the mouth. These lozenges must be kept out of the reach of small children, who may mistake them for lollipops.

Several caveats regarding the use of transdermal fentanyl must be remembered. Absorption is highly temperature dependent, and fever can increase the rate of absorption and alter the kinetics of the drug. This can lead to high serum levels and adverse effects such as sedation or respiratory depression. In addition, the patch may not be effective for the entire 72 hours, and pain may occur sooner; thus, patches may need to be changed more frequently. Furthermore, the patch depends on subcutaneous fat and hydration status for absorption; thus, in cachectic or severely dehydrated patients, other analgesics are likely better choices.

Over the course of time, Mr C’s disease has progressed, and his pain is becoming increasingly difficult to control. Because of this, a celiac plexus block is performed. Pain control is excellent. The same doses of analgesia have been continued after the block. During the next 48 hours, he becomes somnolent and develops respiratory depression.

REASSESSMENT OF OPIOID DOSE

The patient’s opioid requirements have decreased because of the nerve block. Therefore, his pain has decreased considerably, and his opioid requirements have decreased. The previous doses of opioids that he had tolerated now represent excessive doses, and adverse effects emerge. When a procedure is performed that may diminish the source of pain, the opioid requirements must be reassessed and readjusted.

Mr C’s opioid dose is decreased by half and titrated to a level that produces pain control without excessive adverse effects. Three weeks later, Mr C presents with recurrent abdominal pain. Additional history reveals that he has had no bowel movement in the past 3 weeks. An x-ray film of the abdomen shows a large amount of stool in the colon. Treatment with enemas and laxatives resolves the constipation and the pain.

BOWEL MANAGEMENT

When use of narcotics is initiated in a patient, regardless of the route used, a bowel regimen should be initiated. Constipation is almost universal in patients taking opioids; pre-
Table 3. Types of Drugs to Treat Constipation

<table>
<thead>
<tr>
<th>Class and drug</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool softener</td>
<td></td>
</tr>
<tr>
<td>Ducosate sodium</td>
<td>50-500 mg twice daily</td>
</tr>
<tr>
<td>Stimulant laxative</td>
<td></td>
</tr>
<tr>
<td>Senna</td>
<td>187-mg tablet, up to 2 tablets per day</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>5-mg tablet, up to 30 mg/d</td>
</tr>
<tr>
<td>Cascara</td>
<td>325 mg every day</td>
</tr>
<tr>
<td>Saline laxative</td>
<td></td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>15-30 mg</td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>240 mL</td>
</tr>
<tr>
<td>Hyperosmolar agent</td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>15-30 mL, up to 3 times daily</td>
</tr>
<tr>
<td>Sorbitol 70% solution</td>
<td>15-30 mL, up to 3 times daily</td>
</tr>
</tbody>
</table>

vention is more effective than treatment. A thorough history and physical examination should always be the cornerstone of the evaluation of any patient with pain. When pain recurs or is exacerbated, treatment and evaluation should be based on a thorough history and physical examination, and other potential confounding problems should be considered. It would have been easy to assume that this patient’s worsening pain was due to advancing disease, for which he would have been treated with increased doses of opioid. However, he needed enemas and laxatives to relieve his pain (Table 3).

CONCLUSION

Dying does not need to be painful. An appropriate evaluation to determine the etiology of the pain, followed by a rationally designed treatment plan coupled with appropriate analgesic dosing, can control the vast majority of pain in the dying patient.

REFERENCES


Questions About Treating Severe Pain in Dying Patients

1. Which one of the following routes of administration of analgesics should be avoided in a patient who is unable to take oral medications?
   a. Transdermal
   b. Intramuscular
   c. Subcutaneous
   d. Buccal
   e. Intravenous

2. Which one of the following is true regarding administration of analgesia in a patient who presents with severe pain?
   a. Should not be administered until a final pathologic diagnosis has been established
   b. Should be administered only to patients who request it
   c. Should be given immediately while the diagnostic evaluation is being performed
   d. Should be given only with the family’s authorization
   e. Should be given only to patients enrolled in a hospice program

3. Which one of the following agents should be used in a patient with severe pain (a score of 8-10 on a scale of 0-10, with 10 being the worst pain imaginable)?
   a. Acetaminophen
   b. Nonsteroidal anti-inflammatory drug
   c. Tricyclic antidepressant
   d. Strong opioids
   e. Placebo

4. Which one of the following is an adverse effect of opioids in which tolerance does not develop?
   a. Constipation
   b. Lethargy
   c. Euphoria
   d. Respiratory depression
   e. Somnolence

5. Which one of the following is the most common reason somnolence occurs in patients with severe pain who have received their first doses of an opioid?
   a. Overdose
   b. Malingering
   c. Drug-seeking behavior
   d. Sleep deprivation secondary to the pain
   e. Intolerance

Correct answers:
   1. b, 2.c, 3.d, 4.a, 5.d