Introduction

The purpose of this module is to reduce the risk of adverse outcomes for adult patients receiving narcotic analgesia. It does not address the use of opiates as co-anesthetics or their intrathecal or epidural applications.

Deaths from opioid poisoning are increasing dramatically and opioid poisoning has become the leading cause of accidental death in the 35-54 year old age group (CDC, NCHS Data Brief, Number 22, Sept. 2009). It is likely that deaths from opioid induced respiratory arrest are under-recognized and under-reported in hospitalized patients.

Upon completion of this module, the practitioner will have refreshed his or her knowledge base to use opioid analgesic more safely and effectively.

Opioid Module Information

The opiates are alkaloid compounds and their congeners derived from the poppy, Papaver Somniferum. They have been used for centuries for their euphoric and analgesic properties. In general, they produce tolerance, and escalating doses may be required to produce the desired effect. Physical dependence may occur with as little as 1-2 weeks of continuous use. There is no dose ceiling except that imposed by side effects. These include nausea, vomiting, pruritus, constipation, sedation, neurotoxicity and respiratory suppression.

Morphine is the prototypical opioid in clinical use. It acts on the mu (and other) receptors in the brain, spinal cord and peripheral nervous system to produce its therapeutic effects. It is available in oral and parenteral formulations for the treatment of acute or chronic pain of moderate to severe intensity. The usual oral starting dose for opiate-naïve patients is 5-10mg. every 4 hours. Onset of analgesia is 30-60 min. Peak effect is 90 min. and duration 3-4 hours. The oral to parenteral ratio is about 3 to 1, so a starting I.V. dose would be 1-3mg. Onset of analgesic should occur in 5-10 min. Peak effect should be achieved in 15-30 min., and the dose can be titrated every 10-15 minutes. Blood levels will temporarily exceed analgesic levels with I.V. administration so excessive sedation and respiratory depression are more likely with this route.
Patients who have chronic pain may prefer sustained release morphine for convenience and control. To convert to sustained release, calculate the morphine equivalent daily dose (MEDD), which is the total oral morphine for a 24-hour period. Divide the MEDD by 2 or 3, reduce that by 20-30% to get the q 12 or q 8 hr. dose, and then add 10% of the MEDD as a breakthrough dose. For example, a patient requiring 20 mg of morphine every 4 hrs has a MEDD of 120mg. Divide by 3 and reduce by 25% to get 30mg of sustained release morphine (e.g. MS Contin) every 8 hours, then add 10-15mg of immediate release (e.g. Roxanol) every 1-2 hours as needed. If a patient requires more than three breakthrough doses in 24 hours, increase the sustained release dose. Conversion from one opioid to another should be done by calculating the MEDD, multiplying by the conversion factor, decreasing 20-30% for incomplete cross tolerance (standard safety adjustment), and dividing by the number of doses per day.

Hydromorphone (Dilaudid) is another clinically useful opioid that is available in oral, parenteral and rectal formulations. Oral dilaudid is four times more potent and intravenous dilaudid six times more potent than morphine. A typical starting oral dose is 2-4mg every three to four hours. Onset of analgesia is 15-30 min. and peak effect is in 30-60 min., much faster than oral morphine. A typical starting dose for I.V. dilaudid is 0.5mg every 2-3 hours. The conversion ratio for oral to parenteral dilaudid is five to one. Dilaudid is a good choice for patient controlled analgesia or subcutaneous administration.

One of the most commonly used oral opioids is oxycodone alone, combined with acetaminophen (Percocet) or as a sustained release (Oxycontin). It has no parenteral formulation. Oxycodone is slightly more potent than morphine, 1mg of oxycodone equivalent to 1.5mg morphine. The usual starting does of oxycodone is 5-10mg and the dose interval is 4-6 hours. It results in less histamine release, hence less pruritus than morphine. Caveats with oxycodone are: 1) Watch the acetaminophen dose when using Percocet. Don’t exceed the 4gm (8 tabs) limit. 2) Oxycontin has a high addictive potential and high street value. It should be prescribed judiciously with appropriate oversight.

Meperidine (Demerol) should not be used for patients who require repetitive dosing because its metabolite, nor-meperidine, causes neurotoxicity, especially in the elderly. Meperidine is low potency (100mg meperidine = 10mg morphine) and has a short duration of action (2.5-3.5 hrs).

Fentanyl is a potent opioid used as a co-anesthetic and a rapid acting analgesic. When given intravenously its onset of action is almost immediate and duration of activity is 30-60 min. A dose of 1-2
micrograms per kilogram body weight may be administered every 1-2 hours. Respiration must be carefully monitored.

Transdermal fentanyl (Duragesic) is both popular and expensive. It is available in dosage sizes of 25-100 micrograms per hour, each patch lasting 72 hours. However, its transcutaneous absorption is variable and a steady state concentration may not be achieved until several 72-hour applications have been completed. Dose escalation should be very gradual. Also, because of its lipophilic nature, fentanyl may have a long washout after prolonged use. Transdermal fentanyl should only be used in opiate tolerant patients, not as initial therapy for acute pain or postoperative pain. The transdermal dose in micrograms is about equivalent to half the morphine equivalent daily dose. For example, a patient requiring 100mg of morphine a day would require a 50 microgram transdermal fentanyl patch. Transdermal fentanyl should not be used in conjunction with other long acting opioids. It is obviously useful for patients who cannot swallow but may not be well absorbed by cachectic patients with little subcutaneous fat.

Fentanyl is also available as a lozenge or buccal tablet. (Actiq)

Methadone (Dolophine) is a very long acting lipophilic opiate long used for maintenance therapy in heroin addicts. It has some very useful applications in chronic pain management but is potentially very dangerous. In addition to respiratory depression it may prolong the QT-interval and cause Torsade de pointes. Its initial analgesic effect is mild and brief, so there is a temptation to rapidly escalate the dose. It must be used with extreme caution in opiate naïve patients. The starting dose should be low, e.g. 2.5-5mg every 12 hours, and a short acting opioid should be used for breakthrough. The methadone dose should not be increased for 3-5 days. Paradoxically, methadone may be more potent in patients with prior opiate use. The dose equivalency is non-linear and the higher the MEDD the lower the methadone dose equivalency. For example, the methadone dose is 20-30% of the MEDD if the MEDD is less than 100mg, but only 5% of the MEDD if it is over 1000mg.

Methadone is very useful as a co-analgesic to reduce tolerance and side effects, especially neurotoxicity caused by escalating doses of other opiates (Methadone is an NMDA receptor antagonist within the dorsal horn nociceptive neurons as well as a mu receptor agonist). Furthermore, it is not excreted through the kidneys and may be useful in patients with renal failure.

Other opioids in common use include hydrocodone (Vicodin = hydrocodone + acetaminophen), codeine, and tramadol (ultram). Propoxyphene is also a weak opioid but its potential side effects outweigh its
potential analgesic benefit. Agonist/antagonist opioids like Nubain or Talwin have complex pharmacology and are less often used than pure agonists.

A variety of co-analgesics may be used to improve the risk-benefit ratio of opiates. These include NSAIDs, antidepressants, anticonvulsants and steroids. Bone pain responds well to anti-inflammatories, and nerve pain is often relieved with anticonvulsants, antidepressants or steroids.

Neurotoxicity is a serious side effect of opiates and may not be recognized as such in an agitated delirious patient who appears to be in pain. The approach to such a patient should be to reduce the dose or switch to another opiate rather than escalating the dose or adding a benzodiazepine.

Allodynia is a unique manifestation of opiate neurotoxicity, usually from very high doses of morphine or dilaudid. It is a hyperalgesia characterized by painful response to any stimulus, even light touch. It is mediated through the NMDA pathway that makes methadone a logical solution.

Respiratory suppression can be a lethal complication of opiate analgesia. Risk factors include obesity, COPD, sleep apnea and advanced age. Sedation and constricted pupils, except with meperidine, usually precede significant respiratory depression. Beware the patient who is “resting quietly”. Patients who are not easily aroused to clear cognition must have careful assessment and monitoring of their respiration. Pulse oximetry may be misleading in patients who are receiving supplemental oxygen and may be normal in the presence of severe respiratory acidosis. End tidal CO₂ (ETCO₂) is a measure of ventilation, circulation and metabolism. When used with patient controlled analgesia (PCA), ETCO₂ monitoring provides for safe postoperative analgesia. Patients who are moderately to deeply sedated with slow shallow respiration or apnea require ventilatory support and rescue with narcan. Partial opiate reversal can be achieved with narcan titration in doses of 0.2mg or less. However, deeply sedated hypoventilating patients will require total reversal with 0.4-0.8 mg of narcan. Remember that narcan has a short half-life and may need to be repeated.

In general, opiates are metabolized in the liver and their metabolites excreted by the kidneys. Opiates may be used in patients with mild to moderate liver disease but must be titrated cautiously. Methadone should be used with extreme caution, if at all, in patients with hepatic insufficiency. On the other hand, methadone and oxycodone are the safest oral opiates for patients with renal insufficiency. Fentanyl is the safest short acting parenteral opioid for use in renal insufficiency.
Ketorolac (Toradol) is an NSAID available in parenteral formulation that is an opiate alternative in selected patients. It has a parenteral dose limit of 120mg per 24 hours, an oral limit of 40mg per day, and a duration of treatment limit of 5 days. It may cause gastric ulceration and renal insufficiency. Opiates may be used for breakthrough pain along with ketorolac.

Local anesthetics may be infused at the surgical site (On Q) or used for nerve blocks (On Q C-bloc) to reduce or obviate the need for opiates. Lidocaine also comes in a transdermal patch.

Opiate dosing and dose equivalency is hard to remember. The use of order sets like the FMC PCA order set will help to prevent errors. For those using iPhones, the MedCalc program is a free download that provides quick opiate dose conversion. Computerized physician order entry, when available, will provide another solution. In the meantime, one useful and easy to remember approximate conversion is morphine 10mg I.V. = dilaudid 1mg I.V. = fentanyl 0.1mg I.V.

**CONVERSION CHART**

- **Morphine**
  - PO : SQ 3 : 1

- **Dilaudid**
  - PO : SQ 5 : 1

- **Morphine to Dilaudid**
  - PO : PO 4 : 1
  - PO : SQ 20 : 1
  - SQ : SQ 4-7 : 1

- **Fentanyl to Morphine**
  - Parenteral: 100ug : 10mg
  - Actiq: 200mcg = 6mg Morphine po
OPIOID MODULE SELF TEST

1. A hospice patient with metastatic lung cancer is admitted to the hospital with pneumonia. He has bone pain poorly controlled by Roxanol 100mg P.O. q 4 h. He is restless and moans in apparent pain with any stimulation. Assuming he is having neurotoxicity from the morphine, acceptable courses of action would be:
   a. File a complaint with the Pharmacy Board
   b. Add a benzodiazepine
   c. Reduce the dose of morphine and add a co-analgesic

2. A 60 y.o. man is 12-hour post bilateral total knee replacement. His BMI is 33 and he is a 2 ppd smoker x 45 years. He is opiate naïve. He is on a PCA pump with a basal infusion of 2mg morphine per hour and a PCA dose of 1mg with a lockout of 6 minutes. It’s midnight but he is restless, moaning in apparent pain in spite of maxing his PCA and having an additional 2mg bolus by his nurse. The on call physician orders Demerol 100mg I.M. Phenergan 25mg I.M. and dalmane 30mg P.O. At 0200 he is resting very quietly with a pulse ox reading of 90% on 2 L/min. nasal O₂. His nurse should:
   a. Be happy
   b. Be concerned

3. She should:
   a. Let him sleep
   b. Urgently attempt to arouse him and assess his ventilation
   c. Turn up his nasal O₂ to 3L/min.

4. His respirations are 6/min and shallow. He cannot be aroused. Next steps should be:
   a. Stat BMP and give 1 amp of 50% glucose
   b. Turn off the PCA and give 0.4-0.8 mg Narcan
   c. Continue the basal PCA and give .2mg Narcan I.V.
5. He awakens post Narcan, breathes deeply on command and pulse ox has increased to 92%. Now he is complaining of severe pain at the surgical sites. A safe approach to analgesia at this point would be Toradol 30mg I.V. q 6 h.
   a. True
   b. False

6. He achieves pain relief and falls to sleep. You should:
   a. Let him sleep undisturbed till morning
   b. Have him awakened periodically to assess the need for additional Narcan

7. Methadone is useful for all of the following except:
   a. Chronic pain caused by bone mets
   b. As a co-analgesic for patients with opioid induced hyperalgesia
   c. Pain control in patients with renal failure
   d. Severe migraine

8. Methadone is the preferred analgesic of choice for fibromyalgia.
   a. True
   b. False

9. A 50 y.o. opiate naïve man comes to the ER with severe renal colic. A prudent initial analgesic would be:
   a. Morphine 10mg I.V.
   b. Dilaudid 4 mg I.V.
   c. Morphine 2 mg I.V.
   d. Fentanyl 1 mg I.V.
10. You would expect your choice above to reach peak analgesic effect in:
   a. 10 min.
   b. 30 min.
   c. 1 hour
   d. 90 min.

11. A 65 y.o. woman with metastatic breast cancer has pain controlled with roxanol but is having severe pruritus. She is taking 30mg morphine every 4 hours around the clock. You want to switch to oxycodone to lessen the pruritus. An appropriate dose equivalent regimen would be:
   a. Percocet (5/325), 2 tabs q 4 h
   b. Oxycontin 20mg q 4 h
   c. Oxycodone 20mg q 4 h

12. Because of incomplete cross tolerance it is prudent to reduce the equianalgesic dose by 25% when switching to another opioid, therefore the patients dose of oxycodone should be:
   a. Percocet (5/325), 2 tabs q 6 h
   b. Oxycontin 20mg P.O. q 6 h
   c. Oxycodone 15mg P.O. q 4 h

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Please print name Date Completed