

CASE: 44 yo man is admitted for fevers. He is an active heroin user with a reported daily habit of 1-2 grams. The patient is agitated and complaining of 10/10 pain everywhere and threatens to leave the hospital against medical advice if his pain is not addressed. PMH includes being Hepatitis C (+) and a history of MRSA bacteremia. The patient reports being allergic to codeine. What should be done for his pain and potential opiate withdrawal?

Acute Pain Management

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Basics

- Assess and document pain intensity, location, and quality.
- Evaluate response to treatment at regular intervals.
- Individualize the treatment regimen with respect to agent, dose, route and frequency.
- Administer analgesics routinely on schedule if pain is persistent.
- Recognize side effects of treatment and manage appropriately.

Nonopioid analgesics

- Acetaminophen and non-steroidal anti-inflammatory drugs (NSAID's) may be used alone to treat mild pain and some forms of moderate pain.
- Acetaminophen and NSAID's may also be used for more severe pain in combination with opioids to provide an opioid dose-sparing effect.
- Avoid NSAID's in patients with renal disease, end-stage liver disease, peptic ulcer disease, coagulopathies, heart failure, and in those with hypersensitivity to aspirin or other NSAID's.
- There is no published data demonstrating that one NSAID provides more pain relief than another.

Dosing recommendations for commonly used nonopioid analgesics for pain

Agent	Initial dosing for pain	Comments
Acetaminophen	650mg po/pr q4-6h	NTE 4g/day; limit to < 2g/day in patients with liver disease
Aspirin	325-650mg po/pr q4-6h	NTE 4g/day; anti-inflammatory effects with plasma levels of 150-300 mcg/ml
Ibuprofen	400mg po q4-6h	
Naproxen	500mg initially then 250mg po q6-8h	
Ketorolac	30-60mg iv/im initially then 15-30mg iv/im q6h	NTE 5 days due to increased risk of GIB

* The above table is not all-inclusive

Opioids

- Opioids should be used to treat moderate to severe pain.
- Moderate potency opioids include hydrocodone, oxycodone, codeine, meperidine, and morphine.
- High potency opioids include hydromorphone and fentanyl.
- There is not a ceiling effect with regard to analgesia with pure μ agonists.
- Opioid tolerance and dependence as well as psychological dependence and addiction are uncommon following treatment for acute pain.
- Respiratory depression is uncommon when opiates are given at appropriate doses to patients with pain.
- There are different and unpredictable degrees of incomplete cross-tolerance to various opioid effects amongst agents (analgesia and adverse effects). Trials with multiple agents may be necessary to obtain optimal efficacy and tolerability.

Dosing recommendations for commonly used opioids for pain

Agent	Typical starting dose	Indication	Comments
Morphine	2-10 mg iv/im/subq q3-4h or 15-30 mg po q3-6h	Severe pain	Active metabolite may accumulate in setting of renal failure
Morphine controlled-release	15-30 mg po q8-12h	Severe pain that is persistent or chronic	Dosage must be individualized
Oxycodone	5-15 mg po q3-4h	Moderate to severe pain	
Oxycodone controlled-release	10-20 mg po q12h	Severe pain that is persistent or chronic	Dosage must be individualized
Hydromorphone	0.5-2 mg iv/im/subq q3-4h or 2-8 mg po q3-4h	Severe pain	
Fentanyl	25-100 mcg iv q1-2h	Sedation and procedural pain	Buccal lozenge also available
Meperidine	25-100 mg iv/im/subq q3-4h	Moderate to severe pain	Limit use < 48 hours and < 600mg/day; Avoid if CrCl < 30 ml/min
Methadone	2.5-10 mg iv/im q4-8h or 5-20 mg po q4-8h	Severe pain	May accumulate in adipose tissue and cause delayed toxicity

* The above table is not all-inclusive

Kinetics of common intravenous opioids

Drug	Time to onset	Time to peak	Duration of effect
Fentanyl	1-2 minutes	5 minutes	1-2 hours
Hydromorphone	2-3 minutes	10-15 minutes	~ 2 hours
Meperidine	10 minute	30 minutes	3-4 hours
Methadone	2-3 minutes	5-6 minutes	6-12 hours
Morphine	2-4 minutes	15-20 minutes	~ 2 hours

Factors Influencing Opioid Selection and Dosing

- Pain severity
- Prior opioid exposure
- Age
- Comorbidities
- Route of administration

Opioids to Avoid for Acute Pain Management

- Agents with long half-lives such as methadone are not preferred, as they are difficult to titrate and present challenging management problems when delayed toxicity develops.
- Meperidine should generally be avoided due to potential adverse reactions. The metabolite of meperidine (normeperidine) has a long half-life and may induce central nervous system (CNS) toxicity including mood changes, tremors, and seizures. This may occur in patients with renal impairment or with prolonged use, but it has occurred in patients without these risks. It is important to remember that this is not reversed by naloxone and may actually be potentiated by naloxone.

Renal Impairment

- Dosing adjustments are suggested for most narcotics in the presence of severe renal impairment. This is particularly true for meperidine and morphine.
- Meperidine is metabolized to normeperidine. Normeperidine accumulates in patients with renal impairment, which can lead to CNS toxicity, as mentioned above.
- Morphine is conjugated to a more active metabolite (morphine-6-glucuronide). M6G is excreted by the kidney, and elimination is directly related to creatinine clearance. An increased risk of respiratory depression has been observed in uremic patients.

Hepatic Impairment: Dosing adjustments are suggested for narcotics in the presence of advanced liver disease due to impaired metabolism.

Adverse Reactions

- Constipation: Most common and anticipated side effect. Prophylaxis with a bowel regimen is advised (stool softener plus a laxative).
- Nausea: Tolerance often develops rapidly over 1-2 days.
- Sedation and cognitive impairment: Eliminate nonessential CNS depressants and evaluate other potential causes, decrease the opioid dose or switch to a different agent, consider the addition of a psychostimulant if previous measures are inadequate.
- Respiratory depression: Always accompanied by other signs of CNS depression. Use naloxone as necessary.
- Itching: Mediated through histamine release (not a “true” allergy). Antihistamines help or switch agents if intolerable.
- Myoclonus is a rare reaction.
- Urinary retention occurs infrequently and is more common in the elderly.
- Hydromorphone is associated with fewer adverse reactions (i.e. less sedation, nausea, and itching), but it is also associated with increased psychological dependence.

Codeine Allergic Patients:

- Identify true allergies depicting an immunologic reaction (i.e. generalized rash or dyspnea) from adverse reactions (itching or nausea). This is an important distinction that will affect drug selectivity.
- Agents with the **least cross-reactivity with codeine** include meperidine, fentanyl, and methadone.
- Higher cross-reactivity with codeine occurs with morphine, oxycodone, hydromorphone, and hydrocodone.

Transitioning off patient controlled analgesia (PCA): Calculate 24-hour morphine equivalent once sufficient pain management has been achieved and convert to agent of choice using the equianalgesic table. Reduce dose by 20-30% to account for potential variability in oral absorption and differences in agents if changing the opioid medication. If indicated, give an oral dose of a long-acting opioid prior to discontinuing the PCA.

Rules to remember when managing moderate to severe acute pain

1. Reassess the patient frequently to evaluate the efficacy of the current regimen. Remember to assess pain with respect to dose (i.e. Does the pain improve with medication administration?) and to duration (i.e. Is the frequency of medication administration adequate?). Titrate to effect/side effects and transition to oral agents when possible.
2. Use an NSAID in addition to an opioid analgesic when possible. This can provide an opioid dose sparing effect which may minimize side effects. A non-selective NSAID is appropriate unless the patient is at a high risk for complications. Acetaminophen is a good choice for those who cannot receive traditional NSAID's.
3. Breakthrough pain meds should be included in regimen and should generally equal 25-50% of incremental long-acting opioid dose or 10-20% of the 24-hour opioid total. Higher doses may be appropriate and necessary.

4. Dosage increases of 50% should be considered for inadequate analgesic relief.
5. Prescribe a prophylactic bowel regimen when using opioid analgesics.
6. Avoid the use of meperidine when possible.

Equianalgesic Interchange (Approximate)

Agent	IV/IM/SQ	Oral
Morphine	10mg	30mg
Oxycodone	N/A	20mg
Hydromorphone	1.5	7.5
Methadone	1-10mg	2-20mg
Fentanyl	0.1mg	N/A (actiq = buccal)
Meperidine	75mg	300mg

Case Follow-up: The patient had staphylococcal bacteremia with an epidural abscess. He was initially started on methadone 40mg po bid for opioid withdrawal and then transitioned to once daily methadone administration for this purpose (80mg). Morphine extended release (MS Contin) 30mg po tid and naproxen 500mg po bid with morphine immediate release (MSIR) 15-30mg prn for breakthrough pain (btp) was started for his pain management. His MS Contin dose was increased to 60mg po bid and the MSIR was increased to 30-45mg prn btp. This regimen provided reasonable pain relief. He did not have a "true" codeine allergy in that it gave him nausea in the past. Docusate, senna, and prn bisacodyl were started as a bowel regimen.

References

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