What Do You Mean The Morphine Isn’t Working?
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Objectives
• Discuss the current U.S. opioid epidemic
• Review recommendations for safe prescribing and use of opioid analgesics
• Examine appropriate use of non-opioid analgesics in hospice and palliative care
• Explore patient cases highlighting methadone, high dose opioid infusions, and opioid sparing medications

Opioid Epidemic

Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015

www.cdc.gov
Opioid Epidemic

2,100,000 People with an opioid use disorder
42,249 People died from opioid overdoses
948,000 People used heroin
$504,000,000 Economic cost

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Pain Assessment

• NQF #1634 Pain Screening
  • Measure Description: Percentage of patient stays during which the patient was screened for pain during the initial nursing assessment.

• NQF #1637 Pain Assessment
  • Measure Description: Percentage of patient stays during which the patient screened positive for pain and received a comprehensive assessment of pain within 1 day of the screening.
  • location, severity, character, duration, frequency, what relieves or worsens that pain, and the effect on function or quality of life

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Pain Assessment

• Pain Intensity Assessment Tools
  • Visual Analogue Scale
  • Numeric Rating Scale
  • Verbal Descriptor Scale
  • FACES Scale (Wong-Baker)
  • Faces Pain Scale- Revised
  • Pain Thermometer

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Opioid Risk Tool (ORT)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of substance abuse</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
</tr>
<tr>
<td>Heroin use</td>
<td>2</td>
</tr>
<tr>
<td>Pain level</td>
<td>0</td>
</tr>
<tr>
<td>Personal history of substance abuse</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2</td>
</tr>
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<td>2</td>
</tr>
<tr>
<td>Pain level</td>
<td>0</td>
</tr>
</tbody>
</table>

REMS

• Education
  – Expectations: goals and quality of life
  – Opioid Therapy: safe storage, reliable caregiver, tablet inventory, pain diary, laws
  – Non-Drug Therapy: relaxation, communication, support groups

• Treatment Agreement
  – 4 A’s: Analgesia, Activities, Adverse Effects, Aberrant Behaviors
  – PDMP data
  – Prescriptions: small quantities, ER formulations

Opioid Prescribing
Adjuvant Therapy

Acetaminophen
- Mild Pain/Fever
  - Cost effective formulations:
    - Tablets
    - Capsules
    - Suppositories
    - Oral Liquids

Anti-Inflammatory
- NSAIDs
  - Examples: Ibuprofen, Naproxen, Meloxicam, Celecoxib, Diclofenac, Sulindac, Chlороprin, Piroxicam
  - AVOID: Ketorolac, Indomethacin

- Corticosteroids
  - Examples: Dexamethasone, Prednisone
  - Oral concentrate & Oral elixir

Patient Case: Jessie

- Jessie is a 67 yo female admitted to hospice with primary dx of pancreatic cancer with liver mets
- CC: Lower abdominal pain
  - Rating 7/10
  - Describes as stabbing, aching and constant
- Hx: HTN, Non-smoker, 5’4” 130 lbs
- Current analgesics:
  - Morphine ER 200mg PO q8h
  - Morphine IR 90mg PO q2h pm BTP (using 3 doses/day)
- Total Oral Morphine/day (OME): 870mg
**Patient Case: Jessie**

Morphine PO 870mg × 1.5mg IV Hydromorphone = 43.5 mg IV Hydromorphone
30mg PO Morphine

43.5 mg IV Hydromorphone × 0.75 (25% reduction) = 32.6 mg IV Hydromorphone

32.6 mg IV Hydromorphone ÷ 24 hours = 1.4 mg IV Hydromorphone/hour

1.4 mg Hydromorphone × 6 = 0.2 mg IV Hydromorphone Q10 minutes PRN breakthrough pain

**Patient Case: David**

- David is a 49 yo male admitted to hospice with primary dx of cirrhosis
- CC: abdominal pain and distension
  - Rating 7/10
  - Describes as dull, aching and constant
- Hx: alcoholism, illicit drug use, 5’9” 160 lbs
- Current analgesics:
  - Morphine IR 15mg PO q4h prn pain (using 6 doses/day)
- Total Oral Morphine/day (OME): 90mg
Fentanyl (Transdermal)

- Synthetic opioid
  - Opioid agonist
- Extra precautions
  - Potency
  - Heat exposure (Black Box Warning)
- Prolonged half-life and duration of action
  - Drug depot effect
- Patch strengths
  - 12mcg, 25mcg, 50mcg, 75mcg, 100mcg
  - 37.5mcg, 62.5mcg, 87.5mcg

Precaution:
- Opioid naïve patients
- Cachectic patients
- Do NOT increase dose frequently
- At least 12 hours to see benefit after patch placement
- May take up to 36 hours to reach target blood concentrations
- When patches are removed, about half of the drug is eliminated from the body after 17 hours
- An increase in body temperature can increase absorption by up to 30%

Patient Case: David

- Total Oral Morphine/day (OME): 90mg
  - 90mg x 0.25% = 22.5mg OME
  - 90mg - 22.5mg = 67.5mg OME
  - 67.5mg OME ÷ 2 = Fentanyl 33.75 mcg/hour
- Fentanyl 25mcg 1 patch changed Q72h
- Oxycodone 10mg PO q6h prn breakthrough pain
- Consider: Diuretic titration
Patient Case: James

- James is a 60 yo male admitted to hospice with primary dx of prostate cancer
- CC: Lower back and hip pain
  - Rating 10/10
  - Describes as stabbing and burning
- Hx: Diabetes, Non-smoker, 5'7" 145 lbs
- Current analgesics:
  - Morphine ER 60mg PO q8h
  - Morphine IR 20mg PO q2h prn BTP (using 5 doses/day)
- Total Oral Morphine/day (OME): 280mg

Methadone

- Synthetic opioid
  - Mu-opioid receptor agonist
  - Inhibits the reuptake of serotonin and norepinephrine
  - N-methyl-D-aspartate inhibitor
- Bad reputation
  - 2006 Public Health Advisory
- Long duration of action
- Efficacious
  - Chronic pain
  - Neuropathic pain
  - Refractory pain
- Cost effective

Methadone

- Most effective opioid for neuropathic pain
- Active N-methyl-D-aspartate (NMDA) receptor antagonist
  - Reduces CNS sensitization to pain/hyperalgesia
  - Reduces CNS amplification of pain sensation
- Few other known NMDA receptor antagonists:
  - Dextromethorphan
  - Ketamine
  - Memantine
Methadone

- Routes of Administration
  - PO, PR, IV, SubQ

- Half-life
  - Long, but variable (4-130 hours)
  - Increases with repeat dosing

- Drug Interactions

- Duration of action
  - 3-6 hours with INITIATION of dosing
  - Increased to 8-24 hours with REPEATED dosing
  - Takes 5-7 days to reach steady state

EKG Monitoring Guidelines

- Center for Substance Abuse Treatment Expert Panel
- U.S. Consensus Guideline
  - American Pain Society (APS)
- General Guidelines
- Not written specifically for hospice patients

QT Prolongation Risk Factors

- Female
- Impaired liver function
- Arrhythmias, CAD, CHF
- QT prolonging medications
  - Antipsychotics
  - Antidepressants
- Electrolyte imbalances
  - Methadone > 200mg/day

Approach

- Avoid multiple risk factors
- Arrhythmia is not an absolute contraindication
- Risk vs. benefit conversation
- Monitor for tachycardia, syncope, palpitations, diaphoresis
- Consider baseline EKG with periodic follow-up
Methadone

<table>
<thead>
<tr>
<th>24 Hour Oral Morphine Equivalent</th>
<th>Morphine : Methadone (per 24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg/24 h</td>
<td>2 : 1</td>
</tr>
<tr>
<td>30 – 99 mg/24 h</td>
<td>4 : 1</td>
</tr>
<tr>
<td>100-299 mg/24 h</td>
<td>8 : 1</td>
</tr>
<tr>
<td>300-499 mg/24 h</td>
<td>10 : 1</td>
</tr>
<tr>
<td>500-999 mg/24 h</td>
<td>15 : 1</td>
</tr>
<tr>
<td>&gt;1000 mg/24 h</td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

Patient Case: James

- Methadone Equianalgesic dosing ratio
  - 8:1
- 280mg OME divided by 8 = Methadone 35mg per day
- Dose reduce by 25-50% = 17.5mg to 26 mg
  - Cross-tolerance
- Recommendation:
  - Discontinue Morphine ER and Morphine IR 20mg
  - Begin Methadone 10mg po q12h and Morphine IR 45mg po q2h prn breakthrough pain
- Consider: Anti-inflammatory
Patient Case: Lynn

- Lynn is a 45 yo female admitted to hospice with a primary dx of breast cancer
- CC: pain in chest wall and peripheral neuropathy
  - Rating 7/10
  - Recently admitted for GIP stay secondary to pain
- Hx/Demo: 2 children at home
- Current analgesics:
  - Gabapentin 800mg po q8h
  - Hydromorphone 11mg/hour continuous IV infusion with 3mg IV q15 minutes prn breakthrough pain
- Prognosis is months

Ketamine

- FDA approved as a general anesthetic
  - Typically given via the IV or IM route for general anesthesia induction or maintenance
- Mechanism of action: unknown
  - N-methyl-D-aspartate (NMDA) receptor antagonist
  - Additional receptor activity at: nicotinic, muscarinic and opioid receptors
  - Preliminary studies and reports suggest additional anti-inflammatory effects
- Produces dissociative analgesia and sedation
- Abuse potential
  - "Special K"

Ketamine

- Data is available to support its use in:
  - Cancer related neuropathic pain
    - Reduction in pain intensity
  - Cancer pain
    - Decreased opioid consumption
  - Ischemic pain
    - Significant reduction in pain intensity at 24 hours and 5 days after initiation
  - Complex regional pain syndrome & neuropathic pain etiologies
    - Reduction in pain intensity; reduction in opioid utilization
Ketamine

- No studies comparing titration schedules or routes of administration

**Oral Administration**
- Initial dose: 10-25mg TID to QID
- Titrate by 10-25mg per day
- Maximum dose per day ~200mg

**IV Administration**
- Initial dose: 50-100mg/day
- Continuous or intermittent infusions
- Titrate by 25-50mg/day
- Usual effective dose ~100-300mg/day

Ketamine

- Adverse Effects
  - Psychotomimetic: dysphoria, hallucinations, vivid dreams/nightmares, restlessness, psychosis
  - Excessive salivation
  - Tachycardia
  - Newer concerns: neuropsychiatric, urinary and hepatobiliary toxicity
  - **Common adverse effects at subanesthetic doses:** feeling “spaced out”, nausea, sedation, delirium
    - Pre-medicate: haloperidol or lorazepam
    - Caution: known brain mets

Ketamine

- **Patient Counseling**
  - Report any unusual thoughts or changes in movement
  - Take this medication exactly as prescribed
  - Store in a safe place and do not share with others
  - You may require less of your maintenance pain medications over time
    - Report feelings of sedation
  - Do not stop or start new medications without speaking to your care team
  - You should not take ketamine if you have a history of seizures, head trauma, increased blood pressure, or are sensitive to ketamine
Patient Case: Lynn

- Psychiatric history screening - negative
- Ketamine test dose
- Ketamine 25mg PO TID
- Opioid dose reduction: 50%
- Stop ketamine
  - Burst therapy

Questions

References

- AAHPM Methadone Dose Conversion Guidelines.
References


