Pain Management in Cancer Patients

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Pain in Cancer Patients

- Nociceptive pain
  - Somatic: muscle, skin bone
  - Visceral: liver, reproductive tract, bowel, lungs
- Neuropathic pain: burning, numbness, tingling

Pain in Cancer Patients

- Surgical/procedural pain: LP Headache, Biopsy site pain, surgical pain post tumor resection
- Radiation-related: mucositis, skin irritation
- Chemotherapy-related: Peripheral neuropathy, Mucositis, Cystitis
- Disease associated: Pathologic fracture, Obstruction or Perforation, VTE
Pain in Cancer Patients

WHO’s Pain Relief Ladder

Where to Start: Assessment

- Location of pain
- Changes in pattern of pain
- Intensity / Severity
- Aggravating or Relieving factors
- Cognitive response to pain
- Cognitive ability / impairment
- Goals

Where to Start: Assessment

- Pharmacologic
  - Non-opioids
  - Opioids
  - Adjuvants
- Anticancer therapies
- Interventional therapies
- Physical therapies
- Cognitive-Behavioral therapies
Where to Start: Assessment

- Patient Characteristics
  - Performance status
  - Cognitive ability
  - Age
  - Gender
  - Drug interactions
  - Organ system dysfunction
  - Allergies
  - Previous History

Non-Opioid Agents

- Acetaminophen: analgesic, antipyretic; no anti-inflammatory effect
  - Co-analgesic with opioids
  - Mild to Moderate pain, musculoskeletal
  - Contraindicated in hepatic dysfunction
- NSAID’s: analgesic, antipyretic, anti-inflammatory
  - Co-analgesic with opioids
  - Beneficial in pain related to bone metastases
  - Contraindication and caution in decreased renal function, platelet dysfunction, or bleeding disorders, history of GI bleeding

Opioid Agents

- Morphine:
  - Oral: 5-10mg q4h
  - IV: 0.5-1mg q4h
- Hydromorphone:
  - Oral: (1)-2mg q4h
  - IV: (0.1)-0.2mg q4h
- Oxycodone:
  - Oral: (2.5)-5-10mg q4h
Opioid Agents

- **Fentanyl:**
  - IV: (10)-25mcg q1h

- **Methadone:**
  - Oral: 5mg q12h (2.5mg in the elderly)
  - IV: 0.2mg q1h

- **Hydrocodone/APAP:**
  - Oral: 5-10/315mg q4h

- **Tramadol:**
  - Oral: 50mg q4h PRN, max 400mg/day
  - Adjustments for renal and hepatic dysfunction
  - Mu-opioid agonist, Norepinephrine and serotonin reuptake inhibition
  - No adjustments for mild-moderate renal and hepatic dysfunction. Not studied in severe impairment
  - Same mechanism as tramadol.
  - Just say NO!

- **Meperidine**
- **Pentazocine**
- **Butorphanol**
- **Nalbuphine**
- **Buprenorphine**

Adjuvants

- **Multipurpose agents:** Glucocorticoids, TCAs, SNRIs, Alpha-2 adrenergic antagonists, cannabinoids, lidocaine, capsaicin
- **Neuropathic agents:** TCAs, SNRIs anticonvulsant analgesics (gabapentin, carbamazepine, pregabalin, lamotrigine, valproate), mexiletene, lidocaine, ketamine
- **Bone pain:** bisphosphonates, calcitonin
Adjuvant Agents

- Clinical pearl for ketamine:
  - Oral, sub-q, intranasal, IV, sublingual, topical
  - Oral dosing: 10-15mg every 6 hours
  - Unrelieved neuropathic pain
  - Reduce need to escalate opioid dose
    - Empirically reduce opioid 25-50% when initiating to reduce sedation
  - No oral formulation available, use injectable given orally, mask taste with juice or cola

Methadone

- Unique mechanism of action:
  - Mu & Delta opioid receptor agonist
  - N-methyl d-aspartic acid (NMDA) receptor antagonist (theoretically why it’s useful in neuropathic pain)
  - Blocks reuptake of serotonin and norepinephrine (another mechanism beneficial in neuropathic pain)

- Prolonged half-life allows for every 8-12hr dosing (pro and con, also makes dose titration tricky)
- Multiple routes of administration: IV, Sub-q (irritating), oral, rectal and epidural (nasal and sublingual are not commercially available)
- May be effective when other opioids fail
- Inexpensive oral medication
- Dose conversion between other opiates and methadone not well established.
Methadone

- Oral to parenteral conversion: 2:1
- Oral to rectal conversion: 1:1

Methadone Dose Conversion Policy Avera McKennan

24 hour Oral Morphine Equivalent  Methadone Conversion Ratio
<30 mg/day 1:2
30-99 mg/day 4:1
100-299 mg/day 8:1
300-499 mg/day 10:1
500-999 mg/day 15:1
>1000 mg/day 20:1

Opiate Conversion Table

Conversion factors for commonly used narcotics
- **PO: IV/SC**
  - Morphine: 3:1 (30mg PO = 10mg IV)
  - Hydromorphone: 5:1 (7.5mg PO = 1.5mg IV)

- **PO: PO**
  - PO Oxycodone: PO Morphine 2:3 (20mg Oxycodone = 30mg Morphine)
  - PO Hydrocodone: PO Morphine 1:1 these are considered equivalent in dosing
  - PO Hydromorphone: PO Morphine 1:4 (7.5mg Hydromorphone = 30mg Morphine)

- **Transdermal:PO**
  - Fentanyl patch: Morphine PO 1.2-3 (1mg Fentanyl patch = 50-75mg Morphine PO)

- **IV:IV**
  - IV Hydromorphone: IV Morphine 1:7 (1.5mg Hydromorphone = 10mg Morphine)
  - IV Fentanyl: IV Morphine 10:1 (100mcg Fentanyl = 10mg Morphine)

Methadone

- Baseline EKG for methadone initiation unless patient is under Hospice services
- Then check for every 100mg methadone TDD
- 5-7 days between dose adjustments, repeat EKG
- Potassium and Magnesium baseline and with every dose adjustment – not if under Hospice services

Methadone

- Oral
  - Onset of analgesia ~ 2.8 hours
  - Absorption in GI within 30 minutes -> Peak at 4 hours, decline at 24 hours
  - Bioavailability 76%
  - CYP 450 enzyme inhibitor (3A4 weak, 2D6 moderate)
  - Biphasic elimination
    - Initial distribution = 4-6 hours
    - Extended phase = 30-60 hours

Methadone

- Half-life 8-100 hours (average is 24 hrs)
- Steady state ~ achieved after ~ 1 week (may take up to 4 weeks)
- Precautions:
  - Sleep apnea or underlying lung related comorbidities, higher risk of opioid induced respiratory depression
  - Do not adjust doses more often than every 5-7 days (long half-life, potential accumulation of drug)
  - Drug – drug interactions: screen each and every medication; enzyme inducers, inhibitors, agents that prolong QTc interval
Methadone

- **Contraindications**
  - Allergy to methadone
  - EKG >/= 450 ms at baseline
  - Patient with altered mental status
  - Increased intracranial pressure
  - Cardiac arrhythmia diagnosis
  - Monoamine Oxidase Inhibitor (MAOIs), i.e. Parnate, Nardil
  - Medication regimen with numerous agents that can prolong QTc interval

**Methadone Case Study #1**

- KG is 72 yo woman with limited stage lung cancer who develops shingles; she has c/o post herpetic neuralgia. She has tried multiple adjuvant agents with minimal success. She does not take any other opioids, her medication list is as follows:
  - Lisinopril 20mg once daily
  - HCTZ 25mg once daily
  - Sertraline 50mg once daily.
- What would be an appropriate recommendation for methadone dosing?

**Methadone Case Study #2**

- JR is a 64 yo male admitted to hospice with a terminal diagnosis of pancreatic cancer. His analgesic regimen is TD fentanyl 200mcg/hr and oxycodone 20mg PO q4h PRN BTP (taking about 6 doses per day). Convert to methadone, assume the patient is not on any medications known to interact with methadone. JR’s pain is fairly well controlled, but he has a skin dermatitis r/t adhesive of patch.
Pain

- No maximum dose on narcotics, the correct dose is the effective dose.

- Titrate dose accordingly:
  - Every 24 hours if still taking oral, based on previous 24 hour breakthrough dose use
  - When death is imminent and no longer able to take oral, use continuous intravenous infusion and may titrate every 1-2 hours

Acute Pain in the Opioid-Naïve Patient

Cleveland Clinic Guidelines:

- Morphine 1mg IV per minute for 10 minutes
- Wait 5 minutes, reassess
- Repeat above until response or a max dose of 30mg
- Alternatives: fentanyl 20mcg per minute or hydromorphone 0.2mg per minute

Acute Pain in the Opioid-Naïve Patient

Cleveland Clinic Guideline:

- If oral route desired
- Morphine immediate-release 5mg PO every 30 minutes until pain relieved
- Oxycodone 5mg or hydromorphone 1mg are alternatives
Acute Pain in the Opioid-Naïve Patient

NCCN Guidelines:
- Morphine 1-5mg IV (or equivalent of alternate opioid) and reassess at 15 minutes
- If pain persists, double the dose and reassess again in 15 minutes
- Repeat up to 3 cycles

Acute Pain in the Opioid-Naïve Patient

NCCN Guidelines:
- Morphine 5mg PO every 30-60 minutes
- Reassess and repeat until total of 30mg given
- Useful for home patients with "starter kit"

Acute Pain During Chronic Opioid Therapy

Cleveland Clinic Guideline for Parenteral Dose Titration:
- Calculate the previous 24-hour around-the-clock (ATC) and rescue doses
- Convert to a parenteral hourly dose using conversion chart
- Give an initial bolus of twice the hourly rate
- Repeat the hourly dose every 15 minutes until pain relieved
- Reassess and calculate the true hourly dose
Acute Pain During Chronic Opioid Therapy

Fast Facts #54:
- Calculate/convert patients current opioid regimen to an hourly parenteral equivalent
- If patient previous regimen is adequate, go with that
- If previous regimen was not adequate, increase 50-100% for moderate to severe pain or 25-50% for mild to moderate pain; must give initial bolus
- Determine a rescue dose (50-150% of hourly rate)

Cleveland Clinic Guidelines for Oral Dose Titratin:
- Calculate the previous 24-hour ATC and rescue doses
- Divide by the frequency of the selected product (2 if every 12hr, 3 if every 8hr)
- If pain remains unrelieved, double the previous rescue dose and give every 30 minutes until relieved

References