Methadone and Cancer Pain

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Introduction

- 70-90% of patients with cancer will experience moderate to severe pain
- Pain tends to get worse with time as the disease progresses
- Mainstay of treatment is strong opioid therapy
- Methadone is a strong synthetic opioid that can play a significant role in the management of cancer related pain due to its advantages of:
    - Rapid-onset of analgesic effect
    - Long half-life
    - Extremely low cost
- However, its complex pharmacological properties are a concern and deterrent for providers

Today we will discuss:

- Methadone pharmacology
- Methadone as a first-line opioid
- Methadone as an add-on to ongoing opioid treatment
- Methadone rotation
- Methadone for neoplasm related neuropathic pain
- Methadone for cancer pain in pediatrics
- Safety challenges of methadone use

Pharmacology

- challenging to prescribe due to its wide variability in pharmacokinetics between individuals which makes the effects of dose, plasma concentrations and pharmacologic effect difficult to predict
    - Understanding the pharmacology is important!
- Mechanism of action: highly potent mu opioid agonist, prevents monoamine reuptake in periaqueductal gray region of the brain, and inhibits presynaptic NMDA receptors
    - Significance → by inhibiting serotonin and norepinephrine reuptake in the CNS and antagonizing the NMDA receptor, methadone can mitigate pain and promote recovery while also modulating pain stimuli propagation to reduce the development of hyperalgesia and opioid tolerance

Chemical Structure

- Methadone has 2 different chemical structures: R and S methadone, each with different pharmacologic properties
- It is most commonly available as a 50:50 racemic mixture
- R-methadone is approximately 50x more potent than S-methadone in the provision of analgesia due to a tenfold greater affinity for the opioid receptors
- Both structures inhibit serotonin and norepinephrine reuptake as well as exert non-competitive NMDA receptor antagonism
- With respect to safety considerations, detrimental side effects can occur if either structure's plasma concentration rises above therapeutic levels
    - For example, elevated levels of S-methadone can lead to cardiotoxicity because of its stronger affinity for voltage gated K+ channel, leading to QT interval prolongation
    - Alternatively, higher levels of R-methadone are more likely to cause serotonin syndrome

Administration

- Most commonly given in PO form, although it is also available in rectal, sublingual, IM, IV, intrathecal, and subdural routes
- Following oral administration, peak plasma drug concentration is 2.5-3 hours depending on if it is given in solution vs tablet form
- The bioavailability range is 41-99%, with mean of 70-80%

Pharmacokinetics

- Due to high lipid solubility, methadone exhibits a rapid and extensive initial distribution phase into tissues
- Methadone plasma concentrations follow a bi-exponential curve
  - Rapid alpha phase with a half-life of 1.9-4.2 hours
  - Slower beta phase with a half-life of 8-47 hours
- Alpha phase correlates with duration of methadones analgesia with is typically 6-8 hours
- Although the plasma drug level in the beta phase is subanalgesic, it is sufficient to prevent opioid withdrawal symptoms
  - This is why methadone as treatment for OUD is typically once daily dosing, whereas for malignancy related pain it is dosed every 8-12 hours
- As a result of methadone's long elimination half-life, dose titration should only occur every 5-7 days to avoid the potential for drug accumulation and overdose

Metabolism and Drug-Drug Interactions

- Methadone undergoes extensive hepatic metabolism, primarily through the CYP450 pathway
- It does not accumulate in the setting of renal failure and is therefore considered a good option for pain management in patients with chronic renal insufficiency and ESRD
- Enzyme inducers (result in subtherapeutic methadone levels): **anticonvulsants** (phenytoin, carbamazepine, phenobarbital), antiretroviral agents (rifampin)
- Enzyme inhibitors (result in supratherapeutic methadone levels): **antibiotics** (ciprofloxacin, erythromycin, trimethoprim), **antidepressants** (citalopram, fluoxetine, sertraline), **anti-fungals** (fluconazole), **benzodiazepines**, cardiac drugs (verapamil, nifedipine, amiodarone), NSAIDs, neuroleptics, PPIs, TCAs and cannabinoids

Methadone as First-line Treatment for Cancer Pain

- Recent study has shown that first-line, low-dose methadone resulted in:
  - a rapid decrease in pain intensity
  - minimal need for titration
  - No evidence of accumulation or sedation
- In the study, patients were included if they were opioid naive or receiving oral morphine equivalents of <60 mg/day
  - In opioid naive patients, methadone was started in doses of 2 mg TID
  - In those receiving OME of <60 mg/day, methadone was started at 3 mg TID

- Significance → as cancer patients are having increased survival time with new therapies, methadone can be considered an advantageous option given it requires minimal dose increases over time compared to traditional opioid therapies
- Additional support for this finding
    - Another study compared advanced cancer patients receiving morphine vs methadone.
    - Initial doses were chosen according to the pain intensity (24-144 mg/day of morphine, 8-28 mg/day of methadone).
    - Doses of methadone remained constant over the 14 day period, while a 63% increase in morphine doses were reported.
    - Pain intensity significantly decreased in both groups and adverse effects were similar

Take Home Points

- Studies have shown that methadone may be effective as a first-line drug in management of cancer pain
- It provides similar analgesia to other opioid regimens and has similar adverse effect profiles
- The primary advantage is related to dose stability over time with slower rate of escalation compared to other opioid therapies
- Additionally, using methadone as first-line as opposed to rotating to it from higher dose opioids takes away the complexity and unpredictability of conversion ratios

Methadone as an Add-On to Ongoing Opioid Treatment

- In cases where a sufficient analgesic effect has not been achieved despite increasing the opioid doses, the traditional practice has been to attempt a complete rotation over to methadone
- In 2004, it was first described as an “opioid semi-switching” regimen where patients with cancer-related pain who had at least doubled their opioid doses in the past week had methadone added in an initial dose of 20% of the ongoing opioid regimen
    - This was successful in both stopping additional opioid escalation and achieving better analgesic effect
- Several additional studies have been done regarding adjunctive therapy with low-dose methadone
    - Patients are started on 2.5-5 mg BID combined with their ongoing opioid therapy
    - Doses typically stabilized around 10-15 mg per day
    - Improved pain control is reported in anywhere from 50-75% of cases

Take Home Points

- Use of methadone as adjunctive therapy has been shown to be beneficial in patients with complex cancer pain
  - Decreases need for additional escalation of doses in their ongoing opioid therapy and can potentially allow for decreased doses within the first 1-2 weeks of initiation
  - Provides better pain relief without increasing side effects
- Average dose of adjunctive methadone therapy is 5-10 mg per day, given in twice daily dosing, and did not exceed 20 mg per day
- Good candidates for adjunctive methadone therapy would be:
  - Patients with mixed nociceptive and neuropathic pain
  - Patients who are requiring fairly rapid escalation in opioid therapy without much benefit

Rotation to Methadone

Methadone Rotation

- **No clear consensus on superiority** of one methadone rotation method over another
- **Stop-and-Go Method**
  - Immediate replacement of opiate with methadone
- **3-Day Rotation**
  - Stepwise reduction of current opioid by ⅓ each day and replacing it with ⅓ equianalgesic dose of methadone
  - Some evidence this may be safer, especially when rotating from higher morphine equivalent daily doses
- Variability in methadone conversation ratios and dose reduction percentages used in different studies

Neoplasm Related Neuropathic Pain

Methadone and Neoplasm-related Neuropathic Pain

- 40% of cancer pain is associated with neuropathic and nociceptive pain simultaneously (mixed pain)

- Methadone has antagonist activity on NMDA-receptors, making it potentially relevant to treat neuropathic pain

Methadone and Neoplasm-related Neuropathic Pain

- A French study by Fawoubo et. al., rotated advanced cancer patients with refractory pain to methadone
  - Mainly head & neck and lung cancers
  - 48 patients included, 17 completed to endpoint
- At Day 28 there was a clinically significant decrease in pain intensity
  - Mainly compression/squeezing, allodynia,
- Other studies show impact on neuropathic pain but are limited
  - Concurrent use of steroids, lack of neuropathic specific pain scales

Methadone Use in Pediatric Cancer

Pediatric Cancer Pain

- **Pain is the most common symptom** reported by children with advanced cancer
- Methadone is an attractive treatment option as it is the **only long-acting opioid available in liquid form**
- Limited research on use in children aside from reports of prolonged QTc interval

Pediatric Cancer Pain

- Retrospective chart review study conducted by *Madden et al*, at MD Anderson Cancer Center from December 2014 to March 2017
  - 62 patients started on long acting opioid therapy
  - 52 patients (84%) started on methadone (0.1 mg/kg PO q12 hours)
  - NO episodes of opioid-induced neurotoxicity and NO cardiac arrhythmias detected
  - Significant improvements in pain, insomnia, and fatigue
  - NO significant effect on psychological outcomes (anxiety, nervousness, etc)
- Methadone is a safe and effective long-acting opiate in children with advanced cancer pain -including as a first-line long-acting opiate

Methadone in Pediatric End-of-Life Care

- Retrospective review of pediatric patients at St. Jude Children's Research Hospital who received methadone in their last 30 days of life
  - All died in inpatient setting
  - Time frame: October 2009 - October 2017
- Wide range in dosing regimens
- Older pediatric patient population
  - 75% of patients >/= 15yo
- High concurrent use of anxiolytics (80% of patients)
- EKGs obtained prior to initiation in 50% of patients
  - NO patients required methadone discontinuation due to prolonged QTc

Pediatric Palliative Physician Attitudes, Beliefs, and Practices Regarding Methadone

- Electronic survey examining demographics, practices, attitudes, and beliefs of palliative care physicians toward use of methadone in children with advanced cancer
- 105 pediatric palliative physicians responded (>/= 50% of clinical time)
- 77% of physicians reported prescribing methadone
  - Of those who did NOT primary reason was due to institutional policies
- Starting dose determined by equianalgesic dosing with appropriate dose reduction reported by 85% of responders, 8% reported initiating with weight based dosing
- Initial EKGs obtained for QTc monitoring in 65% of cases and subsequent EKGs obtained more often by Fellowship trained palliative physicians
  - Especially in children with underlying cardiac illness of liver dysfunction

Safety Challenges in Methadone Use

Safety Challenges

- Adverse effects include: Nausea/vomiting, drowsiness, constipation, and confusion
  - Comparable to those of other long acting opioids (MS Contin, transdermal fentanyl)
- Wide ranging bioavailability: from 36 -100%
- Lipophilic nature with wide tissue distribution
- Largely hepatically and intestinally cleared via CYP3A4, CYP2B6, and CYP2D6
  - Makes it an excellent choice in pts with renal dysfunction
  - Use with caution in patients with advanced liver disease
  - Close monitoring needed when coadministered with other CYP inducers and inhibitors
    - Caution in patients receiving active treatment (i.e. TKIs, platinum agents, etc)

Safety Challenges

- QT Prolongation
  - More frequent in children with underlying cardiac disease
  - Occurs at higher frequency in patients receiving targeted cancer therapies (i.e. TKIs)
  - Can occur due to electrolyte abnormalities associated with cytotoxic chemotherapy-induced diarrhea, emesis, mucositis, and poor nutrition

Conclusions

Methadone is safe and effective for management of cancer pain in adult and pediatric patients, even as a first line long acting analgesic.

Future Directions

- Larger studies with greater patient diversity needed

- Need for greater provider and patient education
  - To overcome biases and improve utilization
  - Improved comfort with prescribing and monitoring

- More research needed on role in treatment of neuropathic cancer pain

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