PALLIATIVE PEARLS
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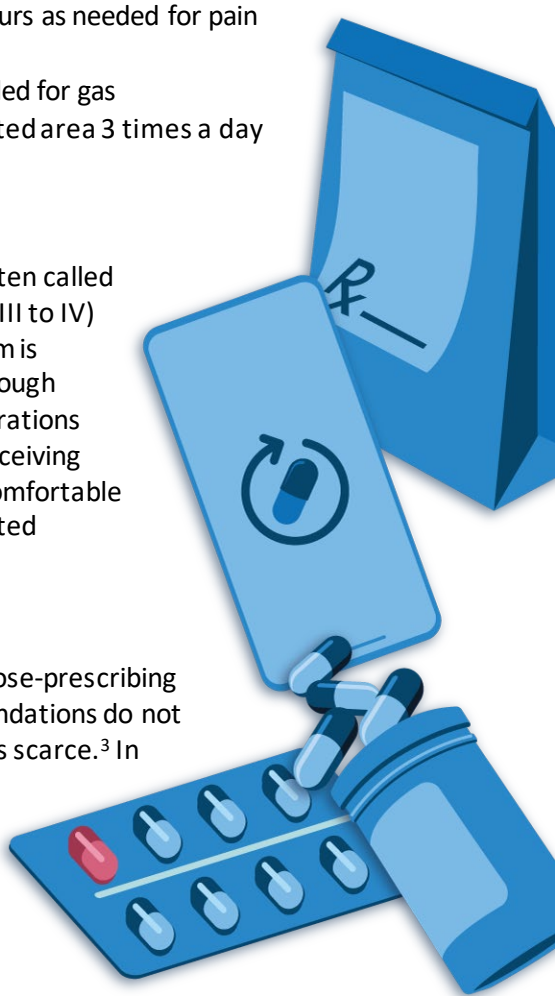
Methadone and the Pediatric Patient: Dosing Guidance | June 2021

PATIENT CASE

DW is a 5-month-old male with a primary diagnosis of osteogenesis imperfecta with secondary of pulmonary disease and GERD. He weighs 3.52 kg (7.78 pounds) and has no known drug allergies. DW is receiving hospice care at home.

MEDICATIONS

- Acetaminophen 160mg/5ml; 1.4ml (44.8mg) via NG tube every 6 hours as needed for pain or fever
- Famotidine 40mg/5ml; 0.4ml (3.2mg) via NG tube twice a day for reflux
- Morphine 20mg/ml oral liquid; 0.4ml (0.8mg) via NG tube every 2 hours as needed for pain
- Senna syrup; 1.25ml via NG tube daily as needed for constipation
- Simethicone drops; 0.3ml (20mg) via NG tube every 6 hours as needed for gas
- Zinc oxide 40% ointment; apply a thick layer topically to the affected area 3 times a day as needed to prevent rash
- Oxygen



Osteogenesis imperfecta (OI) is an inherited connective tissue disorder, often called "brittle bone disease". Patients with moderate to severe type of OI (types III to IV) suffer multiple fractures with minimal or no trauma.[1,2] DW's hospice team is seeking a recommendation for a long-acting pain medication for him. Although DW is responding to morphine therapy, the team hopes to offer longer durations of pain relief for the benefit of both DW and his parents. He is currently receiving morphine 0.4ml (0.8mg) every 2 hours around-the-clock and appears uncomfortable as each 2-hour interval nears. One of the palliative care physicians suggested methadone.

PEDIATRIC PAIN

Pediatric patients, encompassing all individuals under the age of 18, are dose-prescribing challenges for the palliative care clinician. Often, labeled dosing recommendations do not include pediatrics and palliative care literature specific to this population is scarce.[3] In these cases, the experience of the palliative care practitioner, specific medication properties, and patient characteristics guide the practical use of medications.

Nonpharmacological pain therapy:[4]

- Developmental interventions – Involve the patient in decision-making where appropriate and provide honest, developmentally appropriate information
- Physical interventions – Positioning, judicious use of temperature changes, healing touch, and acupressure
- Sensory interventions – Art therapy, music therapy and aromatherapy
- Psychology-based interventions – Verbal distraction through conversation, breathing exercises, visual distractions such as lava lamps and computer games

Pharmacological pain therapy:[5]

When nonpharmacological therapy fails to completely manage pain, medication therapy must be employed. A comprehensive pain assessment is recommended to identify the site(s) of pain, the type of pain – somatic (e.g., body aches and inflammatory pain); visceral (organ pain); and/or neuropathic – and severity as determined by an age- and development-appropriate scale. For infants, such as DW, a scale that allows the clinician to observe behavior to assess pain is most appropriate. The FLACC Scale is one example.[6]

For mild, somatic types of pain, over-the-counter remedies such as acetaminophen and ibuprofen are employed. When somatic pain becomes moderate to severe, short-acting opioids may be employed with consideration to corticosteroids (e.g., prednisolone) or muscle relaxants (e.g., baclofen), where applicable. Visceral pain of any severity responds well to opioid therapy and/or corticosteroids.

Neuropathic pain of any severity is often challenging to manage and may employ trials of medications used for dual indications in palliative care. The most common medication used for neuropathic pain is gabapentin (Neurontin®). Other medications to consider include anticonvulsants or, in patients with concomitant depression, tricyclic antidepressants (TCAs). Most opioids have no role in the treatment of neuropathic pain.[7] Methadone, however, has actions on both opioid and N-methyl-D-aspartate (NMDA) receptors making it useful for patients with mixed nociceptive and neuropathic pain. It is also the only oral opioid in liquid formulation with long-acting properties when administered routinely.

METHADONE

Common Adverse Reactions:[5]

- Dizziness, drowsiness
- QTc prolongation
    - The QT interval is the ECG (electrocardiogram) measurement representing the total time from ventricular depolarization to complete repolarization
    - QTc is the QT interval corrected for heart rate
    - Prolongation of the QTc interval (e.g., >450 ms) is a surrogate marker for the risk of developing a potentially fatal ventricular arrhythmia called torsades de pointes (TdP)[8]

Drug-Drug Interactions:[5,8,9]

- Medications that *decrease* methadone concentrations include phenobarbital, carbamazepine, and some anti-retroviral therapies (e.g., ritonavir) – manage these interactions by encouraging the use of breakthrough pain medication

- Medications that *increase* methadone concentrations include amiodarone, azole antifungals (e.g., fluconazole), antidepressants (e.g., citalopram, amitriptyline), and antibiotics (e.g., erythromycin) – manage these interactions by avoiding their use or empirically reduce methadone dose by 25% or more.
- Medications that increase the QTc interval (e.g., haloperidol, olanzapine, ondansetron, tricyclic antidepressants such as amitriptyline) – manage these interactions by avoiding concomitant use with methadone when possible. When unable to avoid the interaction, monitor closely as indicated in the "Monitoring" section below.

Drug-Disease State Interactions:[9]
Considering methadone's propensity to prolong the QTc interval, it is recommended to avoid it or closely monitor its effects on patients with risk factors for QTc interval prolongation including:

- Electrolyte abnormalities such as hypokalemia or hypomagnesemia
- Impaired liver function
- Structural heart disease (e.g., congenital heart defects, history of endocarditis, heart failure)
- Genetic predisposition such as congenital prolonged QT syndrome or familiar history of prolonged QT syndrome

Potentially Appropriate Candidates for Methadone Therapy:

- Neuropathic pain
- Unrelieved pain and/or intolerable side effects of currently administered high-dose opioids
- Patients with true allergies to morphine and other opioids
- History of dysphagia and/or using a feeding tube to administer medications
- Significant renal impairment

Potentially Inappropriate Candidates for Methadone Therapy:

- Multiple drug-drug interactions identified
- One or more of the following conditions are present: arrhythmia, electrolyte abnormalities, sleep apnea, history of syncope
- Patients who live alone, may be non-adherent to medications and/or have poor cognition

Oral Dosing Guidance for Pain:
Weight-based dosing varies in the literature; however, all approaches are conservative and considered appropriate:

- Shega JW, et al, (2017)[4] - 0.1mg/kg/dose by mouth every 8 hours
- Ferrell B. (2016)[10] - 0.1-0.2mg/kg/dose every 4 hours for the first 2-3 doses, then every 6-12 hours (max: 5mg/dose initially)
- Lexicomp (2021)[11]
    - Infants ≤ 6 months of age: 0.025 to 0.05 mg/kg/dose every 4 to 8 hours
    - Infants > 6 months of age, children, adolescents (patient weight < 50 kg): 0.1 to 0.2 mg/kg/dose every 4 to 8 hours
    - Infants > 6 months of age, children, adolescents (patient weight ≥ 50 kg): 5 to 10 mg every 4 to 8 hours

Monitoring:[9]

- Monitor for the following symptoms during methadone initiation and titration: excessive drowsiness/level of arousal, slow respiration or periods of apnea, pinpoint pupil size[5]
- ECG monitoring and hospice and palliative care patients: The patient's clinical situation and prognosis should guide the clinician's approach to ECG monitoring. If a patient is actively seeking disease-modifying therapies, QTc monitoring is recommended. If the patient has chosen supportive care only, it is recommended the clinician be attentive to risk factors for QTc prolongation and manage accordingly.[8,12]

PATIENT CASE ASSESSMENT AND RECOMMENDATIONS

Evaluating the benefits and the risks, it is decided to initiate methadone therapy. Methadone has a long-acting duration with routine dosing, and has effects on both opioid and NMDA receptors, making it beneficial for somatic (inflammatory and bone pain and muscle aches), visceral (organ pain, referred pain) and neuropathic pain. It is also inexpensive and available in a concentrated liquid, making it feasible for children unable to swallow solid dosage forms. Although methadone has numerous drug interactions and disease state interactions, there are no interactions assessed nor anticipated for DW.

Initiating methadone therapy:

- Continue the "as needed" morphine liquid regimen at 0.4ml (0.8mg) via NG tub every 2 hours as needed
- Calculate the total morphine usage/day.
    - DW is receiving 9.6mg morphine/day (0.8mg x 12 doses) with end-of-dosing-interval pain.
    - Considering patient's age and the total daily morphine dose being less than 60mg, weight-based, opioid-naïve dosing is chosen[6] instead of a morphine-to-methadone conversion ratio approach.
- DW weighs 3.52 kg - a conservative dose of 0.025 mg/kg/dose (=0.1mg/dose)[11] is recommended
- Begin methadone 5mg/5ml solution; 0.1ml (0.1mg) via NG tube every 8 hours
- Encourage the use of "as needed" morphine, especially during the first 7 days of methadone use
- On day 5-7, assess use of breakthrough morphine and adjust methadone regimen accordingly

Follow-up 2 months later:
The hospice team indicates methadone has been well tolerated by DW over the past 2 months and he has been very comfortable. He has been gradually titrated to the following dose and increased frequency: methadone 5mg/5ml; 0.2ml (0.2mg) via NG tube every 6 hours. Morphine breakthrough dosing has continued with infrequent use.

For more on pediatrics, consider review of these prior cases on pediatric-related topics:

- Principles of Pediatric Dosing
- Neuropathic Pain Management in Pediatrics
- Management of Terminal Secretions in the Pediatric Patient
- Medication Selection for Patients on Ketogenic Diets

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