Perils & Pearls When Prescribing

RANDALL W KNOEBEL, PHARMD, BCOP
CLINICAL PHARMACY MANAGER
UNIVERSITY OF CHICAGO MEDICINE

KRISTEN WELSH, PHARMD
CLINICAL PHARMACY SPECIALIST
RUSH UNIVERSITY MEDICAL CENTER
Disclosure

• I have no actual or potential conflict of interest in relation to this presentation
Learning Objectives

• List some medications that are frequently involved in drug-drug interactions and how they can be mitigated

• Describe some of the impacts age has on both the pharmacokinetics and dynamics of opioid analgesics

• Identify alternative modes of opioid delivery when the oral route is insufficient
Meet SM

- 69 YOM presents to hospital with newly diagnosis acute myeloid leukemia and history of seronegative rheumatoid arthritis, multiple lumbar spine surgeries for radiculopathy, chronic myalgias, and cervicalgia.

- He suffers from severe chronic neck and low back pain that at one time responded to oxycodone; fentanyl patch; trigger point injections with steroid, local anesthetic and botulinum toxin; and physical therapy.

- Pain not only impairs his function significantly, but also was affecting his sleep, relationships and mood.

- The patient was prescribed oral methadone 5 mg every 8 hours with immediate-release hydromorphone for breakthrough pain.
Methadone

- Methadone is a synthetic opioid approved by the United States Food and Drug Administration (FDA) in 1947 for a number of pain-related syndromes
- Available as a racemic mixture that targets both the opioid and the NMDA receptors
- Methadone offers a broader coverage of multidimensional pain syndromes – including ones only partially responding to opioids
- Increased interest based on unique pharmacology, potential efficacy in difficult-to-treat pain syndromes, and low cost
- Unique challenges in dosing due to uncertain potency, long and variable half-life, and numerous drug-drug interactions
Methadone Pharmacokinetic & -dynamic Properties

• Readily absorbed orally with ~85% of dose reaching blood stream (3x that of morphine)

• Biphasic elimination
  • α-elimination – rapid, distribution into adipose tissue, related to analgesic period
  • β-elimination – slow, elimination from body, non-analgesic but attenuates withdrawal

• Highly protein bound

• Highly reliant on hepatic cytochrome enzyme system primarily CYP3A4 and, to a lesser extent, CYP2B6, CYP2D6 and CYP1A2

• Blocks human ether-a-go-go related gene (HERG) potassium channel producing negative chronotropic properties (QTc prolongation)

After initiation of methadone 5 mg TID, and eventual titration to 7.5 mg TID; his pain and function improved. He denied side effects from therapy.

During this time he was initiated on a trial for his leukemia which was complicated by persistent neutropenic fevers and radiographic evidence identifying a probably invasive fungal infection.

Voriconazole therapy was initiated.

During the following two weeks, the patient’s control of pain continued to improve, but he and his wife reported increased and progressive sedation, fatigue and cognitive dysfunction.
Drug-Drug Interactions (DDI)

- WHO reports that drug-drug interactions are a leading cause of morbidity and mortality
- Responsible for 45% of hospital admissions in those > 70 yo
- Methadone represents ~5% of all opioid prescriptions, accounts for 1/3 of opioid related deaths (interactions frequently implicated)
Pharmacokinetic Interactions (DDI)

• Pharmacokinetic DDI – if drug alters absorption, distribution or elimination of second drug

• Pharmacokinetic interactions are influenced by the degree to which a drug reduces (inhibits) or increases (induces) the activity of the target enzyme.

• If drug interaction is identified, consider discontinuation or reduction of offending agent

• Overdose symptoms attributed to methadone are typically NOT observed after a single dose

• CLOSE MONITORING IS ESSENTIAL!
CYP3A4 Inhibitors
- Inhibitors decrease clearance
  - Increase blood levels
- Dose reduction of methadone may be needed
- Reduce calculated methadone dose by ~25%

CYP3A4 Inducers
- Inducers increase clearance
  - Decrease blood levels
- Encourage use of breakthrough opioid as needed
- Monitor for withdrawal symptoms

Important Medications
- Amiodarone
- Macrolides (excluding azithromycin)
- Azole antifungals
- Diltiazem, verapamil
- Grapefruit juice

Important Medications
- Phenytoin
- Carbamazepine
- Rifampin
- St. John’s wort
Additional Methadone Drug Interactions

• Some drug interactions relate to how drug combinations may affect physiological responses
  • Additive effects with CNS depressants
    • Hypotension, sedation, respiratory depression

• Consider preexisting disease states
  • Malnutrition, impaired renal or hepatic function, infection

• TCAs alter methadone metabolism
  • Amitriptyline can increase α-1-glycoprotein

• Methadone metabolites inhibit metabolism
Pharmacodynamic DDI – QTc Prolongation

• Pharmacodynamic DDI – If multiple drugs act on the same receptor, site of action or physiologic system (i.e. QTc prolongation, respiratory depression)

• The effect on QT interval is dose-related and robust in patients taking greater than 100 mg of methadone orally every day

• Pre-existing QT prolongation is the most consistent predictor of torsade de pointes
  • Definition = QTc of 450 msec; QTc > 500 msec has 4.2 times higher rate of sudden death

QT Prolonging Drugs
- Antiarrhythmics – Amiodarone, sotalol, dofetilide
- Antiimicrobials – Floroquinolones, Azole antifungals
- Antidepressants – Tricyclics, SSRI, SNRIs
- Antipsychotics – haloperidol, quetiapine
- Others: 5HT3 inhibitors, triptans, cisapride
Methadone Management

- Overdose symptoms are typically not observed after a single dose
- Polypharmacy should be considered the rule, rather than exception
  - Review medications at each visit
  - Advise patient to contact you if changes in medications
  - Educate patient about side effect
  - Utilize a drug reference to identify drug interaction or consult with pharmacist
  - Instruct patient to fill all medications at same pharmacy
Follow-up visit with SH

• Decision was made to halve the methadone dose during voriconazole treatment. Within a week the patient experienced a resolution of the aforementioned side effects. His pain remained well controlled, and AML remission permitted a two month vacation to Florida.

• Key Points:
  • Methadone while highly effective poses unique challenges due to a long and variable half-life and numerous drug-drug interactions.
  • Close patient monitoring is imperative particularly in the days following methadone initiation, dose increase or initiation of concomitant medications known to influence methadone’s metabolism.
  • Evaluation of the QTc interval is recommended for all patients prior to starting methadone therapy and within 30 days of methadone initiation or dose increase.
Meet TJ

- 75 YOM with metastatic prostate cancer (dx in 2008, mets to bone and liver) admitted for pain control, ECOG performance status of 4.

- **PMH:**
  - CKD (SCr 1.2 mg/dL)
  - Hypertension
  - Hyperlipidemia
  - Diabetes, type II
  - CAD s/p stent placement
  - A. Fib

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Challenges of Geriatric Pharmacotherapy

- New drugs available each year – Underrepresented in clinical trials
- Managed-care formularies
- Poly-pharmacy – drug-drug interactions
- Multiple co-morbid disease states
- Heterogeneity of aging
- Effects of aging physiology on drug therapy
  - Pharmacokinetics – what the body does to a drug
  - Pharmacodynamics – what the drug does to the body
Aging

Homogenous

Heterogenous
What the body does to the drug

PHARMACOKINETICS
Pharmacokinetics

• Absorption
  • bioavailability: the fraction of a drug dose reaching the systemic circulation

• Distribution
  • locations in the body a drug penetrates expressed as volume per weight (e.g. L/kg)

• Metabolism
  • drug conversion to alternate compounds which may be pharmacologically active or inactive

• Elimination
  • a drug’s final route(s) of exit from the body expressed in terms of half-life or clearance
Effects of Aging on Oral Absorption

• Physiologic Alterations:
  • Gastric acid secretion declines with age
  • Slowed GI motility
  • Reduced GI blood flow

• Impact on Opioid Kinetics
  • Rate of absorption may be delayed
    • Lower peak concentration (Cmax)
    • Delayed time to peak concentration (Tmax)
  • Overall amount absorbed (bioavailability) is unchanged (AUC)

Hepatic First-Pass Metabolism

• For drugs with extensive first-pass metabolism, bioavailability may increase because less drug is extracted by the liver
  • Decreased liver mass
  • Decreased liver blood flow

• Variable change in first-pass metabolism
  • Elders likely have higher exposure to drugs than younger people, hard to predict
Effects of Aging on Parenteral Absorption

• Effects of age
  • Decreased subcutaneous (SC) fat
  • Reduced tissue blood perfusion

• Results
  • Slower absorption from SC/IM route
  • Topical administration of drugs maybe altered
    • Transdermal fentanyl alterations in cachectic cancer patients
      • Delayed peak ~ 48 hours
      • ~ 50% reduced plasma concentrations compared to normal weight patients

## Effects of Aging on Distribution

<table>
<thead>
<tr>
<th>Aging Effect</th>
<th>Vd Effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ body water</td>
<td>↓ Vd for hydrophilic drugs</td>
<td>ethanol, lithium, morphine</td>
</tr>
<tr>
<td>↓ lean body mass</td>
<td>↓ Vd for drugs that bind to muscle</td>
<td>digoxin</td>
</tr>
<tr>
<td>↑ fat stores</td>
<td>↑ Vd for lipophilic drugs</td>
<td>diazepam, trazodone, fentanyl</td>
</tr>
<tr>
<td>↓ plasma protein (albumin)</td>
<td>↑ % of unbound or free drug (active)</td>
<td>diazepam, valproic acid, phenytoin, warfarin</td>
</tr>
<tr>
<td>↑ plasma protein (α₁-acid glycoprotein)</td>
<td>↓ % of unbound or free drug (active)</td>
<td>quinidine, propranolol, erythromycin, amitriptyline, methadone, fentanyl</td>
</tr>
</tbody>
</table>

Properties of Commonly Opioids

Protein Binding

- **Fentanyl**
- **Morphine**

Locus of Action
- "Receptor"
- Bound ↔ Free

Tissue Reservoirs
- Free ↔ Bound

Systemic Circulation

Lipophilic Drugs
- Methadone
- Fentanyl

Hydrophilic Drugs
- Morphine
- Codeine
- Tramadol
- Oxycodone

Free Drug
- Bound Drug

AAG

- Codeine
- HYDROcodone
- HYDROmorphine
- Morphine
- Oxycodone
- Tramadol

Free drug

Lipophilic Drugs

Hydrophilic Drugs
Additional Considerations

• Flow-limited drugs are impacted most by age-related changes in metabolism
  • I’ve Pickl’d Pam
    • Imipramine, Verapamil, Etomidate
    • Propranolol, Isoniazid, Chlorpromazine, Ketamine, Lidocaine, Diltiazem
    • Propranolol, Amitriptyline, Morphine

Concepts in Drug Elimination

• **Half-life (t ½)**
  - Time for serum concentration of drug to decline by 50% (expressed in hours)

• **Clearance (Cl)**
  - Volume of serum from which the drug is removed per unit of time (mL/min or L/hr)

• **Reduced elimination → drug accumulation and toxicity**
  - \( t \frac{1}{2} = 0.693 \times \text{Vd/Cl} \)
Effects of Aging on the Kidney

• Decreased kidney size
• Decreased renal blood flow
• Decreased number of functional nephrons
• Decreased tubular secretion
• Result: ↓ glomerular filtration rate (GFR)
  • Decrease of ~ 6-10% per decade beginning at age 40

Estimating GFR in the Elderly

- Creatinine clearance (CrCl) is used to estimate glomerular rate
- Serum creatinine alone not accurate in the elderly
  - ↓ lean body mass ⇒ lower creatinine production
  - ↓ glomerular filtration rate
- Serum creatinine stays in normal range, masking change in creatinine clearance
Determining Creatinine Clearance

• Measure
  • Time consuming
  • Requires 24 hr urine collection

• Estimate
  • Cockroft Gault equation

\[
\text{IBW in kg} \times (140 - \text{age}) \quad \frac{\text{Scr in mg/dL}}{72} \times 0.85 \quad \text{for females}
\]

Ideal Body Weight (IBW)

IBW (Male) = 50 + 2.3 (Ht (inches) – 60)
IBW (Female) = 45.5 + 2.3 (Ht (inches) – 60)
Example: CrCl vs Age in a 5’5”, 55kg Woman

<table>
<thead>
<tr>
<th>Age</th>
<th>Scr</th>
<th>CrCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.1</td>
<td>65</td>
</tr>
<tr>
<td>50</td>
<td>1.1</td>
<td>53</td>
</tr>
<tr>
<td>70</td>
<td>1.1</td>
<td>41</td>
</tr>
<tr>
<td>90</td>
<td>1.1</td>
<td>30</td>
</tr>
</tbody>
</table>
# Opioids in Renal Dysfunction

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Active Metabolites</th>
<th>Name</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Yes</td>
<td>M3G, M6G</td>
<td>Use Caution</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Yes</td>
<td>H3G</td>
<td>Recommended</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Yes</td>
<td>O-demethyl tramadol</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Yes</td>
<td>H3G</td>
<td>Recommended</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Yes</td>
<td>Oxymorphone</td>
<td>Use Caution</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>No</td>
<td>N/A</td>
<td>Recommended</td>
</tr>
<tr>
<td>Methadone</td>
<td>No</td>
<td>N/A</td>
<td>Recommended</td>
</tr>
<tr>
<td>Codeine</td>
<td>Yes</td>
<td>3G, 6G</td>
<td>Not Recommended</td>
</tr>
</tbody>
</table>

3G = 3-glucuronide – No analgesic activity, neuro-excitatory  
6G = 6-glucuronide – Analgesic activity, accumulates in CNS

Opioid Pharmacodynamics in Elderly

• Numerous pharmacokinetic alterations resulting in accumulation of opioids

• No consistent age-related PK changes in IV fentanyl observed

• Therefore, purely on the basis of PK data there does not appear to be a clear reason to decrease opioids or change the dosing interval in elderly patients

PK-PD Relationship in Elderly

Red Line = 10 mg MS IR (80 year old)
Green Line = 5 mg MS IR (80 year old)
Black Line = 10 mg MS IR (40 year old)

IMPACT ON AGE
Opioids should be started at 25-50% of the recommended adult doses in patients > 60 years of age

You determine TJ to be a candidate for an opioid pain medication what do you recommend?
Practice Recommendations

• When starting in opioid naïve
  • Lower end of range should be chosen in patients with decrease clearance

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Normal Starting Dose</th>
<th>Suggested Starting Dose in Older Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (PO)</td>
<td>5-15 mg</td>
<td>2.5-7.5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5-10 mg</td>
<td>2.5-5 mg</td>
</tr>
<tr>
<td>Hydromorphone (PO)</td>
<td>2-4 mg</td>
<td>1-2 mg</td>
</tr>
</tbody>
</table>

Fentanyl & Methadone should be avoided in opioid naïve patients
Practice Recommendations

• When converting/rotating opioid in tolerant patients

• Be conservative, account for incomplete cross tolerance
  • If moderate to severe pain at time of conversion, reduce 25% when converting
  • If mild pain at time of conversation, reduce 50% when converting
Morphine or Hydrocodone
PO 30mg

Hydromorphone
PO 7.5mg

Morphine or Hydrocodone
IV 10mg

Hydromorphone
IV 1.5mg

Morphine or Hydrocodone
PO 30mg

Hydromorphone
PO 7.5mg

Hydromorphone
IV 1.5mg

Morphine or Hydrocodone
PO 30mg

Hydromorphone
PO 7.5mg

Hydromorphone
IV 1.5mg

Morphine or Hydrocodone
PO 30mg

Hydromorphone
PO 7.5mg

Hydromorphone
IV 1.5mg

Oxycodone
PO 20mg

Morphine or Hydrocodone
PO 30mg

Hydromorphone
PO 7.5mg

Hydromorphone
IV 1.5mg

Morphine or Hydrocodone
PO 30mg

Hydromorphone
PO 7.5mg

Hydromorphone
IV 1.5mg

Oxycodone
PO 20mg

Fentanyl Patch Conversion
Morphine 60 mg PO = Fentanyl 25 mcg/hr

Accounting for incomplete Cross Tolerance

<table>
<thead>
<tr>
<th>Other Opioids</th>
<th>Fentanyl</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate – Severe: ↓ 25%</td>
<td>Do not adjust</td>
<td>Reduce by 75-90%</td>
</tr>
<tr>
<td>Mild Pain: ↓ 50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indelicato RA and Portenoy RK. JCO 2003;21(9):87s-91s
Prepared by: Randall Knoebel
Summary

- Age alters PK and PD of opioids
- Successful pharmacotherapy means using the correct drug at the correct dose of the correct indication in an individual patient
- Risks of ADEs can be minimized by appropriate dosing
PEDIATRICS
PEDIATRIC PHARMACOKINETICS

Absorption
Distribution
Metabolism
Elimination
### Pediatric Patients

- Encompasses a large variety of age and weight classifications:

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term Neonate</td>
<td>&lt; 37 weeks GA</td>
</tr>
</tbody>
</table>
| Neonate                | < 28 days of life                           | Pediatric Dosing: < 50 kg
| Infant                 | < 1 year of life                            |
| Toddler                | 1-3 years of life                           |
| Child                  | 3 – 12 years of life                        | Pediatric Dosing: < 50 kg
| Adolescent             | > 12 years of life                          | Adult Dosing: > 50 kg (+/- puberty)

- Patients should not be treated as small adults
Absorption

**Oral absorption:**
- Decreased GI motility
- Increased gastric pH of intestinal contents:
  - Bioavailability acid labile (*penicillin, ampicillin*)
  - Bioavailability weak acids (*phenytoin, APAP*)
- Decreased blood flow to GI tract

**Intramuscular absorption:**
- Decreased skin thickness, blood flow, muscle mass and surface area
- Avoid route in neonates and children
Distribution

Increased total body water = \( \uparrow \) Vd of water soluble drugs
  • Aminoglycosides

Decreased albumin = \( \downarrow \) binding of highly protein bound
  • Barbiturates

Decreased alpha-1 acid glycoprotein = \( \downarrow \) binding sites
  • Opioids
## Metabolism

### PHASE 1 REACTIONS

<table>
<thead>
<tr>
<th>Types</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation, Demethylation, Hydroxylation</td>
<td>Oxycodone metabolism utilizes CYP 2D6 system</td>
</tr>
<tr>
<td>CYP 450 system</td>
<td></td>
</tr>
</tbody>
</table>

# Metabolism

## PHASE 2 REACTIONS

<table>
<thead>
<tr>
<th>Type</th>
<th>Age</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfation</td>
<td>8-9 months</td>
<td>Acetaminophen (neonates)</td>
</tr>
<tr>
<td>Acetylation</td>
<td>20-22 months</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>24 months</td>
<td>Acetaminophen (children)</td>
</tr>
</tbody>
</table>

Renal Clearance

<table>
<thead>
<tr>
<th>Age</th>
<th>Schwartz Equation (mL/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>5-10</td>
</tr>
<tr>
<td>Neonate</td>
<td>10-15</td>
</tr>
<tr>
<td>1 - 2 weeks</td>
<td>20-45</td>
</tr>
<tr>
<td>6 months</td>
<td>73</td>
</tr>
<tr>
<td>Adult</td>
<td>70-100</td>
</tr>
</tbody>
</table>

- **Creatinine Clearance**: not well defined
  - Lower muscle mass
  - Indicative of maternal creatinine

- **Urine Output**: may not indicate drug elimination

- Overall lack of data for renal adjustment for medications in pediatric patients
# Pharmacokinetic Overview

<table>
<thead>
<tr>
<th>Change</th>
<th>Rationale</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oral: may be slowed and impaired</td>
<td>Change in gastric pH, decreased gastric motility</td>
<td>Some</td>
</tr>
<tr>
<td>• IM: unpredictable</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased Vd of hydrophilic drugs</td>
<td>Increased total body water, decrease mass</td>
<td>Many</td>
</tr>
<tr>
<td>• Decreased protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hepatic metabolism impaired</td>
<td>Enzymatic activity not fully developed</td>
<td>Many</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Decreased renal function</td>
<td>Developmental stage</td>
<td>Most</td>
</tr>
</tbody>
</table>
PEDIATRIC CONSIDERATIONS
Indications for Opioids in Pediatrics

- **Pain:**
  - Sickle Cell Disease
  - Acute (trauma, accident)
  - Oncology related
  - Chronic pain syndromes
  - Post-operative

- **Sedation:**
  - Mechanical ventilation (in combination with benzodiazepines)

- **Neonatal Withdrawal Syndrome:**
  - Morphine or methadone used (in combination with benzodiazepines)
Pediatric Pharmacotherapy

- Individualized patient specific dosing
  - mg/kg/dose or mg/kg/day

- Patient tolerability
  - Taste/flavor, ability to swallow tablets

- Limited data in pediatric patients
  - Limited high-quality evidence, ethical considerations

- Large variation in opioid tolerance or naivety

- Increased toxicity and risks
Question

Which of the following correctly matches drug : toxicity?

1. Codeine : morphine overdose (CYP2D6 expression)
2. Codeine : lack of pain control (CYP2D6 expression)
3. Fentanyl : chest wall rigidity
4. Tramadol : respiratory depression
5. All of the above
Respiratory Depression

Pediatrics are at increased risk:

• **Airway:**
  • Neonates already have depressed respiratory drive
  • Pediatric airways are more prone to obstruction

• **FDA warnings:** all opioids have risk to cause
  • Risk of respiratory depression with codeine use following tonsillectomy and adenoidectomy procedures
  • Increased warning with use of tramadol in pediatric patients

• **Medication Errors:**
  • mg/kg/dose dosing versus mg/dose, requires calculation
  • Confusion with adult dosing
  • Unfamiliarity with medications and dosing
Patient Case

JP is a 60 kg, 12 yo female patient who is s/p major surgical procedure. She rates her pain scores as 9/10. Which of the follow is an appropriate initial treatment?

1. Morphine 0.5 mg/kg/dose IV x1
2. Hydromorphone 0.01 mcg/kg/dose IV x1
3. **Morphine 4 mg IV x1**
4. Fentanyl 2 mcg/kg IV x1
# Opioid Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Usual Pediatric Dosing</th>
<th>Usual Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>PO</td>
<td>0.2 – 0.3 mg/kg/dose</td>
<td>10 – 20 mg</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>0.05 – 0.1 mg/kg/dose</td>
<td>2 – 4 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV</td>
<td>0.5 – 2 mcg/kg/dose</td>
<td>50 – 100 mcg</td>
</tr>
<tr>
<td>Methadone</td>
<td>PO</td>
<td>0.05 – 0.2 mg/kg/dose</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>0.05 – 0.1 mg/kg/dose</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO</td>
<td>0.03 mg/kg/dose</td>
<td>1-2 mg</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>0.01 mg/kg/dose</td>
<td>0.2- 0.6 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>PO</td>
<td>0.1-0.2 mg/kg/dose</td>
<td>5-10 mg</td>
</tr>
</tbody>
</table>
Patient Case

CV is a 5 yo male, presenting to the ED following a 2 story fall with suspected left tibia fracture. Intravenous access had been attempted, but the team is having difficulty obtaining access. Which of the following is a potential option for analgesic administration?

1. Intranasal morphine
2. Inhaled acetaminophen
3. **Intranasal fentanyl**
4. Topical methadone
# Alternative Routes of Opioid Administration

<table>
<thead>
<tr>
<th>Route</th>
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