Not Quite the Kitchen Sink

MOQC Biannual Meeting
January 2020

Michael A. Smith, PharmD, BCPS
Disclosures

- No relevant financial disclosures
- Panel member for National Comprehensive Cancer Network (NCCN) Adult Cancer Pain Guidelines
Learning Objectives

• Review current cancer pain guidelines
• Discuss cancer pain management with the following agents: buprenorphine, methadone, ketamine, and lidocaine
• Understand limitations and monitoring requirements for the use of buprenorphine, methadone, ketamine, and lidocaine
Patient Case

• WD is a 36yo M who presents with increased pain around his GJ tube and malnutrition

• Notable medical history
  – Pancreatic cancer s/p whipple 2017, gemcitabine 2018
  – Neuroblastoma s/p nephrectomy as an infant
  – Leydig cell tumor
  – Spinal Schwannomas
  – Gastroparesis s/p GJ one month ago
  – Chronic back pain and opioid dependence
Patient Case cont’d

• Major complaints
  – Pain – chronic back pain, generalized abdominal pain/cramping with concerns for recurrent pancreatic cancer, visceral pain at site of G tube
  – Gastroparesis with nausea and vomiting

• Patient is strict NPO
• NCCN Adult Cancer Pain Guidelines
  – Updated annually with new versions each January

Current Pain Medications

• Hydromorphone PCA:
  – Settings: 0.2 mg/hr, 0.4 mg Q10min
  – 24 hour usage: 400-600 OMEs

• Pain is well controlled on the PCA with pain score of 5-7/10 consistently; patient is also sleeping well with no apparent ADEs

• Now what?
Planning for the Future

• Current goals of care are to discharge home, but patient remains strict NPO and cannot go home on an oral regimen.
Kitchen Sink Time

- Buprenorphine
- Ketamine
- Lidocaine (mexiletine)
- Methadone
How to Approach

- Safety, first and always
- Effective for patient’s type of pain
- What’s left and what’s best (for now)

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Safety: Buprenorphine

- No true contraindications other than allergies
- No dosage adjustments in renal disease
- May consider lower starting doses in severe hepatic disease
Safety: Ketamine

• No true contraindications other than allergies
• No dosage adjustments in renal or hepatic disease
• Caution:
  – Tachycardia, hypertension
  – Head injuries
Safety: Lidocaine

- Do not use in patients with significant cardiovascular disease
- No dosage adjustments in renal disease
- Low and slow in hepatic disease
- Large pharmacokinetic variability...
Safety: Methadone

- Do not use in patients with prolonged QTc, significant cardiovascular disease, or medication adherence issues
- No dosage adjustments in renal or hepatic impairment, but still go low and slow
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Nociceptive pain
- Effects similar to traditional opioid with lower risk of respiratory depression and side effects

Mechanism
- Partial mu agonist, kappa antagonist, delta agonist, ORL-1 agonist
  - Very high affinity for mu opioid receptors

Effective: Buprenorphine
### Don’t Forget Your Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonism</th>
<th>Antagonism</th>
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| Mu       | - Supraspinal analgesia  
           - Respiratory depression  
           - Euphoria  
           - Sedation  
           - Decreased GI motility  
           - Dependence | Mostly opposing effects |
| Kappa    | - Spinal analgesia  
           - Sedation  
           - Dyspnea  
           - Dependence  
           - Dysphoria  
           - Respiratory depression | - Decreased stress-induced drug seeking behavior  
                            - Antidepressant |
| Delta    | - Psychomimetic  
           - Dysphoria | Mostly opposing effects  
                            - Anxiety |
Pharmacokinetics

• A: about 50% oral bioavailability
  – Naloxone – low sublingual and GI bioavailability with high first pass metabolism

• D: highly protein bound with extensive distribution

• M: liver metabolized, CYP 3A4 substrate

• E: fecal (70%) and renal (30%) elimination
  – Dissociation half-life of 5-6 hours
  – Elimination half-life of 24-42 hours

• Analgesic effect of about 6 hours
  – Formulation dependent
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Effective: Ketamine

• Nociceptive pain (via opioids) and refractory neuropathic pain

• Mechanism:
  – Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with SNRI activity
  – Minor opioid agonism, but likely not clinically relevant
  – Induces dissociative anesthesia
  – Functional and electrophysiological dissociation between the thalamocortical and limbic systems
  – Prevents higher centers from perceiving auditory, visual, or painful stimuli
Pharmacology

• Mechanism:
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NMDA glutamate receptors are widely present in the CNS

- Play a major role in glutaminergic system
- Glutamine – excitatory neurotransmitter released with noxious peripheral stimuli

Ketamine allosterically binds to NMDA receptor preventing glutamate signaling

NMDA activity – plays a role in neuropathic pain signaling
Pharmacokinetics

• A: oral bioavailability 16%

• D: moderate protein binding and distribution
  – Brain, heart, lungs first, then redistribution

• M: liver metabolism via demethylation

• E: renal elimination of mostly changed drug (no dose changes needed)
  – Half-life of 2 to 3 hours

• Onset and Duration
  – IV within 30 seconds and full effect within 2 minutes lasting up to 60 minutes
## Ketamine

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• Nociceptive and neuropathic pain

• Mechanism:
  – Sodium channel blockade

http://hyperphysics.phy-astr.gsu.edu/hbase/Biology/actpot.html
Pharmacokinetics

- A: oral bioavailability 90% (mexiletine)
- D: moderate protein binding and distribution
- M: liver metabolism
- E: biphasic, prolonged in CHF, liver disease, shock, and severe renal disease
  - Usual half-life is 1-2 hours
- Onset and Duration
  - Effects usually seen within 4 hours of initiation
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Nociceptive and neuropathic pain

Mechanism:

- Mu agonist
  - Kappa and delta agonism to a lesser extent
- NMDA antagonist
- Inhibits the re-uptake of serotonin and norepinephrine

Effective: Methadone
PK: Absorption

- 80% bioavailable after oral administration
- Rapidly absorbed from the GIT
- Peak plasma concentrations reached 2.5-4 hours post-dose
- Rectal bioavailability is approximately 76%

PK: Distribution

- Lipophilic
- 88% plasma protein bound
  - Primarily binds alfa-1 acid glycoprotein
- Vss 1.7-5.3 L/kg in chronic pain patients

PK: Metabolism

- Extensively liver metabolized by N-demethylation to inactive drug
- 3A4 (2B6, 2C8, 2C9, 2C19, 2D6)
- Induces its own metabolism
- Empiric dose reductions survey:
  - 1 – 10%
  - 4 – 25%
  - 1 – 30%
  - 1 – 50%
  - 1 – no reduction

## Drug Interactions: Inhibitors

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<th>Dose Adjustment</th>
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<td>Fluconazole</td>
<td>+35</td>
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<td>Fluoxetine</td>
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<td>Amiodarone</td>
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<td>Phenytoin</td>
<td>-50</td>
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<td>Rifampin</td>
<td>-30-65</td>
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<td>Phenobarbital</td>
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<td>Efavirenz</td>
<td>-48</td>
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<td>Ritonavir</td>
<td>-36</td>
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PK: Elimination

• Long and variable elimination half-life
  – Range: 5-130 hours
  – Mean: 20-35 hours
• Low extraction ratio drug
• Fecal, renal, and minor biliary
• Changes in urinary pH affect elimination
  – pH above 6 – renal clearance ~4%
  – pH below 6 – renal clearance ~30%

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• Sublingual and parenteral administration available for now and later
• Would help decrease his opioid related risks
Best (For Now): Ketamine

- Parenteral administration available for now
- Oral administration available for later
- Would help decrease his opioid consumption
Best (For Now): Lidocaine

- Parenteral administration available for now
- Oral (mexiletine) available for later
Best (For Now): Methadone

- Parenteral administration available for now
- Oral administration available for later
- Would help decrease his opioid consumption
So What Did We Do?

- Patient using 26 mg IV hydromorphone via PCA with pain scores not changing 9-10/10

- What do you think we did?

- What would you have done?
Buprenorphine!

- PCA stopped at 0200
- Buprenorphine 1 mg at 0800 Q30Min x 4 doses
- Then buprenorphine 2 mg Q4HRs x 4 doses

(plus some ketorolac)
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