Choosing an Opioid

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Objectives

- Describe the relative advantages of one opioid over another, and what clinical conditions might favor one over another

Required Reading

- Herndon, C, et al. Pain Management in Chapter 77 of DiPiro's Pharmacotherapy (11th ed) (or Chapter 60 in the 10th ed.)

Commonly used Oral Opioids

- Morphine
- Oxycodone
- Hydrocodone (with acetaminophen)
- Less Commonly used are:
  - Hydromorphone
  - Tramadol
  - Tapentadol
  - Codeine (discouraged, off many formularies)
  - Buprenorphine

Commonly used IV Opioids

- Morphine
- Hydromorphone
- Fentanyl

- Less commonly used:
  - Methadone
  - Buprenorphine
  - Codeine (discouraged)

Choosing An Opioid – Typically Avoid

- Codeine +/- APAP
  - Pro-drug → morphine via CYP2D6
  - Up to 30% slow metabolizers→ no effect
  - Ultra-fast metabolizers → increased effect → sedation, respiratory depression, even deaths
  - High N/V rate

Choosing An Opioid – Typically Avoid

- Tramadol (Ultram)
  - Weak serotonin, norepinephrine reuptake inhibitor as well as opioid receptor agonist
  - A CYP2D6 substrate (prodrug) (viz., codeine)
  - **Increased seizure risk**
  - **Serotonin syndrome risk due to SSRI-like effects**
  - **Drug interactions**
  - **Association with hypoglycemia**
  - Accumulates in liver and renal insufficiency - AVOID

Choosing An Opioid – Typically Avoid

- Meperidine
  - Short-acting, causes CNS excitability/seizures due to metabolite build-up
  - Not reversed by naloxone
  - Rarely used for pain in US, if ever anymore.
  - More commonly used IV for the treatment of severe rigors

Which Oral Opioid to Use?

- Morphine
  - PROs:
    - Least expensive
    - Multiple ER and IR formulations, including liquids
    - Few pharmacokinetic drug interactions
  - CONs:
    - 15mg size of IR tablet is an awkward starting dose
    - Accumulation of the neurotoxic morphine-3-glucuronide metabolite in high doses and/or renal dysfunction often leads to adverse effects

Morphine Characteristics

- Peak concentration after IR dose is within 1 hour.
- Predominantly glucuronidated by the liver:
  - Morphine-6-glucuronide: 5x more potent
  - Morphine-3-glucuronide: neurotoxicity
    - Delirium, dysphoria, hallucinations
    - Myoclonic jerking
- Glucuronides are renally excreted
  - Avoid morphine for GFR <30mL/min

Alternatives to Morphine

- Oxycodone
  - Less dependence on kidneys for elimination
  - “Cleaner” metabolites
  - No IV formulation in US
  - Slightly more potent than morphine
    - Use 2mg oxycodone when converting from 3mg morphine
    - I suggest a 1:1 conversion when going from oxycodone to morphine

Alternatives to Morphine

- Hydrocodone
  - Less dependence on kidneys for elimination than morphine
  - "Cleaner" metabolites
    - Some metabolism to hydromorphone
  - Roughly as potent as morphine
  - Useful for relatively low opioid dose needs
  - Not commonly used in cancer pain and palliative care because of the combination with APAP
    - APAP limits the ability to increase the opioid dose

Alternatives to Morphine

- Hydromorphone
  - IV and PO (IR & ER) formulations
  - More potent than morphine
  - Preferred over morphine in cases of:
    - Decreased GFR (but still some renal excretion)
    - Need for subcutaneous infusion
    - Hyperalgesia or adverse effects from IV morphine
  - Some cases of hyperalgesia reported at high, prolonged doses as well

Alternatives to Morphine

- Fentanyl
  - Metabolized to inactive metabolite
    - Good option in patients with severe renal impairment
    - Susceptible to multiple drug interactions
  - Transdermal patch can be considered 1:1 equivalent to IV infusion
  - **Transdermal patches should only be used in patients with established opioid needs**
    - **Same with ER oral dosage of other opioids**

Choosing An Opioid: Renal Insufficiency

- **Morphine**: not completely contraindicated, as CAN dose reduce for GFR<60 and monitor, but definitely if plan on ongoing &/or high doses with significant disease, choose something else
- In moderate/severe renal dysfunction, **fentanyl & methadone** are likely best choices
  - still use caution
- **Oxycodone, hydromorphone** can often be used in even moderate renal impairment
  - Initial doses must be lower than usual, and the size and frequency of dose escalations smaller

Choosing An Opioid: Liver Disease

- Hepatic insufficiency
  - All opioids have significant first pass-hepatic metabolism
    - Glucuronidation is more robust that Type 1 processes
  - AVOID: **~~codeine~~, methadone, fentanyl**
  - LOW & SLOW
    - Fentanyl or methadone are not contraindicated
    - Their doses must be much more conservative and dose adjustments made more slowly

Routine Opioid Adjunct Rx

- Scheduled Acetaminophen or NSAID, as appropriate
- Scheduled laxative (Senna and/or PEG)
- IN Naloxone (NARCAN®)
  - Prescribed naloxone more likely covered by insurance
  - Pharmacist can recommend/dispense under State's Standing Order
    - "Dosing confusion", "Grandchild mis-adventure"

Adding APAP and/or NSAIDs to Opioids

- Post-operative study showed that the addition of Acetaminophen (paracetamol, APAP) or NSAIDs decreased pain scores and rescue opioid needs by 25-33%.
- No consistent benefit of APAP over NSAIDs
- Consider:
  - GI, renal, CV risk of NSAIDs
  - Anti-coagulation status

Schedule Laxatives

- Laxatives should be scheduled for patients on opioids, not PRN. Adjust schedule prn.
  - Senna-docusate
  - PEG 17gm 1-2x daily
- Add laxatives PRN for constipation
  - Bisacodyl (tablets or suppository)
  - Magnesium Citrate
  - Naloxegol (PO) or methylnaltrexone (SC) (peripheral opioid antagonists)($$)

Methadone for Pain

- A useful opioid analgesic, but is more difficult to use because it demonstrates:
  - Widely variable kinetics – conversions between drugs are complex (4-20:1)
  - Long $t_{1/2}$: Slow to reach therapeutic plateau (1-2 **weeks**), and slow to be eliminated
  - Multiple drug interactions (CYP3A4/5, CYP2B6)
  - Can prolong the QTc
    - Increased risk of torsades de pointes)
    - Typically not started if QTc is >470 msec

Methadone Time to Steady-state

- The half-life of most opioids is about 3 hours, but for methadone and buprenorphine it is 3-5 DAYS
- Steady state is achieved for most oral opioids within 1-2 DAYS
- Steady state is achieved for a new regimen of methadone or buprenorphine after 1-2 WEEKS

Prescribing Methadone for Patients on Medication-assisted Therapy (MAT)

- Legal without MAT authorization if used for treating pain (DOCUMENT!): usually Q8H dose
- Legal in hospital setting to "maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, …"
  - 21 CFR 1306.07
  - So MD can prescribe outpatient methadone MAT regimen to a patient hospitalized for other issues