PainWeek

Comedy of Errors: Methadone and Buprenorphine

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Disclosures

- Nothing to disclosure

Learning Objectives

- Explain the pharmacology of methadone and buprenorphine
- Describe methadone and buprenorphine in a case-based model focusing on analgesic conversion

Methadone

- Potent, synthetic μ analgesic, NMDA antagonist
  - Racemic mixture of R- and S-enantiomers
  - Analgesia is largely due to R-enantiomer; S-enantiomer is predominantly NMDA antagonist
- Highly variable elimination $t_{1/2}$ 14-40hr (or more)
  - No active metabolites
  - Makes conversion challenging
  - Accumulation is its strength and liability
- Hepatic metabolism – largely CYP450 3A4
- QTc prolongation

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Methadone Clinical Pearls

- **Methadone has no sense of humor!**
  - Mistakes made here are often fatal
- **"Start Low – Go Slow"**
- The reason to use methadone should not simply be cost or an insurance directive
  - If you want/need to use this drug, get an experienced mentor to work with you until you are sufficiently experienced

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Methadone Kills One of 3 Ways

- Single overdose
  - Many methadone initiation protocols recommend total starting dose to be 15-30mg/day (in divided doses for pain)
    - Rational is that the limited literature describing methadone overdose has been in excess of 40mg/day, even in opioid naïve patient
  - Lethal dose for children is much lower

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Methadone Kills One of 3 Ways (cont'd)

- Accumulated toxicity
  - "Today's dose isn't lethal; tomorrow's dose isn't lethal but all the 3rd days' dose PLUS ½ the 2nd days total dose PLUS ¼ of the 1st days dose *accumulates* to a fatal dose"
  - The most lethal period in methadone treatment is the first 7-10 days (induction phase)
    - Over zealous dose increases are a big risk
  - No dose increases until after the first 3 days
    - Assuming a drug $t_{1/2}$ of 24 hrs, patient has achieved 87.5% of steady state after the 3rd day
      - If sedation isn't a problem at this point, unlikely that a cautious dose increase will result in sedation d/t accumulated toxicity
  - After initiation phase is over, dose should be increased no more frequently than q7-10days

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Methadone Kills One of 3 Ways (cont'd)

- Drug-drug interactions
  - "methadone dose isn't fatal – the benzodiazepine by itself isn't fatal; but the 2 drugs together lead to a fatal outcome"
  - Most commonly seen with combinations of sedatives PLUS methadone
    - BUT – drug metabolism can also pose significant risks

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Drug Metabolism

- Rapid metabolizers—GENETIC
  - Tend to need more total drug and doses more frequently
    - Some people simply metabolize through the relevant CYP 450 pathways leading to a significantly lower drug half-life than 24hrs
- Poor metabolizers—GENETIC
  - Dose lasts longer
    - Total daily dose tends to be lower

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Drug Metabolism—*Iatrogenic*

- While genetic variations tend to be fixed, CYP 450 active drugs can *temporarily* alter these pathways changing a normal metabolizer into a rapid or even poor metabolizer
  - CYP 450 inducer—eg, phenytoin
  - CYP 450 inhibitor—eg, macrolide antibiotics

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Methadone Case Example

- 65 yo woman on methadone 5 mg q8h
  - Dx post herpetic neuralgia
    - Also on carbamazepine for her neuropathic pain
  - Patient has been stable, with good pain control but bothered by carbamazepine s/e
    - Decision is made to switch to gabapentin
- Patients husband calls after 5 days to complain his wife is somnolent; difficult to rouse

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What's Happened?

- Patient *was* on a stable dose of methadone, beyond the first 2 weeks of high risk initiation BUT
  - A potent 3A4 inducer was discontinued
    - Gabapentin does NOT affect 3A4 pathway
  - So, in effect, the patient has had a significant effective increase in her methadone dose because she no longer rapidly metabolizes methadone

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Methadone Conversion

- Several things to consider
  - Is the patient on lower dose morphine (<300mg/day MME)
    - Methadone : morphine ~1:10 but varies!
  - Do you want fast or slower conversion
    - UK protocol vs Edmonton protocol
  - Any concurrent disorders, ie, substance use?
    - Age; resp illness, etc

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Edmonton Protocol

- General principles
  - Calculate approximate daily methadone equivalency
    - Highly variable—many tables online
  - Incur "opioid debt," ie, reduce first opioid by 20% (for a 5 day rotation cycle)
  - Add methadone in divided dose (bid/tid)
    - Titrating upward as first opioid is reduced
  - By day 5, off first opioid—titrate methadone according to best practices

http://www.palliative.org/NewPC/_pdfs/education/ACB%20Hospice%20Palliative%20Manual.pdf

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Buprenorphine

The Versatile Molecule

Consider the Case of Mr. Black

- 65 year old former bank chairman with longstanding history of painful, burning legs
  - Dx peripheral neuropathy due to poorly controlled diabetes
  - Reason for referral is to assess current opioid use
  - Patient states "I just can't seem to come off these Percocet®"
    - Current pain medications:
      - Oxycodone/APAP 5/325 "up to 10 per day"
      - Pregabalin 75mg twice daily
      - Duloxetine 30mg twice daily

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Mr. Black (cont'd)

- According to the referral note, Mr. Black has improved significantly since the addition of pregabalin/duloxetine however…. 'he hasn't been able to stop his use of oxycodone'
  - "I've tried to stop my Percs but each time, my pain gets much worse"
    - Past medication regimen includes controlled release oxycodone 80mg 'up to 4 times per day' (total of 320mg/day) with oxycodone immediate release 10mg 'maximum of 10 per day'

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So, back to the case…

- Mr. Black's risk assessment was deemed to be:
  - "LOW"
- His worsening pain on discontinuing IR opioids
  - Not evidence of ongoing opioid responsive pain but rather withdrawal mediated pain
  - His multiple failed attempts at stopping use of IR oxycodone suggested a new strategy was necessary
  - What about buprenorphine in this situation?
    - What will its role actually be?

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Buprenorphine

- Developed in 1966 by Reckitt & Coleman in Hull, England
  - –John Lewis, doctoral student under Sir Robert Robinson (identified the structure of morphine in 1925)
  - –Pharmacologic profile disclosed in 1972 at College on Problems of Drug Dependency annual meeting
  - –Developed as a 'safe, effective analgesic with very little physical dependence'
  - –Marketed as an injectable in very low doses (ie, 0.4mg/ml)

Brief Overview: What We Thought

- Buprenorphine is a semisynthetic partial μ agonist (and κ antagonist)
  - –Initially used as analgesic; now 1º maintenance agonist therapy (MAT)
  - –Linear μ effect at lower doses
  - –Morphine equivalency of ~40:1 over linear range
  - –Improved safety profile due to "ceiling effect"
  - –Available as SL mono/naloxone-combo tablet – for DATA 2000

Pharmacology

- Derived from opium alkaloid thebain
- Terminal elimination t½ ~24-60 hours but:
  - –Analgesic duration of action is ~6-8 hrs
  - –MAT duration of action is ~24-48 hrs
- Poor oral bioavailability but well absorbed by sublingual/parenteral/transdermal route
- CYP 450 3A4 (lesser 2C8) metabolism through N-dealkylation (like methadone)
  - –But serum levels don't dictate therapeutic effect (compared to methadone)

Pharmacology (cont'd)

- Very high receptor affinity
  - –Once attached, remains until the receptor is recycled
  - –Less than complete receptor occupancy needed to effect MAT action
  - –Can precipitate withdrawal in full μ dependent users
    - But can always add full μ agonist to patient on buprenorphine without fear of inducing withdrawal

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Buprenorphine Redux

- The partial μ agonist role is under review*
  - –Evidence suggests that the molecule may be a full agonist in the role of analgesic
    - While being a partial agonist in terms of respiratory depression
- Buprenorphine is thought to have antinociceptive effects through ORL-1 receptors°
  - –ORL-1 may play a role in apparent ceiling effect of the drug
- Buprenorphine is complicated!

*Pergolizzi et al, Pain Practice 2010 10(5):428-450
°Lutfy and Cowan, Curr Neuropharm 2004 2(4): 395-402

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Buprenorphine Available Forms

- Buprenorphine *was* available only as an injectable
- More recently, as sublingual and transdermal formulations
  - –Buprenorphine 'mono-product'
    - SL tablets of buprenorphine HCl
  - –Buprenorphine 'combination-product'
    - SL tablets of buprenorphine HCl/naloxone 4:1
  - –Buprenorphine transdermal system
    - 7 day matrix patch (5, 10, 20μ/hr)
    - 4 day matrix patch (35, 52.5, 70μ/hr)
  - –Buprenorphine trans-buccal q12h dosing

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Conversion From High-Dose Full-Opioid Agonists to Sublingual Buprenorphine

- 2 papers outline the use of SL buprenorphine conversion in physically dependent pain patients – both were observational reports based on retrospective chart analysis
  - Jonathan Daitch et al Pain Physician 2012 15:ES59-66
  - Jonathan Daitch et al Pain Medicine 2014 15(12); 2087-2094

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Conversion of Chronic Pain Patients

- Results show a significant decrease in pain scores and in the second study, improvements in quality of life
  - Overall decrease of 51% in pain scores before/after conversion with no statistical difference between initial pain ratings of 0-7 vs 8-10
  - QoL improved from 6.1 before conversion to 7.1 (P=0.005)
    - As well, the greater QoL improvements were seen in those converting from the higher doses of opioids
  - Average dose of buprenorphine SL was 28.11±5.94mg

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Back to Mr. Black

- Might he be a candidate for conversion to buprenorphine?
  - If yes, in what capacity?
    - Opioid rotation?
      - At what dose conversion?
    - Opioid maintenance?
      - At what daily dose?
    - Opioid withdrawal management?
      - At what dose?

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Mr. Black

- After thorough discussion about risks (especially of ongoing maintenance with buprenorphine) and benefits
  - Patient was advised to reduce his immediate release oxycodone by 50% at which point a 5μ/hr TDS-buprenorphine was applied
    - He was encouraged to not use his oral oxycodone but to take only if necessary
  - Over the week, he continued to reduce his oral opioid
    - The goal was
      - 1) Discontinue his oxycodone/acetaminophen use and
      - 2) Remain on lowest dose of TDS-Buprenorphine necessary to eliminate w/d symptoms

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Mr. Black (cont'd)

- On day 3, he was asked to call in to speak with our nurse regarding progress
  - If necessary, the patch was increased to 10μ/hr after day 3
  - He was cautioned NOT to interpret a worsening of his pain symptoms as evidence of failure until he was on a steady (and optimal) dose of TDS-buprenorphine

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Mr. Black conclusion

- Successfully discontinued oxycodone/APAP use after first week on TDS-buprenorphine
  - Ultimately stabilized on 10μ/hr transdermal patch
  - Elected to remain on patch; minimal side effects
    - May decide to discontinue the patch at a later date

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Acute Pain Management

- Can you add full agonists to patients chronically using partial agonists?
  - Will you ppt w/d? – NO, NEVER
- Should you *chronically* use full agonists *with* patients on partial μ agonists?
  - NO – generally not
- Are full agonists effective with patient's on buprenorphine? YES

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Final Thoughts

- Consider using buprenorphine in low AND high dose opioid users who are unable to discontinue use through simple tapers
  - High doses of opioids more often reflect patient tolerance NOT patient need
  - While general trends may be useful, there is no reliable way to 'estimate' ultimate stabilizing dose of drug
    - Goal is NOT 'therapeutic equivalency', the goal is opioid stability

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Questions

1) The analgesic window for SL buprenorphine is:
1. 4 hrs
2. **8 hrs**
3. 12 hrs
4. 24 hrs

2) Buprenorphine is a partial μ agonist and a potent κ:
1. Agonist
2. Inverse agonist
3. **Antagonist**

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Questions

3) In terms of methadone for the treatment of chronic pain, the long $t_{1/2}$ makes once-daily dosing practical

1. True
2. **False**

4) With respect to rapid and slow drug metabolism, *iatrogenically slow* metabolisers can be defined as:

1. **The temporary slowing of drug metabolism by the addition of a potent inhibitor of the relevant CYP 450 pathway**
2. The temporary slowing of drug metabolism by the addition of a potent inducer of the relevant CYP 450 pathway
3. Irrelevant since in pain management we titrate dose to effect

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References

- Canadian Opioid Guidelines
  - http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf
- Transbuccal buprenorphine delivery system
  - https://www.belbuca.com/hcp/#
- Danielle Daitch MD1 et al Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients. Pain Medicine Volume 15, Issue 12, pages 2087–2094, December 2014
- Heit HA and D Gourlay, Buprenorphine: New tricks with an old molecule for Pain Management, Clinical J of Pain, 2008; 24:93-97
- dgourlay@cogeco.ca (Dr Douglas Gourlay – feel free to contact)

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