



Comedy of Errors: Methadone and Buprenorphine

Douglas Gourlay MD, MSc, FRCP(C), DFASAM

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

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

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

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 $\frac{1}{2}$ the 2nd days total dose PLUS $\frac{1}{4}$ 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

Methadone Kills One of 3 Ways (cont'd)

- Accumulated toxicity (cont'd)

- 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

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

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

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

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

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

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

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



15



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

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’

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?

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 1^o 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 $t_{1/2}$ ~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)

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

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^o
 - 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

^oLutfy and Cowan, Curr Neuropharm 2004 2(4): 395-402

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, 20 μ /hr)
 - 4 day matrix patch (35, 52.5, 70 μ /hr)
 - Buprenorphine trans-buccal q12h dosing

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

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

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?

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 5 μ /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

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 10 μ /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

Mr. Black conclusion

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

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

Buprenorphine Metabolism

- Certainly, CYP450 3A4 induction/inhibition *can* affect serum levels of parent, BUT
 - Serum levels of drug have a much less direct impact on therapeutic effects
 - Compared with methadone – serum level goes up – CNS levels go up and receptor occupancy goes up – levels go down, receptor occupancy goes down
 - But buprenorphine receptor dissociation is so slow, effect is less dramatic

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

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)