

Methadone A Guide For Use In Palliative Care

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Objectives

- Introduction
- Pharmacology
- Indications
 - Malignant pain
 - Neuropathic pain syndromes in palliative care
- Pharmacokinetics
- Adverse effects
- Dosing rules



Methadone

- Synthetic opioid
- Chemical name
 - 6-dimethylamino-4, 4-dephenyl-3heptanone
- Methadone = racemic mixture of 2 isomers
- R (Levo) - Opioid agonist activity
 - Activates mu, kappa and delta receptors
- S (dextro) - 2 nonopiate analgesic receptor activities
 - Moderate (presynaptic) NMDA antagonism
 - Potent inhibitor of serotonin and norepinephrine neuronal reuptake
 - Downward modulation of pain is via descending tracts of PAG (via monoamine reuptake)

Pharmacology

- High oral bioavailability
 - 70-90% (well absorbed)
- Highly protein bound (~ 80%)
 - To alpha-1-acid glycoprotein (AAG) = acute phase reactant
 - Plasma levels fluctuate depending on pathological condition
- Lipophilic
 - Large Vd
 - Cachectic pts - smaller Vd, decreased drug clearance, so care with dosing





Indication

- NOT a new drug
- Step 3 of WHO
- Used mainly in OR - malignant pain
 - Neurotoxicity and suboptimal analgesia
 - Morphine allergy
- Neuropathic pain syndromes
- Renal failure
- When all else fails
- Complicated pharmacokinetics, ++drug interactions, possible QT prolongation, so use only by experienced docs

Case 1: Nancy

- 65 yr old NSCLC, new onset chest, back pain
- PHx: CAD, CHF, CRF, DM
- SHx: independent, married, support ++
- Meds: furosemide, nitropatch, ramipril, lorazepam, docusate, and percocet “only if I have to as they make me ill”, acetaminophen 4g/24 hrs
- “Intolerant” of opioids / NSAIDs

Nancy

- Pain: constant, aching, worse with weight bearing, occasional burning radiating to R axilla
- Imaging: pathological # T6-8; No SCC
- Rx: Pall XRT, CT; TCA + AED-intolerant
- 4/52 later: STILL PAIN!

- Now what?

3 Strategies to Prescribing Methadone

- Primary analgesic: Low dose with slow escalation
- Primary analgesic: Acute opioid rotation (inpatient)
- Low dose methadone as co-analgesic?



“Trial” of Methadone 1st Line

- Start low and go slow (CPSO 2004)
- Recommended starting dose 2.5 - 5mg bid – tid (opioid naïve)
 - WHO: 2.5 mg q3h prn (+/- morphine 2.5 mg prn)
- Titrate up slowly q 5-7 days
- Nancy
 - Week 4: Methadone 10 mg tid + 3 mg prn; Pain 1-2/10

Wk	Dose	Dose/Day
1	2.5 mg TID	7.5 mg
2	5 mg TID	15 mg
3	7.5 mg TID	22.5 mg
4	10 mg TID	30 mg
5	15 mg TID	45 mg

Pharmacokinetics

- Large inter-individual variation in methadone pharmacokinetics
- Initial dose detected in serum w/in 30 mins of oral dose
 - Rapid tissue redistribution (2-3 hours)
 - Max concentration in 3-4 hrs
- Analgesia lasts 6-12 hrs
- Slow elimination phase / $t_{1/2}$ (15-60 hours)
 - Up to 130 hours
- SS after 4-5 days of new dose



Pharmacokinetics

- High tissue affinity
 - Accumulates after multiple dosing in brain, lung, liver, gut, kidney, muscles
- High affinity to tissues + gradual release to plasma causes prolonged half life
 - Accumulation > toxicity
- Then, balance between drug bound in tissues, and drug in plasma

Metabolism

- Metabolized by type I cytochrome P450 group of enzymes
- Mainly CYP 3A4
 - CYP 1A2, 2D6 and 2B6 to lesser extent
- Metabolized primarily by microsomal liver enzymes, intestinal wall
 - Via N-demethylation
 - 2 inactive metabolites



Excretion

- Primarily fecal elimination
- Some renal clearance (proportional to pH)
 - Increased with acidic urine
 - Decrease dose in severe RF (not CRF)
- Methadone not eliminated in dialysis
- Clearance of methadone increased by chronic dosing
 - Autoinduction of CYP 3A4

Adverse Drug Reactions

- *Similar to morphine*
- Nausea / vomiting / constipation
 - < usual opioids because no active metabolites
- Drowsiness
- Confusion
 - Significantly fewer neurotoxic SE b/c of lack of active metabolites, but documented in literature
- ↓ BP
- Myosis
- Urinary retention
- Prolongation of QT interval
- *Respiratory depression*



Adverse Drug Reactions

- Most drug interactions involve inducers / inhibitors of cytochrome P450 system, esp CYP 3A4
- Because genetic polymorphism exists for CYP 2D6, metabolism of methadone is genetically AND environmentally determined
- AVOID drugs > prolongation of QT, and CYP 3A4 inhibitors
- Identify underlying cardiac and liver abnormalities

Drug Interactions

- *P450-3A4 inhibitors = methadone toxicity*
- Ciprofloxacin
- Fluconazole
- Diltiazem
- Grapefruit juice
- Clarithromycin
- Metronidazole
- SSRIs
 - Venlafaxine has fewest potential interactions
- *P450-3A4 inducers = underdosed methadone*
- Barbiturates
- Carbamazepine
- Corticosteroids
- Phenytoin
- Methadone
 - Chronic dosing

Drug Interactions

- *P450-2D6 inhibitors = methadone toxicity*
- Methadone
- Haldol
- Metoclopramide
- TCAs
- SSRI's
- *P450-2D6 substrates = underdosed methadone*
- Dexamethasone
- Rifampin

QT Interval Prolongation

- Significance
 - Proarrhythmic state
 - Associated with increased risk ventricular arrhythmia, esp. torsades de pointes
- Drug-induced QT prolongation exacerbated by
 - Hypokalemia, hypomagnesemia, and bradycardia
 - Structural heart disease
 - Drugs which increase QT interval



QT Interval Prolongation

- Risk of TdP particularly high if QT > 500 ms
 - Normal QTc < 450 women, 430 men
- Increase in QT of 20-60 ms should prompt review
- Increase in QT > 60 ms ⇒ serious risk of arrhythmia



ECG Or No ECG?

- Significance of methadone's effect on cardiac conduction controversial
- Screening ECG
- Monitor serum electrolytes
- Repeat if significant dose increase
 - >300 mg / day increased risk
- Repeat if additional risk factors develop
 - Cardiac or metabolic risk factors for TdP
- Drugs interacting with CYP 3A4



Case 2: Charlie

- 36 yr old metastatic rectal cancer, uncontrolled pain
- Intractable rectal / pelvic and leg pain
- Opioid toxicity: myoclonus, nightmares, nausea, mood swings
- XRT ineffective
- Clinical trial with chemo
- CADD IV HM 20 mg / hr (MEDD 4800 mg)
- Dexamethasone 4 mg bid, tapering
- Gabapentin 3600 mg / day
- Lorazepam 2 mg qhs
- Failed trial of TCAs / AEDs

- WHAT NOW?

Equianalgesic Dosing

- MEDD
 - <90 mg/day
 - 90-300 mg/day
 - 300-1000 mg/day
 - >1000 mg/day
- Morphine : Methadone dose (Milan model)
 - 4:1
 - 6:1 - 8:1
 - 8:1 - 12:1
 - 20:1 (no > 30 mg single dose)

Dose ratios methadone and morphine or HM not fixed
Related to MEDD
Methadone more potent with increasing MEDD

Methadone Rotation Guidelines

- **Morley-Makin (UK 1998)**
- Stop prior opioid
- MEDD : Methadone ratio 10:1 (Ottawa uses 30:1, max single dose = 30 mg)
- Dose q3h po prn
- 24-48 hrs to effect
- Dose tid by day 6
- Start prn @ 10% by day 8
- **Edmonton (Bruera et al, 1996)**
- D1: Reduce opioid x 1/3
- Replace with methadone, MEDD : Methadone = 10:1
- Dose q8h
- Prior opioid as prn
- Repeat on days 2, 3
- D3: 10% = BT

Charlie

- D1: D/C HM infusion; leave prn in place
 - Methadone 30 mg q3h prn
- D7: Methadone 30 mg q8h
 - Pain 2/10, starting to ambulate, but drowsy
- D14: Gabapentin reduced to 300 mg qhs
- D28: Methadone 25 mg po bid with good analgesia.
Ready for discharge

Methadone Monitoring

- RR pre and 4 hrs post 1st dose methadone, then q4h until stable dose
- Call MD if RR < 8/min, and check O₂ sat
- Narcan 0.2 mg sc if RR < 6/min; repeat q5mins prn (till RR 12)
- Be prepared to give additional dose after 30 mins, as naloxone is distributed and metabolized
- If 3rd dose required, commence continuous infusion naloxone
 - Dose equivalent to 2/3 of initial dose over 1 hour
 - Maintain IV infusion x 12-24 hours, monitor patient carefully after discontinuation.
 - Rate of infusion may be decreased over time to maintain reversal of side effects without reemergence of pain
- Short acting opioid prn for reoccurring pain

Methadone Dosing

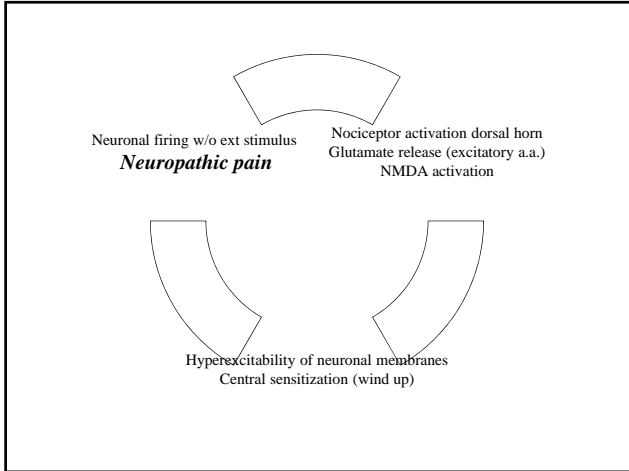
- Long $t_{1/2}$, so dose no < q6h
- Q8h dosing rapidly fills tissue reservoirs, stable concentrations w/in 1-2 days
- Once tissue reservoirs saturated, after 2-4 days, can dose bid
 - Clinically, tid

Case 3: Wayne

- 58 yr old NSCLC, apical lesion with brachial plexopathy
 - Dull aching pain L ant CW, sternum
 - Burning, shooting, squeezing, excruciating pain L arm
 - Hyperesthesia, allodynia
 - BPI 8-10 / 10
- HM contin 48 mg tid (MEDD 720 mg)
- HM 24 mg prn – virtually q4h straight
- Pregabalin 100 mg q8h
- Nortriptyline 50 mg qhs
- Celebrex 100 mg q12h
- SE: Somnolence, constipation

Cancer Pain

- **Complexity of Cancer Pain Syndromes**
- Frequent co-existence of multiple pain etiologies
- Multiple sites involved
- Neuropathic pain -10%
- Somatic pain -41%
- "Mixed pain" -49%
- Cherney et al 1989
- **Challenges in Managing Cancer Pain**
- Features of both acute and chronic pain syndromes
- Multiple sites
- Sick population / unstable disease
- Multiple symptoms
- Multiple treatments / polypharmacy
- Prior opioid use
- Multiple doctors!



NMDA Receptor

- Prolonged activation
 - Central sensitization and neuroplastic changes
 - Hyperalgesia, opioid tolerance, opioid resistance
 - Chronic and neuropathic pain states
- NMDA receptor antagonism
 - Increases opioid responsiveness
 - Reverses allodynia and hyperalgesia



Neuropathic Pain

- Few formal studies using methadone
- Methadone in the management of intractable neuropathic non-cancer pain (DE Moulin et al. Can J Neurol Sci 2005; 32: 340-343)
- Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society (Moulin et al. Pain Res Manage 2007; 12(1): 13-21)
 - Mentions pharmacologic properties of methadone NMDA receptor blocker
- 2 small RCTs (Morley JS et al. Palliat Med 2003; 17:576-87 and Gagnon B et al. Pain Res Manage 2003; 8:149-54)
- “Because methadone is challenging to titrate, lacks high quality evidence of efficacy, and requires special approval from federal and provincial regulators in Canada, it is regulated to fourth-line status as an analgesic for neuropathic pain”

Methadone as a Co-analgesic

- 1 study using methadone as a co-analgesic in NMD
 - 10-20 mg / day (Palliat Med 2003; 17:576-587)
- Have used 1 mg q3h prn in opioid naïve (Ottawa)
- 2.5-5 mg tid in opioid-tolerant (Ottawa)

Case 3: Wayne

- Live on a farm, outskirts of the city
- Wife very supportive, attentive FD
- Refuses PSM admission to hospital
- Methadone 5 mg tid initiated as co-analgesic (outpatient)
- HMContin rotated to CADD for ease of use, 3 mg/hr (= 48 mg tid) and 3 mg q 30 mins prn

Case 3: Wayne

- 1 week later - 12 prns / 24 hrs on average
- BPI now 5-6/10
- HM CADD weaned and methadone increased weekly (using >10:1 MEDD:methadone)
 - Week 2 - HM 2 mg / hr, bolus 3 mg q 30 mins prn, methadone 10 mg tid
 - BPI 3-5/10, increasing mobility L arm
 - Week 3 - HM 1 mg / hr, bolus 2.5 mg q 30 mins prn, methadone 15 mg tid
 - BPI 1-2/10, but significant incident pain limiting activity, prns sedating
 - Week 4 - D/C CADD, methadone 20 mg tid and 5 mg q3h prn



Summary

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|---|--|
| <ul style="list-style-type: none"> • <i>Advantages</i> • Inexpensive • High oral bioavailability • Long-acting • No active metabolites • No accumulation in liver / renal failure • Neuropathic pain (NMDA, 5HT, NE) • Liquid formulation facilitates dosing / titration • Option for opioid allergies | <ul style="list-style-type: none"> • <i>Disadvantages</i> • Highly variable & unpredictable metabolism • Variable protein binding • Drug interactions • Risk of accumulation / OD • Equianalgesic potency of regular dosing unknown • Social stigma • IV formulation not available in Canada • QTc prolongation and risk of TdP |
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Before Prescribing – Consider...

- | | |
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| <ul style="list-style-type: none"> • <i>Patient factors</i> • Prior Rx • Pain mechanisms • ?Opioid toxicity • MEDD • Function / prognosis • Hepatic / Renal function • Route of administration • Support / patient wishes • Finances / drug plan | <ul style="list-style-type: none"> • <i>MD + health care factors</i> • MEDD • In-patient vs. outpatient • MD experience • Pharmacy • Support / attitudes • Finances / drug plan |
|--|--|

Summary

- Methadone generally used as 2nd line opioid for managing moderate-severe cancer pain
- Recommended as 4th line agent for treatment of neuropathic pain (Consensus statement, CPS)
- Pharmacology well elucidated but long half-life and individual variability make drug titration a necessity (*start low, go slow*)
- May be used as either primary analgesic OR low-dose co-analgesic

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