Ketamine and Methadone Supra-Regional Audit Presentation

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External Experts: Dr Anne Garry, Dr Kosta Levshankov
Methadone re-audit
New ketamine audit
Supra- regional
Two parts:-
Health care professionals questionnaire,
Prospective data collection in individual units
Plan for Presentation

• **Methadone:**
  • Current Standards, Literature review, Audit results.

• **Ketamine:**
  • Literature review, Audit results.
  • Standards and Guidelines for methadone and ketamine.
  • Comments from external experts
  • Discussion
Current Standards for conversion of a strong opioid to methadone

Dr Sarah Fradsham
Methadone standards

1. The decision to convert a patient to methadone should be clearly documented in the case notes. [Grade D]
2. Methadone should always be prescribed in milligrams (mg). [Grade D]
3. Methadone should be administered orally during the dose titration phase. [Grade D]
Methadone standards

4. If administering methadone via a subcutaneous infusion, then sodium chloride 0.9% should be used for dilution. [Grade D]

5. Syringe driver sites should be changed every 24 hours. [Grade D]

6. If a patient is discharged home on oral methadone, the discharge letter should include a named contact and telephone number for further advice. [Grade D]
Methadone Quiz!

Dr Helen Bonwick
Methadone

Literature Review

Ruth Clark
Methadone

• Opioid agonist used for analgesia
• Unique pharmacological properties¹:
  • (Affinity for mu opioid receptors)
    – N-methyl-D-aspartate (NMDA) receptor antagonist
    – Serotonin and norepinephrine reuptake inhibitor
    – Affinity for delta opioid receptors
Properties of Methadone

- Lack of active metabolites\textsuperscript{2,3}
  - Safe for use in renal and liver impairment\textsuperscript{2}
- Excellent oral bioavailability\textsuperscript{3}
- Short onset and long duration of action\textsuperscript{3}
- Incomplete cross tolerance with other opioids\textsuperscript{3}
- Multiple routes of administration\textsuperscript{2}
- Low cost\textsuperscript{2}
Cochrane Review

- Looked at 9 Randomised Controlled Trials
- Overall: “Similar analgesic efficacy to morphine”
- Use beyond a few days led to accumulation and delayed onset of adverse effects
- Majority single dose studies
- Variation in dosing and titration
- No superiority for neuropathic pain
- Meta analysis was not possible due to variation in trials
- One study combined methadone with ibuprofen which was shown to beneficial in bone pain
Neuropathic Pain

- Blockage of NDMA receptor believed to be likely component of neuropathic pain effect\(^5\)
- NDMA is a non opioid receptor\(^5\)
- Cochrane review showed “no superiority for neuropathic pain” \(^4\)

- Cortes \(et\ al\)\(^5\) reviewed all patients treated with methadone in their unit in Spain over two years
- 9 patients were reviewed, presenting with poor pain control with a significant neuropathic component
- Signs of toxicity limited the dosage of current opioids
- Three patients were on fentanyl and 6 morphine
- Different methods of conversion over 1-3 days with stabilization around 7 days
Neuropathic Pain cont ..

- Significant improvement seen in 8 patients and moderate improvement in 1 patient
- Average use 77.7 days (28-180 days)
- One patient changed opioid due to neurotoxicity, 6 died and 2 continued beyond observation period
- Not many adjuvants used, 2 pts had gabapentin and 2 pts dexamethasone
- Concluded that review suggests the efficacy of methadone in pain control with a neuropathic component
Dose Conversions

- No definitive method of conversion
- Some papers support different models dependent on initial opioid dose\(^\text{2-4}\)
- In Cochrane review not all patients had prior opioid exposure
- Titration schedules
  - Two studies involved patients progressing randomly through a series of fixed doses
  - Two were single dose studies or had significant single dose phases
  - Two had detailed titration schedules based on need for additional analgesia and physician assessment
    - One IV and 50% increments or decrements
    - One no details provided but looked at use days 1-8
  - Three dose titrated at physicians discretion but no criteria stipulated
Weschules et al. conducted a Systematic Review of Opioid Conversion Ratios Used with Methadone for the Treatment of Pain

- 22 Clinical studies and 19 case reports or series reviewed
- Various approaches 46-89% successful
- Concluded that no universally safe or effective conversion exists
- Due to large variation in opioid ratios not possible to derive a simple conversion method
- However, successful switch is possible
- Many factors affect conversion
  - Disease, age, gender, pain control, concomitant medications, genotype, previous exposure to opiates
Dose Conversion Methods

• Morley and Makin 1998
  – Loading dose (10\textsuperscript{th} morphine dose up to 30mg), then PRN up to 3 hourly. Total dose from days 4 & 5 divided by 4 and given as BD dosage
  – Steady state reached on days 4 and 5

• Plonk 2005 – linear equation
  – \[
  \frac{M \text{ (or morphine equivalents mg/day) + 15}}{15} = \text{Methadone mg/day}
  \]

• Ayonride 2000
  – 3:1 for M < 100mg/day
  – 5:1 for M 101 – 300mg/day
  – 10:1 for M 301-600mg/day
  – 12:1 for M 601-800mg/day
  – 15:1 for M 801-1000mg/day
  – 20:1 for M > 1000mg/day

Dose Conversion Methods

- Pollock et al. discussed various methods of conversion based on one case
- Patient converted using Morley and Makin
  - Stabilized on a 60mg qds dose (pt felt qds gave better pain control than bd dosing)
  - Over next 2 months dose titrated to 160mg qds
- Authors applied other conversion methods to the patient to compare dose
- Ripamonti, Ayonride, Bruera, Lawlor and Plonk conversions would have resulted in much higher doses initially – 406-850mg/day compared to 240mg/day
- Conclude that method should depend on initial morphine doses
  - Ayonride < 300mg/day
  - Ayonride, Morley and Makin or Plonk 300-1000mg/day
  - Morley and Makin > 1000mg/day
Caution in Use

• Prolongation of the QT interval increases the risk of torsade de pointes TdP, which may lead to life-threatening ventricular arrhythmias

• Reasons for QT interval prolongation include
  – Increasing age
  – Congenital long QT syndrome
  – Female sex
  – Cardiac disease
  – Thyroid disease
  – Metabolic disturbances (hypocalcaemia, hypokalaemia, hypomagnesaemia)

• Other major cause – medications – e.g. Methadone
  – Blocking of the rapid component of the delayed rectifier (repolarisation) potassium channel e.g antiarrhythmics, antipsychotics, antibiotics
  – Causing electrolyte disturbances e.g diuretics
  – Blocking metabolism of methadone
• Concomitant use of other drugs causing QT interval prolongation should be avoided
  – Recent MHRA guidance published regarding domperidone, citalopram and ondansetron causing QT interval prolongation

• Other drugs include\(^{10}\) (not exhaustive list)

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Amitriptyline</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Sertraline</th>
<th>Venlafaxine</th>
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</thead>
<tbody>
<tr>
<td>Antiemetics</td>
<td>Domperidone</td>
<td>Ondansetron</td>
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<td>Antifungals</td>
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<tr>
<td>Others</td>
<td>Alfuzosin</td>
<td>Amiodarone</td>
<td>Tolterodine</td>
<td>Salmeterol</td>
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ECG Monitoring

- No clear evidence as to whether ECG’s should be performed before starting treatment and during treatment
- Cruciani\textsuperscript{8} performed a review - Methadone: To ECG or Not to ECG.. That is still the Question
- Looked at 21 articles, mix of prospective, retrospective cross sectional studies, case series and single case reports
- No randomised controlled trials
- Articles included use of methadone to treat addiction and pain management – majority oral
- Many arguments proposed for and against monitoring
• For included:
  – 16 studies suggest 30% (9-88%) of patients treated with methadone could experience QT interval prolongation
  – 2 studies, several case series and others describe TdP in patients receiving methadone
  – 3 studies describe a correlation between the duration of QT interval and dose of methadone
• Against included:
  – No large controlled trials
  – Most studies did not show QT interval prolongation above 500ms
  – Most articles did not report TdP
  – QT interval shown by most studies was less than 40ms above baseline, therefore considered to be of questionable significance
Drug Interactions

- Methadone plasma concentration possibly increased by fluoxetine, paroxetine, sertraline, st johns wort, voriconazole
  - Leading to toxicity
- Methadone plasma concentration reduced by carbamazepine, phenobarbital, phenytoin, rifampicin
  - Leading to loss of effect and possibly withdrawal
- Antivirals – can affect concentrations of methadone and antivirals
Points of Discussion

• Converting from oral to SC – halve the dose
• What to do in the dying phase
• Converting back – go back to previous opioid equivalent dose
• Place in therapy
  – Americans use as 1\textsuperscript{st} line switch
  – UK, usually last resort
References

2. Pollock AB *et al.* Morphine to Methadone Conversion: An Interpretation of Published Data. *American Journal of Hospice and Palliative Medicine* 2011; 28(2) 135-140
7. Website!!
8. Cruciani RA. Methadone: To ECG or Not to ECG.. That is Still the Question. *Journal of Pain and Symptom Management* 2008; 36 (5): 545-552
Ketamine and Methadone – Practice and Experience Survey

- Supra Regional Survey Monkey Questionnaire
- Ketamine – 50 responses
- Methadone – 46 responses
- Dr Graham Whyte
Methadone Results (n=46)
Have you converted a patient to methadone for pain control in the last 12 months? If yes please state for which of the following indications you would use methadone if clinically appropriate.

- Yes 30.4%
- No 69.6%

Indications:
- Colic pain: 2.2%
- Incident Pain: 2.2%
- Complex Neuropathic Pain: 28.3%
- Bone Pain: 2.2%
- Visceral Pain: 2.2%
- Simple opioid rotation: 8.7%
- Other: 2.2%
Further analysis by professional group

<table>
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<th>% Converted to Methadone past 12 months</th>
<th>Average Confidence Level in Initiating Methadone</th>
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<td>Consultant</td>
<td>54%</td>
<td>6.8/10</td>
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<td>StR</td>
<td>38%</td>
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<tr>
<td>CNS</td>
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When starting methadone...

- Document the reasons in the case notes?
  - Yes: 85.0%
  - No: 12.5%
  - Don't know: 2.5%

- Prescribe the dose in milligrams only?
  - Yes: 60.5%
  - No: 21.1%
  - Don't know: 18.4%

- Prescribe the dose in millilitres only?
  - Yes: 75.7%
  - No: 24.3%

- Prescribe the dose in both milligrams and millilitres?
  - Yes: 47.4%
  - No: 28.9%
  - Don't know: 23.7%
How do you convert a patient from another opioid to oral methadone?

- Fixed dose titration method: 80.0%
- Other (please specify): 22.9%
Alternatives to fixed dose titration

- “Fixed dose 12 hourly and up to bd prn only for breakthrough. If necessary use previous opioid for breakthrough during titration period. Cautious regime but in practice seemed safer than three hourly fixed dose that seemed to cause coma after few days! But only small number of patients seen.”

- “Would "start from scratch & titrate up according to response”
Do you have/use a maximum fixed dose of methadone during the titration phase?

- Yes: 55.0%
- No: 12.5%
- Don't know: 32.5%
When a patient is discharged home on oral methadone which of the following do you do? Please answer each possibility in turn.

- Liaise with the patient’s local pharmacist...
  - Don’t know: 21.4%
  - No: 11.9%
  - Yes: 66.7%

- Provide written information for the local pharmacist about the use of methadone...
  - Don’t know: 23.3%
  - No: 20.9%
  - Yes: 55.8%

- Provide written information for the GP about the use of methadone...
  - Don’t know: 28.6%
  - No: 28.6%
  - Yes: 38.1%
Prospective data collection of current practice: Methadone results

Dr Aileen Scott
ICN
Age

The graph shows the distribution of ages ranging from 30-39 to 80-89, with the highest frequency in the 60-69 age group.
Sex

- Male: 4
- Female: 6
Diagnosis

- Cancer: 8
- Non-cancer: 2
Indication for methadone

- Complex neuropathic pain
- Visceral pain
- Tissue pain
Previous opioids used
Number of previous opioids used

Number of patients

Number of opioids
Adjuvants used

- Pregabalin
- Ketamine
- Gabapentin
- Amitriptyline
- Clonazepam
- Phenol block
- Not stated
Route and regimen

• Oral route used in all patients
• Morley Makin used in 9 patients
  – Titration regimen not stated in 1 patient
Total daily dose current opioid

Daily oral morphine (mg)

- 0
- 500
- 1000
- 1500
- 2000
Fixed dose of methadone

- All prescribed in mg
Days before changed to BD regimen

Number of days

- 5: 2
- 6: 3
- 7: 2
- 10: 1
- Not known: 1
- Not changed: 1
Side effects?
Side effects recorded

- Drowsiness: 3
- Toxicity: 2
- Nausea: 1
- Confusion: 1
- Hallucinations: 0
Discharged on methadone?
Of those not discharged on methadone
Discharge dose
Named contact on discharge letter

- Yes: 1
- No: 3
- Don’t know: 1
## Methadone Comparative

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Methadone

Revised Guidelines and Standards
Ruth Clark
**General Principles**

- There are three different strengths of methadone solution used for pain control. These are 1mg/ml, 10mg/ml and 20mg/ml *(unlicensed preparation).*

- Methadone can potentially interact with drugs that inhibit CYP3A4 and CYP2B6. This includes erythromycin and azole anti-fungals (although 50mg fluconazole is unlikely to be significant *caution should still be used*). Clopidogrel is a potent inhibitor of CYP2B6 and may affect methadone plasma levels.
Guidelines

- Electrolytes should be checked before initiating methadone treatment and periodically throughout, with corrections made as required [Level 4]

- Consider, where available, ECG monitoring at baseline and after dose increases if other risk factors for QT interval prolongation present or using large doses [Level 4]
Calculating the “fixed” dose of methadone to be used during the dose titration phase [Level 4]

- The fixed dose of methadone should be 10% of the total oral morphine dose given over the preceding 24 hours. The upper limit of the fixed dose of methadone should not exceed 30mg.
- When converting from diamorphine, oxycodone or hydromorphone, firstly convert the dose to an equivalent 24-hour oral morphine dose.
The dose titration phase [Level 4]

➢ It is important to discontinue any other strong opioid before giving the first fixed dose of methadone

➢ Prior to the dose titration phase, patients should be warned that it may take 24-48 hours before there is any significant improvement in pain relief, or any reduction in side effects.
The dose titration phase cont

- For the first 5 days, the fixed dose of methadone should be taken orally as required but **not more frequently than every three hours**. This is due to the risk of toxicity from drug accumulation. If the patient requires analgesia within three hours of the previous dose of methadone, an alternative short acting opioid should be used.

- During the dose titration phase, methadone requirement usually drop on days two and three before reaching a steady state on days four and five. On day six, the twice daily dosage regimen is calculated by dividing the total dose of the previous 48 hours by **four**, and using this dose 12 hourly for chronic treatment.
The dose titration phase cont

- If there is an unexpected escalation in pain during the titration phase, the conversion should be considered to have failed and the patient should return to the initial analgesic regimen. There is no recognised conversion from methadone back to another strong opioid. General advice is to base the dose on previous requirement but use lower doses (i.e. 30-50%) and re-titrate. Clinicians need to be prepared to increase the dose and ensure that appropriate rescue doses are available.

- Administration of methadone via a syringe driver is not recommended during the titration phase due to risk of drug accumulation.
Chronic treatment following dose titration [Level 4]

- Methadone is given every 12 hours during chronic treatment.
- There is little consensus as to what should be used for rescue analgesia during chronic treatment. Success has been reported using oral methadone at a dose of either one sixth or one tenth of the 24-hour methadone dose. The rescue dose should not be given more frequently than every three hours.
- If more than two rescue doses are required over a 24 hour period, the twice daily dose should be increased by 30-50%.
Guidelines cont

Routes of administration

- Methadone may be given by subcutaneous infusion if oral administration is not possible. The subcutaneous route is often complicated by site inflammation which may result in frequent site changes. It is not possible to give intermittent subcutaneous injections [Level 4]

- The dose of methadone given in the syringe driver over 24 hours should be half of the 24-hour oral dose. The methadone should be diluted with sodium chloride 0.9% in a 20ml syringe. Syringe driver sites should be changed every 24 hours to avoid local irritation. Dexamethasone 1mg can be added to the syringe driver to improve site reactions. [Level 4]

  - Hyaluronidase (150IU) can be injected subcutaneously at the syringe driver site to avoid local reaction to the methadone [Level 4]

- Methadone may be given by suppository (unlicensed preparation) twice daily. The relative potency of rectal to oral methadone is 1:1 [Level 4]
Discharge of patients on Methadone

- If a patient is discharged home on oral methadone, the discharge letter should include a contact name and telephone number for advice on further management [Level 4]
- Prior to discharge, the designated community pharmacist should be contacted to discuss dose, concentration and the supply of methadone [Level 4]
- Copies of the discharge letter should be sent to all health care professionals involved in the patients care [Level 4]
Standards

- The decision to convert a patient to methadone should be clearly documented in the case notes [Grade D]
- Methadone should always be prescribed in milligrams (mg) [Grade D]
- Methadone should be administered orally during the dose titration phase [Grade D]
- If administering methadone via a subcutaneous infusion, then sodium chloride 0.9% should be used for dilution [Grade D]
- Syringe driver sites should be changed every 24 hours [Grade D]
- If a patient is discharged home on methadone, the discharge letter should include a named contact and telephone number for further advice [Grade D]
Time to hear from the experts...
Any Questions?