Guidelines for the use of Methadone in Palliative Care

These guidelines are intended for doctors and nurses specialising in Palliative Medicine and working at, or affiliated to, Compton Hospice.

Good Practice Note

It is essential that methadone for cancer pain is used under specialist supervision.
Dosage recommendations (see below) differ for ***the titration period*** and ***the long term use period***.
Titration requires skilled monitoring to avoid poor pain control or accidental overdose and should be done under close supervision, ideally in a specialist inpatient palliative care unit.
After initial titration and during long term use the drug may be prescribed by the non-specialist but there should be ongoing regular specialist review.

Indications and availability

1. Methadone is a strong opioid, which can be used in place of other strong opioid drugs such as morphine, diamorphine, fentanyl and hydromorphone in the management of cancer pain[1] [2]. Methadone is also indicated for symptomatic relief of cough and in the rehabilitation of patients suffering from opioid dependency, but these applications are not addressed by this guideline.

2. Specific indications for using methadone in the management of cancer pain include:
   - **tolerance** to the analgesic effect of the existing strong opioid drug as demonstrated by the need for continually escalating doses to maintain the analgesic effect
   - **intolerable adverse effects** caused by the existing strong opioid drug, e.g. nausea & vomiting, hallucinations, poor concentration, cognitive impairment, drowsiness.

3. A specific indication for the use of methadone in the management of neuropathic or bone pain has not been established by existing research[3], although clinical experience and pharmacology suggest a role for the drug in these clinical situations.

4. Conversion to methadone is contra-indicated in moribund patients since initial titration requires patient participation.

5. Oral methadone is available in the following commercial formulations:
   - Tablets: **5mg** (Wellcome®)
   - Liquid: three different concentrations (Rosemount® or Martindale®)
     - one milligramme per millilitre (**1mg/ml**) pink=sugar free, green=sweet
     - ten milligrammes per millilitre (**concentrated solution 10mg/ml**) blue & bitter
     - twenty milligrammes per millilitre (**20mg/ml**) caramel colour & bitter (rarely required)

Note: To avoid dosage errors, other concentrations should not be used.
Non-commercial formulations of methadone as capsules and suppositories are available from Stoke Mandeville Hospital (Telephone: 01296 394142)

6. Dose conversion equivalence with other strong opioid drugs cannot be recommended since:
   - incomplete cross tolerance occurs in most cases,
   - the final dose requirement is often less than the dose required during the titration period because of extensive tissue distribution and variable clearance.

7. When converting from an alternative strong opioid drug, it is recommended that these drugs be discontinued completely and not prescribed in future unless methadone proves ineffective.

Titration

8. **The titration regime described in these guidelines applies to patients with severe malignant pain managed as in-patients.**

9. Titration guidelines are to be applied by Palliative Medicine Specialists with experience in opioid dose titration. The unique pharmaco-dynamic properties of methadone can lead to underdosing or overdosing with a risk of poor efficacy or severe toxicity. Alternative titration regimes exist[4 5], and these more conservative schedules may be appropriate for patients with chronic non-malignant pain being managed in the community.

10. The maximum **starting dose** for titration is **50mg**.
    - If converting from TTS fentanyl (more than 100mcg/h) give only one dose of 50mg (loading dose) and reduce subsequent doses to 30mg.
    - If converting from any other opioid drug give 50mg or only 10% of the equivalent daily oral morphine intake if it is less than 500mg per 24 hours.

11. The first dose is best given early in the day, for example when the patient would have been given their first opioid dose of the day. If converting from transdermal fentanyl or subcutaneous diamorphine, the first dose can be given as soon as the patches are removed or the infusion is discontinued. No further administration of the previous opioid should take place as it would delay dose titration and make clinical evaluation more difficult.

12. During the titration period the patient is asked to take another dose as soon as the targeted pain manifests itself again even if it is only by a slight discomfort. The terminology to define this protocol is called "using the drug *ad libitum*".

13. Because of slow rate of enteral absorption of methadone (Peak Plasma Level achieved on average 3 hours after ingestion), a minimum interval of 3 hours between doses is recommended to avoid the possibility of absorption of two doses at the same time leading to accidental overdose.

14. If pain occurs during the first 3 hours after taking a dose of methadone, co-proxamol (2 tablets) can be given and this dose may be repeated after one hour if necessary whilst waiting for the methadone to be absorbed and be effective. The maximum dose of co-proxamol is 12 tablets in 24 hrs. If pain remains problematic before the next dose of methadone is due, seek specialist medical advice.

15. The gradual elimination of the drug mostly by tissue storage and also by metabolism should be compensated by the slow absorption of the dose taken. If the dose has been taken in good time as described in 12, there should be no need for additional analgesia.

16. If the patient continues to experience breakthrough pain within 3 hours on the second or third day after starting the titration, increase the dose given *ad libitum* by one third and review after 24 hours.

17. If, during the first 2-5 days, the patient achieves satisfactory pain control with only one to two doses of methadone daily, the dose should be reduced. If the patient takes methadone once daily, the dose should be reduced by half. If the patient takes methadone twice daily, the total daily dose should be reduced by one third. This practice aims to reduce the risk of overdose if an extra dose is taken at a time when the body tissues are saturated by a sufficient drug reservoir.

Long term use

18. After 5 to 10 days of *ad libitum* regimen, the daily methadone dose requirement tends to stabilise at a level which compensates for metabolism and renal clearance. At this point, and when pain relief is deemed satisfactory, the regular regimen can be established.

19. The regular regimen is between one and three times daily at the convenience of the patient. Dividing the dose may overcome the side effect of sedation experienced by some patients after administration of large single doses of the drug.

20. If pain breakthrough occurs after a regular administration regimen has been established, the next due dose can be given early but no sooner than 4 hours after the preceding dose. For severe breakthrough pain, 2 co-proxamol tablets may be given (maximum 12 tablets in 24hrs).

21. When a dose has been brought forward, no additional dose is required at the time when that dose would have been due, provided that pain has not returned. Subsequently if pain recurs, the next due dose may be brought forward similarly.

22. Specialist review of the analgesic strategy is necessary if:
    - severe pain occurs sooner than 4 hours after a methadone dose, and is unrelieved by co-proxamol, or
    - the methadone dose is brought forward on two consecutive occasions.

23. When a patient is discharged into the community, communication with the primary health care team is of paramount importance. The patient is given a letter which they are told to show to any doctor who they may consult. This letter is to ensure that the doctor is made aware of the reason for use of methadone and asks that they avoid prescribing an alternative opioid without prior discussion with the Palliative Medicine Consultant involved in the care of the patient. (See appendix for sample letter).

Side effects and overdose

24. Methadone is an opioid and has side effects typical of this group of drugs. These include constipation, nausea, sedation, cognitive impairment and possibly hallucination. Side effects should be anticipated and managed (see West Midlands Guidelines, 3rd Edition, Chapters 2&3).

25. Patients may experience opioid withdrawal symptoms when changing from morphine to methadone. These symptoms may occur up to a few days after the change and include fatigue, anxiety, restlessness, irritability, insomnia, yawning, salivation, sweating, nausea & vomiting, anorexia, abdominal pain and diarrhoea. Seek specialist advice as it may be appropriate to prescribe methadone to relieve these symptoms.

26. During regular treatment, a reservoir of methadone accumulates in the body tissues which means that significant blood levels persist for some time after stopping methadone. It is essential to understand and recognise this phenomenon, especially when managing accidental overdose or if methadone is to be discontinued and replaced by an alternative opioid.

- **In any methadone overdose situation**, the patient must be admitted as an emergency for close monitoring. Naloxone 0.4mg SC usually reverses rapidly the respiratory depressant effects of opioids but because of its short duration of action and the prolonged effects of methadone, the dose may need repeating as often as hourly depending upon the clinical situation. A continuous subcutaneous infusion of naloxone may be required and the dose over 24hours will be determined by the dose required in the early stages of the emergency management.
- **When changing from methadone to another opioid**, close inpatient supervision will be required and a short acting opioid (normal release formulation) must be used for pain management during the titration period.

Parenteral methadone use

27. In moribund patients, it is often possible to give the total daily dose of oral methadone whenever the patient is awake. The timing of the dose is not essential since those patients who had good pain control before the clinical deterioration have good tissue reserves which can often last up to 24 hours before the patient feels the return of pain. A retrospective review of methadone given by continuous subcutaneous infusion at Compton Hospice identified 37 patients treated in this way. Thirteen had an infusion for less than 24 hours and six patients for between 24 & 48 hrs.

28. In other clinical situations where a patient is unable to take oral medication it may be appropriate to administer methadone by subcutaneous infusion. These include impaired consciousness, risk of aspiration, vomiting and bowel obstruction.

29. Methadone for injection is available in a concentration of 10mg/ml and in ampoule sizes of 1ml, 2ml, 3.5ml and 5ml.

30. The dose given by subcutaneous infusion should be **two-thirds** of the current oral 24 hour dose. This is calculated from the average oral bioavailability of methadone and assumes that IV and SC routes are equivalent. It is acceptable to adjust this to the nearest 10mg to reduce the risk of errors when drawing up injectable methadone.

31. One-sixth of this dose may be prescribed to be given subcutaneously for breakthrough pain. However, repeated administration of subcutaneous methadone will result in accumulation; therefore the situation should be discussed with a specialist at Compton Hospice experienced in the use of methadone.

32. Injectable methadone is irritant when given subcutaneously. Sixty-three percent of syringe driver sites in a retrospective review lasted 48 hours or less. Dexamethasone 0.5mg should be added to the methadone in order to minimise irritation (we have not noted any physical incompatibility). The site should be observed regularly and the appearance documented carefully. The reason for a change of site must be recorded in the notes.

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[1] Fainsinger R, Schoeller T, Bruera E. Methadone in the management of cancer pain: a review. Pain 1993;52:137-147.
[2] Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. Support Care Cancer 2001;9:73-83.
[3] Nicholson AB. Methadone for cancer pain. Cochrane Review. In Press.
[4] Morley JS, Makin MK. The use of methadone in cancer pain poorly responsive to other opioids. Pain Reviews 1998;5:51-58.
[5] Blackburn D, Somerville E, Squire J. Methadone: an alternative conversion regime. European Journal of Palliative Care 2002;9(3):93-96.