

Prescribing information

METHADONE use in chronic pain

This information is intended to support hospital doctors prescribing methadone for chronic pain under the supervision of the Palliative Care Team. Methadone is unlicensed for use in pain and the patient's GP would not normally be asked to take on prescribing. This document may however also serve as a useful GP reference if one of their patients is maintained on methadone by the Palliative Care Team

Clinical use

Methadone is a synthetic opioid which is used in cancer pain that has responded poorly to morphine or other strong opioids despite dose escalation and use of appropriate adjuvant analgesics. It may be particularly helpful in relieving neuropathic pain. Methadone may also be used in patients who develop CNS side effects such as confusion and hallucinations with alternative opioids.

Mode of action

Methadone acts as an agonist primarily at mu receptors, but also has affinity for delta receptors and a weak affinity for kappa receptors. In addition, methadone is a potent N methyl D aspartate (NMDA) receptor antagonist, a property not shared by other strong opioids.

Why choose methadone?

- Pain may become unresponsive to morphine or other opioids because of the development of tolerance. Substitution of an alternative opioid such as methadone, to which receptor tolerance has not yet developed may restore analgesia without side effects.
- Methadone's delta receptor activity makes it a sensible switch to regain analgesia following tolerance to a mu agonist.
- Methadone does not have any known active metabolites - it has been suggested that the accumulation of active metabolites may be the reason that some patients do not respond to morphine or experience CNS side effects.
- Methadone is a potent lipophilic opioid which allows central analgesia to be achieved with a relatively low incidence of peripheral side effects.
- Methadone is a potent NMDA receptor antagonist which may explain the advantage that methadone has over morphine or fentanyl in neuropathic pain

Switching from oral morphine to oral methadone

It is essential that methadone for cancer pain is used under specialist supervision.

Dosage recommendations 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.

Dose conversion equivalence with other strong opioid drugs cannot be recommended since:

- incomplete cross tolerance occurs in most cases,
- the final methadone dose requirement is often less than the dose required during the titration period because of its extensive tissue distribution and variable clearance.
- The **maximum methadone starting dose** for titration is **30mg**.

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 patch** the first dose is given 12 hours after patch is removed or
- **subcutaneous diamorphine or morphine** in a syringe driver, the first dose can be given as soon as the infusion is discontinued.

Ideally no further administration of the previous opioid should take place as it may delay dose titration and make clinical evaluation more difficult. See point 4 page 2

Switching from oral morphine to oral methadone

Titration Period of methadone	
1.	Stop morphine MR on day of titration. Switching from other strong opioid see page 1
2.	Calculate total 24 hourly morphine (or morphine equivalent)
3.	<p>Give 1/10th of this 24 hour morphine dose as methadone the titration dose (up to a maximum of 30mg) up to every 3 hours when required, Do not give more frequently than every 3 hours.</p> <p>(i.e for doses <300mg give 1/10th but for doses >300mg give 30mg)</p> <p><i>The slow rate of enteral absorption of methadone recommends a minimum interval of 3 hours between doses to avoid the accidental overdose of two doses being absorbed at the same time. (Peak Plasma Level achieved on average at 3 hours)</i></p>
Breakthrough analgesia within the first 24 to 48 hours of starting methadone	
4	<p>Stop the regular prescription of paracetamol.</p> <p>If pain occurs during the first 3 hours after taking a dose of methadone. Paracetamol 2 tablets may be given. Maximum dose 8 tablets/day.</p> <p>If paracetamol is not effective while waiting for the methadone to be absorbed, alternative breakthrough may well be required.</p> <ul style="list-style-type: none"> • Oramorph/ Sevredol (if original opioid was morphine) or • OxyNorm (if original opioid was oxycodone) or • Oramorph, OxyNorm, Alfentanil spray or Fentanyl lozenges (If original opioid was fentanyl patch) <p><i>The aim is (if possible) for no further administration of the previous opioid to take place as this delays dose titration and makes clinical evaluation more difficult.</i></p> <p>If pain still remains problematic before the next dose of methadone is due, seek specialist medical advice</p>
Day 2 and 3 of titration	
5.	If the patient continues to experience breakthrough pain within 3 hours after starting the titration, increase the dose given by one third and review after 24 hours.
First 2 to 7 days of titration	
6.	<p>If during each day of titration the patient achieves satisfactory pain control with only one to two doses of methadone daily, the titration dose should be reduced, daily if necessary.</p> <ul style="list-style-type: none"> ▪ If the patient takes methadone once daily, dose should be reduced by half. ▪ If the patient takes methadone twice daily, dose should be reduced by a third. <p>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.</p>
Long term use of methadone following titration	
7.	<p>After 7 to 10 days of titration, the daily methadone dose requirement tends to stabilise at a level which compensates for metabolism and renal clearance. When pain relief is satisfactory, the regular regimen can be established.</p> <p>Day 7 to 10 calculate the total amount of methadone taken over the previous 2 days. The regular regimen is between one and four 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.</p> <ul style="list-style-type: none"> • 24 hourly regime divide dose (taken over 2 days) by 2 ▪ If using a 12 hourly regime divide by 4 ▪ If using an 8 hourly regime divide by 6 ▪ If using a 6 hourly regime divide by 8
Breakthrough pain for long term use of methadone	
9.	For severe breakthrough pain, 2 paracetamol tablets may be given (maximum 8 tablets in 24hrs). If this doesn't help use breakthrough methadone
10.	Prescribe "when required" i.e prn methadone every 4 hours for breakthrough pain (this dose should be 1/12th of the daily methadone dose)
11.	Increasing the dose of methadone - The dose of methadone can be increased every 4-6 days if more than 2 breakthrough doses continue to be required each day

Notes on prescribing

- **Methadone requirements** usually drop during day 2 or 3 & reach steady state day 6/7.
- **Therapeutic failure** If there is worsening of the pain during the titration phase the conversion should be considered to have failed.
- **Onset of pain relief** - Patients should be counselled that it may take 24-48 hours before any significant improvement in pain relief is achieved
- **Opioid withdrawal** This has been reported when switching from morphine to methadone. It can be alleviated by small rescue doses of morphine or previous opioid as required.

Switching to rectal methadone

Initially use the same dose rectally as orally. Doses may need to be increased by 50-150%. Suppositories are available as an unlicensed formulation from Boots.

Switching to 24 hour subcutaneous methadone infusion

When given by continuous subcutaneous infusion, methadone can cause skin reactions. If this occurs this can be reduced by

- Using sodium chloride 0.9% as diluent
- Adding 500 microgram of dexamethasone
- Using a more dilute solution i.e use of a 20 to 30ml syringe
- Changing the syringe every 12 hours
- Changing the site every 1-2 days
- Inject hyaluronidase 1500u into the site prior to infusion via the butterfly needle

1.	Administration of methadone via a syringe driver is not recommended during the titration phase due to the risk of drug accumulation.
2.	Initially when switching from oral methadone to subcutaneous methadone, half the oral dose should be used.
3.	Prescribe "when required" i.e prn methadone s/c every 3 hours for breakthrough pain (this dose should be 1/12 th of the 24 hour infusion dose of s/c methadone)
4.	Increasing the dose of methadone - The dose of methadone can be increased every 4-6 days if more than 2 breakthrough doses continue to be required each day.

Methadone is physically compatible with dexamethasone, haloperidol, hyoscine butylbromide, levomepromazine, metoclopramide and midazolam.

For full details contact Pharmacy Medicines Information tel 725960

Pharmacokinetics

Methadone is a lipophilic drug which has a high oral bioavailability by the oral and rectal route. Analgesic action is usually maximal after 1-2 hours and in steady state lasts approximately 6-12 hours. There is a considerable increase in the duration of action after multiple dosing. It is highly protein bound and widely distributed.

It is metabolised in the liver mainly by hepatic N demethylation to biologically inactive metabolites. Urinary excretion is a minor pathway and faecal excretion accounts for the greatest part of the dose. The half life ranges from <10 to >75 hours and shows wide inter patient variation and accumulation in tissue can occur with continuous use creating an extensive reservoir.

Dose adjustments

Hepatic impairment does not normally affect the metabolism of methadone and dose adjustment should not be necessary in stable disease, although acute changes in hepatic function may require dosage adjustments.

Dose adjustments are not normally required for patients with renal impairment.

With chronic dosing there may be the need to either reduce or increase the dose of methadone and the patient should therefore be closely monitored. After multiple dosing there is a considerable increase in the duration of action of the drug which may necessitate a dose reduction. Alternatively hepatic enzyme induction and sequestration of methadone at extravascular binding sites may necessitate a dose increase.

Side effects

Side effects are similar to those of morphine, but methadone may be less sedating. When given by continuous s/c infusion, inflammation at the site of administration is common, necessitating site rotation. Dose related cardiac side effects (prolongation of the QT interval) have been reported, but the significance with the dose usually used in palliative care is unknown.

Contra- indications

There are no absolute contra-indications in advanced disease except allergy, but the circumstances in which methadone would not normally be used or should be used with care include:

- Allergy to methadone or preservatives
- Respiratory depression
- Severe COPD or acute asthma
- Concurrent use of monoamine oxidase inhibitors

Caution is also advised in the following

- The elderly - care as increased half life
- Pain partially responsive to methadone - care to avoid dose escalation
- Pain suspected to have a psychological component
- Patients intolerant of low doses of other opioids

Drug interactions

Methadone is primarily metabolised by the cytochrome P450 liver isoenzyme CYP3A4 and induction or inhibition of this enzyme is the mechanism behind many of methadone's drug interactions. Other isoenzymes such as CYP2D6, 1A2, 2C9 and 2C19 play a minor role in methadone's metabolism.

The table below gives some examples of the more common potential interactions.

Drug	Possible mechanism	Action
Rifampicin Phenytoin Carbamazepine Phenobarbitone	Increased metabolism of methadone	May need to increase methadone dose
Cimetidine Fluvoxamine MAOIs TCADs Ciprofloxacin Fluconazole Grapefruit juice	Methadone metabolism inhibited	May need to decrease methadone dose
Desipramine	Possibly reduced metabolism of desipramine	Monitor - may need to reduce desipramine dose
CNS depressants	Potential of CNS depression	Increased drowsiness
Zidovudine	Possible increased metabolism of methadone and decreased metabolism of zidovudine	May need to increase methadone dose and/or decrease zidovudine dose

Patient information

Patients should be issued with a Trust patient information leaflet (Methadone in pain)

Prescribing responsibility

As the use of methadone in pain is unlicensed, treatment will normally be supplied by the Consultant initiating treatment.

In patients receiving methadone for opiate dependence, hospital policy is not to issue methadone on discharge or to out-patients. To distinguish patients receiving methadone for pain all prescriptions for this group of patients must be endorsed "for use in pain" so that on presentation of the prescription at Pharmacy the indication for use is clear.

Cost (Drug Tariff August 2007)

Methadone mixture 1mg/mL	500mL	951p	
Methadone tablets 5mg	100x 5mg	594p	
Methadone mixture 10mg/mL	50mL	500p	(£20 per 200mL) Rosemont
Methadone injection 10mg/mL		86p	per 10mg dose

References

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If you need any further information and ask to speak to Dr Anne Garry or Jane Crewe at YH or one of the doctors at the St Leonard's hospice