

The Use of Methadone in Palliative Medicine 2018

For patients with palliative care needs, methadone should only be prescribed under the supervision of a specialist palliative care team

The use of methadone is complex, owing to its long half-life, accumulation after repeated doses and wide inter-individual variations.

Indications for Use

- Moderate to severe pain, neuropathic pain, cough, pain relief in severe renal impairment

Pharmacokinetics

- Methadone is a synthetic opioid with mixed properties; it is a mu-opioid receptor agonist, an NMDA receptor blocker and a pre-synaptic blocker of serotonin reuptake.
- It is absorbed well from all routes of administration, with 80% oral bioavailability (range 36—100%).
- It has a high volume of distribution due to its lipid solubility, and is extensively protein-bound (up to 90%).
- The result is a long and widely variable plasma half-life, leading to potential problems with accumulation. Initial doses will typically have a half-life of hours whereas, after stable dosing has been reached, the half-life may increase to some days.

Preparations

- Methadone 1mg/ml Oral Solution
- Methadone 10mg/ml Oral Solution—Available for hospital use only
- Methadone Injection 10mg/mL 1ml vials (Martindale) - unlicensed in Ireland

Important Considerations

- Before prescribing methadone, the complexity of a subsequent switch from methadone to another opioid should be considered.
- When switching from a strong opioid other than morphine, the total equivalent daily dose of morphine should first be calculated.
- If there has been recent rapid escalation of the pre-switch opioid dose, calculate the initial dose of methadone using the pre-escalation opioid dose.
- The use of a loading dose of methadone aids tissue saturation, speeding up the onset of methadone's analgesic effect. However, based on the clinical context a decision may be made to omit the loading dose (e.g. when converting from a transdermal patch).
- Patient factors should be considered when deciding on the timing of the administration of the first dose of methadone. The Palliative Care Formulary advises that when switching from modified-release morphine, the first dose of methadone should be given ≥ 6 h (pain present) or 12h (pain-free) after the last dose of the 12 hour preparation of morphine.

ORAL DOSE CONVERSION

When rotating strong opioids to methadone, various methods of rotation have been proposed. The method favoured by OLG&CS is the Palliative Care Formulary 'Stop and Go, p.r.n dose' Approach.

PALLIATIVE CARE FORMULARY 'STOP AND GO' APPROACH

1. The initial opioid is discontinued when methadone is started. Calculate the total 24 hour oral morphine equivalent dose the patient has been taking.
2. Give a single **loading dose** of oral methadone **one-tenth** of the total 24 hour oral morphine equivalent dose up to a **maximum of 30mg** of methadone.
3. A three hourly '**as required**' dose of methadone **one-thirtieth** of the total 24 hour oral morphine equivalent dose is prescribed, up to a **maximum of 30mg** of methadone.
4. If additional analgesia is required for breakthrough pain, i.e. for patients in severe pain, an alternative opioid may be prescribed 'as required' for second line use. This dose should be 50–100% of the p.r.n. dose used before switching, and can be administered hourly.
5. On **day six**, the amount of methadone taken in total over the previous 48 hours is calculated and divided by 4 to give a regular twice daily dose.

ORAL DOSE CONVERSION—WORKED EXAMPLES

Example 1: Patient receiving the equivalent of 120mg oral morphine in 24 hours

Loading dose = 12mg oral methadone

'As required' dose = 4mg oral methadone

Example 2: Patient receiving the equivalent of 450mg oral morphine in 24 hours

Loading dose = 30mg oral methadone (one-tenth equates to 45mg however this exceeds the maximum dose advised)

'As required' dose = 15mg oral methadone

Example 3: Patient receiving the equivalent of 1200mg oral morphine in 24 hours

Loading dose = 30mg oral methadone (one-tenth equates to 120mg however this exceeds the maximum dose advised)

'As required' dose = 30mg oral methadone (one-thirtieth equates to 40mg however this exceeds the maximum dose advised)

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Subcutaneous Dose Conversion

When switching from oral to subcutaneous methadone one of two ratios can be used, **2:1 or 1:1**. Dose calculation and titration should be carefully individualised. The Palliative Care Formulary recommends a 2:1 conversion however notes that a 1:1 conversion ratio may be more appropriate for those receiving doses of less than 80mg/24h methadone.

For further information see 'How do you convert methadone from an oral dose to an equivalent subcutaneous dose?' Available on <http://www.olh.ie/7-departments/166-palliative-meds-info/>

Cautions

Methadone can cause QT prolongation. Caution is advised in patients at risk of QT prolongation.

Subcutaneous administration can cause marked local inflammation necessitating site rotation. The solution should be diluted generously.

Serotonin syndrome may occur with concomitant use of serotonergic agents.

Hepatic Impairment

Methadone is extensively metabolised in the liver. There is a lack of consensus on the need for dose adjustment in hepatic impairment. Dose reductions of up to 50% have been suggested in hepatic failure. Methadone should be prescribed cautiously in hepatic impairment, and doses should be titrated according to patient response and tolerance.

Renal Impairment

Methadone has no clinically relevant metabolite, and hence has been suggested for use in those with severe renal impairment. However, this should only be carried out under the specialist supervision of a palliative care team. Methadone should be introduced at a low dose and titrated very slowly in this setting. Reductions of 50% have been suggested where creatinine clearance is less than 10ml/min.

Drug Interactions

Methadone has the potential for numerous and complex drug interactions, due to its metabolism via the Cytochrome P450 enzyme system mainly by isoenzymes 3A4, 2B6, and 2C19 and to a lesser extent by isoenzymes 2C9 and 2D6.

Drugs that may **increase** the effect of methadone include:

- Amiodarone
- Ciprofloxacin
- Clarithromycin, Erythromycin
- Clopidogrel
- Erythromycin
- Fluconazole, Voriconazole, Itraconazole
- Diazepam (high dose)
- SSRIs

Drugs that may **reduce** the effect of methadone include:

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin
- Anti-retrovirals

* Note that tobacco smoking can also decrease methadone plasma concentrations

Methadone can interact with other drugs. Please consult with pharmacy for advice. Product information is available on www.hpra.ie

Issues for Discharge and Outpatients

Methadone **MUST** be prescribed on the designated methadone prescription form issued by the Minister for Health.

For further information contact Pharmacy to request a copy of 'Methadone – From Hospital to Home – Practical Information'