

8. Guidelines for the use of methadone for cancer pain

Caution: Therapeutic Inequivalence

Methadone has both opioid and non-opioid properties, and a much longer half-life than other opioids (e.g. approximately 8–80h vs 2.5h for morphine). There is therefore no single potency ratio for methadone and other opioids, e.g. when switching from regular morphine, the eventual 24h dose of methadone is typically 5–10 times smaller than the previous dose of morphine, sometimes 20–30 times smaller, and occasionally even smaller. Cumulation is inevitable and is the reason for the week-long intervals between adjustments in the regular dose. Any switch must be closely supervised. Unless familiar with its use, seek specialist advice.

Indications for use

Methadone is used in various situations, including:

- at some centres, as the strong opioid of choice, instead of morphine
- at some centres, as the preferred strong opioid in patients with renal failure/on dialysis
- neuropathic cancer pain not responding to a typical regimen of an NSAID and morphine combined with a tricyclic antidepressant and an anti-epileptic
- neurotoxicity with morphine at any dose (e.g. sedation, hallucinations, dysphoria, delirium, myoclonus, allodynia, hyperalgesia) which does not respond to a reduction in morphine dose
- as an alternative to spinal analgesia and non-drug treatments when pain is unrelieved despite increasing doses of morphine and adjuvant analgesics, together with features of neurotoxicity.

Dose titration

1. When prescribing PO methadone as first-choice strong opioid:
 - start on methadone 5mg q12h *and* 5mg q3h p.r.n.
 - if pain relief remains minimal, consider increasing to 10mg q12h after 1–2 days (and 5mg p.r.n.), but generally do *not* increase the regular dose for one week
 - if necessary, continue to titrate the regular dose upwards by 1/3–1/2 once a week
 - with higher regular doses, increase the p.r.n. dose to 1/4 of the q12h dose.
2. If the patient is already receiving PO morphine, use one of the methods described below. Pharmacologically, Method 1 is preferable. If the patient and staff are not comfortable with a wholly p.r.n. regimen, Method 2 can be used (*see over*). If using oxycodone or hydromorphone, follow the guidelines as for morphine, except give 1/5 of the oxycodone and 1/2 of the hydromorphone 24h PO dose as q3h p.r.n. doses of PO methadone, *up to a maximum of 30mg*.
3. *With both methods, q4h normal-release morphine is stopped abruptly when methadone is started.* If switching from m/r morphine, give the first dose of methadone at least 6h after the last dose of a 12h preparation, or 12h after the last dose of a 24h preparation.

Method 1: Oral morphine to oral methadone, p.r.n. only (after Morley & Makin 1998)

Give q3h p.r.n. doses of PO methadone 1/10 of the previous 24h PO morphine dose, *up to a maximum of 30mg*.

On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12h dose, with 1/4 of the regular q12h dose q3h p.r.n.

If ≥ 2 doses/day of p.r.n. methadone continue to be needed, the dose of regular methadone should be increased by 1/3–1/2 once a week.

Method 2: Oral morphine to oral methadone, q12h & p.r.n. (after Blackburn *et al.* 2002)

Give a loading dose of methadone *at bedtime* 1/10 of the previous 24h PO morphine dose, up to a maximum of 30mg. *If very elderly or cachectic, omit loading dose.*

Prescribe 1/2 of the loading dose as a regular q12h dose (generally starting on the same day at bedtime), and 1/4 of the regular q12h dose q3h p.r.n.

In the event of severe uncontrolled pain, despite repeated p.r.n. doses, a second loading dose can be given. This is most likely in the first 48h after the switch.

If the patient complains of pain within 3h of a regular dose, take the next regular dose early (but the one after that at the normal time).

If the patient is very drowsy, omit one dose and then continue with a reduced regular dose.

If ≥ 2 doses/day of p.r.n. methadone continue to be needed, the dose of regular methadone should be increased by 1/3-1/2 once a week.

4. For patients in severe pain unable to wait 3h before giving the next dose, options include:
 - methadone 5–10mg q1h p.r.n. (i.e. a small fixed dose)
 - the previously used opioid q1h p.r.n. (50–100% of the p.r.n. dose used before switching)
 - if neurotoxicity with previous opioid, use an alternative strong opioid.
5. The switch to methadone is successful (i.e. improved pain relief and/or reduced toxicity) in about 75% of patients. Note: occasionally, a patient:
 - becomes over-sedated on either regimen; and will need a much smaller dose than expected. (some centres monitor level of consciousness and respiratory rate routinely q4h for 24h)
 - develops opioid withdrawal phenomena; and will initially need p.r.n. doses of the previous opioid to control these.

PO methadone to methadone SC/CSCI

1. To convert from PO methadone to methadone SC, halve the PO dose.
2. Due to its long half-life, methadone can be given SC q12h. Methadone for injection is available as 10, 25 and 50mg/ml, allowing a wide range of doses to be given in a small volume of injection, i.e. ≤ 2 ml. If methadone SC causes pain or skin reactions, use CSCI instead.
3. CSCI methadone may cause a skin reaction; this is reduced if:
 - saline 0.9% is used as diluent
 - a more dilute solution in a 20ml or 30ml syringe is used
 - the syringe is changed q12h
 - the site is changed every day.
4. Additional rescue doses of methadone SC can be given for breakthrough pain, using 1/6–1/10 of the 24h CSCI dose q3h p.r.n. (and see point 4 above).
5. If ≥ 2 doses/day of p.r.n. methadone continue to be needed, the methadone 24h CSCI dose should be increased by 1/3–1/2 once a week (more frequently only if prognosis <1 week).

Other opioids CSCI to methadone CSCI

Direct CSCI switching between other opioids and methadone is not recommended. The safest approach is to parallel one of the methods for PO switching, detailed above, using bolus injections of methadone SC instead of PO doses. Convert the opioid 24h CSCI dose to its PO equivalent and determine the methadone PO dose (Dose titration, point 2). The SC dose of methadone is half the PO dose; the maximum initial dose of methadone SC will be 15mg.