

Recommendations for the use of Methadone as an analgesic in cancer patients

Introduction

Pain occurs in up to 70% of patients with advanced cancer and in about 65% of patients dying from non-malignant disease. In about 10% of these patients the pain is difficult to control. Their pain often falls into one of three categories:

- it responds poorly to opioids,
- it is episodic and breaks through despite background opioid analgesia,
- it is caused by non-physical factors such as psychosocial distress.

The European Association for Palliative Care guidelines on the use of morphine and alternative opioids in cancer pain confirm oral morphine as the opioid of choice for moderate to severe pain. If the pain is uncontrolled with a dose of morphine that gives the patient intolerable side effects, suggested measures include exploring psychosocial issues, managing the side effects, reducing the dose of opioid, switching to an alternative opioid such as methadone, or changing the route of administration. The use of adjuvant drugs or co-analgesics may be appropriate. Many such patients will have neuropathic pain.

Methadone

Methadone is a synthetic opioid introduced into clinical practice approximately 40 years ago. Several studies/case reports have described its efficacy as an analgesic in advanced cancer and in chemical dependency management. In palliative care, with the vogue for opioid rotation, many alternative opioids have been examined, and after encouraging results with methadone safer protocols for prescription have been developed. Methadone has the additional advantage of being very cheap (about 20-30x less expensive than equianalgesic doses of hydromorphone).

The use of methadone in palliative care has been well reviewed (Ripamonti et al., Pain 1997; 70:109-115). Methadone has unusual properties, which we do not fully understand. Methadone may be given orally (in tablet or liquid form), rectally, intravenously or subcutaneously. Its receptor binding profile differs from that of pure μ agonists and it can be remarkably potent at small doses. Whilst having some activity at μ opioid receptors, methadone has additional significant agonist activity at delta receptors and has very different distribution and metabolic pathways. An updated Cochrane review (Cochrane data base systematic review 2007 Oct17; (4):CD003971) contains new information supporting the previous conclusions that methadone has similar analgesic efficacy to morphine. In this review a new study is reported which addresses a clinically relevant concern about short term/single dose studies.

Use beyond a few days may result in methadone accumulation leading to delayed onset of adverse effects. In an assessment over 28 days there was a higher rate of withdrawal due to side effects in the methadone group. This observation reinforces the advice that experienced clinicians should take responsibility for initiation and careful dose adjustment and monitoring of methadone.

Several publications confirm a clinical role as a second-line opioid analgesic.

Methadone has an especially long and variable half life in plasma of around 24hours (range 13 to 100hrs). (Fainsinger 1993; Ripamonti 1997; Morley 1998; Davis 2001) There is evidence that the morphine to methadone equianalgesic dose varies depending on the morphine-equivalent dose. In other words at low morphine-equivalent doses the ratio will be lower. In a study by Ripamonti the dose ratios varied between 2.5:1 and 14.3:1 (median 7.75:1). Thus caution is recommended when switching from any opioid to methadone, especially in patients who are tolerant to high doses of opioid. (Ripamonti, C et al J.Clin.Oncol. 1998 Oct: 16(10):3216-21)

Note: These guidelines apply to patients with severe cancer pain and managed as inpatients. Caution should be used when these guidelines are used in an outpatient or domiciliary setting.

Indications for Methadone Use

- If pain is inadequately controlled on high doses of morphine, oxycodone or fentanyl.
- If the patient exhibits signs of opioid neurotoxicity.
- If the patient has neuropathic pain unresponsive to other opioids and adjuvants although studies have not demonstrated the superiority of methadone over other opioids in controlling neuropathic pain.

For Patients Already Taking Opioids

NOTE: It is recommended that this conversion take place in hospital with palliative care consultation.

For patients who are on opioids, convert to the Morphine Equivalent Daily Dose (MEDD) using the following conversion factors:

- Oxycodone; multiply total daily oxycodone dose by 2
- Fentanyl; 100ug patch is equivalent to a MEDD of 300-400mg/day. Because of incomplete cross tolerance it is suggested to use the lower figure of 300mg

Procedure

- i) Stop all opioids.
- ii) Using the MEDD calculate 10% of that dose (however if the MEDD exceeds 300mg /day use 30mg of methadone as a maximum) and give this as a loading dose.
Eg. If the MEDD is 300mg then the loading dose is 30mg of methadone and the regular daily dose is 15mg B.D.
- iii) For breakthrough pain use the same dose as the loading dose of Methadone q 3hrs prn in the above example.

Maintenance Dosing after five days

For maintenance add up the total daily dose of Methadone used in 24hrs. and divide by 2 and give 12hrly. With the usual 50% dose given as a prn for breakthrough pain.

Ref: *Morley J and Makin M (1998) Pain Reviews 5: 51-58*

For initiating Methadone in patients who are opioid naive

Start with 2.5mg methadone q 12-hourly (frail patient consider 1mg) or 5mg nocte.

Give the same dose prn not more than 3-hourly.

Methadone Conversion to SC Injections or continuous subcutaneous infusion

Converting Methadone to subcutaneous injections or for constant infusion using a Graseby pump use 50% of the oral dose.

Side-effects of Methadone:

Are similar to other opioids in that as with other opioids methadone can cause neurotoxicity (delirium, myoclonus and/or hyperalgesia). Because of its long and unpredictable half-life leading to drug accumulation it is important to monitor the patient, especially after they have been taking methadone for some days. In the recent Cochrane review by Nicholason, previously quoted, it was found that for patients on methadone for greater than 28 days, there was a higher rate of withdrawal due to side effects. Even after stabilization patients should be monitored and the dose adjusted particularly as they decline. Medical and nursing staff caring for patients on methadone must therefore be alert to the possibility of accumulation and resultant side-effects particularly towards the end of the first week of treatment and beyond.

Side-effects are reversible but owing to the prolonged half-life of methadone sometimes it is necessary to reverse the analgesia using naloxone which may require continuous infusions.

Precautions

Many drugs will interfere with the metabolism of methadone. Some such as carbamazepine, phenytoin, phenobarbitone and rifampicin will potentiate the metabolism of methadone.

Others such as amitriptyline, macrolide antibiotics or cimetidine will decrease the metabolism.

In patients on multiple medications it is suggested to consult a Palliative Care Consultant for guidance.

Reversing Methadone or other opioid toxicity

On rare occasions it may be necessary to partially reverse the opioid induced side-effects with the competitive antagonist, naloxone. In the case of methadone the use of naloxone is potentially complicated by the long half-life of the opioid. Naloxone has a reported half-life of 30-80 mins (mean 64 +/- 12 mins) with maximal clinical effects seen 2-3 mins after IV and ~ 15 mins after SC injections.

There are few reports in the literature concerning the reversal of methadone toxicity. Often a single or 2-3 repeated doses of naloxone may be all that is necessary. Some clinicians propose the use of naloxone infusions for 12-24 hours to allow methadone levels to drop (methadone half-life ~ 13-26 hours).

Indications for opioid reversal with Naloxone

- i) If consciousness is significantly decreased
- ii) If respiratory rate < 8 breaths per minute
- iii) If Oxygen sats < 85%

Then:

Give naloxone slowly IV 0.2mg, if no effect after 5 mins repeat and continue to repeat at 5 min intervals until effect is achieved (if > 2mg given unlikely that methadone toxicity is cause of clinical picture). Naloxone may be prescribed in an emergency to be given by nursing staff IM or SC

It may be necessary to give a second dose (equal to the total dose given initially to obtain desired effect) after about 30 mins because of the rapid rate of metabolism of the naloxone.

If a third dose is required then consider commencing continuous infusion of naloxone starting at a dose equivalent to 2/3 of the initial dose over 1 hour. This may be given by intravenous infusion (0.9% saline or 5% dextrose as the diluents) or via SC infusion. The infusion should be maintained for 12-24 hrs (the time required will vary so patient should be monitored for re-appearance of pain and for the reoccurrence of signs of toxicity once the infusion has been discontinued. The rate of infusion may need to be decreased over time to maintain reversal of side-effects without re-emergence of pain.

Methadone may be recommenced at a lower dosage or an alternative opioid with a shorter half life may be chosen.

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