

Methadone in Palliative Care – St. Columba's Hospice, Edinburgh.

History

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 as a means of controlling the opioid abstinence syndrome. As an analgesic its limitations in terms of unpredictable accumulation and resultant toxicity soon became obvious and the use of methadone was relegated to the prescription of the occasional small dose as an anti-tussive. Interest was rekindled with its use in opiate maintenance/withdrawal programs particularly in conjunction with treatment for HIV infection. 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 in a recent publication (Ripamonti *et al.*, Pain 1997; **70**:109-115)

Uses

a) Alternative Opioid: Methadone appears to be a logical opioid to which to rotate/switch since it is very different, pharmacologically, from morphine. Whilst has having some activity at mu opioid receptors methadone has additional significant agonist activity at delta receptors and has very different distribution and metabolic pathways. Several publications confirm a clinical role as a second-line opioid analgesic. Methadone may be given orally (in tablet or liquid form), rectally, intra-venously or subcutaneously

b) Neuropathic pain: Methadone has potentially greater effects on neuropathic pain than either morphine or hydromorphone. In addition to agonist activity at opioid receptors, methadone has antagonist activity at NMDA receptors (a system thought to be closely involved in the development of chronic neuropathic pain syndromes), and possibly a small enhancing effect on the activity of central inhibitory neurotransmitters.

c) Maintenance therapy for chronic (intra-venous) opioid abuse.

Side-effects

Similar to other opioids but thought to have a lower incidence of neurotoxicity (delirium, myoclonus and/or hyperalgesia) than either morphine or hydromorphone. The main problem with methadone, however, is a long and unpredictable half-life leading to a danger of drug accumulation and progressive side-effects despite a consistent dose. At present most patients (in units where methadone is used) are commenced on treatment as in-patients until the dose has been stabilised. Side effects are reversible but owing to the prolonged half-life of methadone continuous infusions of naloxone are often required.

Precautions

- Elderly/confused patients unable to comply with prn requests
- Predominant incident pain where repeated requests may predispose to accumulation
- Coprescription of amitriptyline, macrolide antibiotics or cimetidine decreases methadone

metabolism

- Carbamazepine, phenytoin, phenobarbitone and rifampicin increase metabolism.

The following protocol is an effort to combine Canadian and European published experience and works safely in our experience:

Protocol for the Use of Methadone

a) For conversion from other opioids:

1. Ensure patient is on regular short-acting formulation of opioid.
2. Give regular 6am dose of first opioid and then stop prescription.
3. A first dose of Methadone is prescribed at 10am and thereafter is prescribed TO BE GIVEN ON A PRN BASIS, no more frequently than q3h, for pain or symptoms of opioid withdrawal.
4. The equivalent dose of oral methadone to be given as a single dose and then as required is initially 1/30TH OF THE PREVIOUS 24HR TOTAL DOSE of oral morphine (or morphine equivalent of other opioid), but no higher than 30mg.
5. A q1h prn dose of the original opioid should be made available for breakthrough analgesia if this is required before the three hours allowed between methadone doses.
6. The dose of methadone can be altered at the end of the first day or during the second 48 hrs if it is clearly either too small or too large.
7. On day 3 commence regular methadone q8h; the dose calculated from the total dose used on day 2. Often this will simply mean prescribing the calculated prn dose on a regular q8h basis. Methadone may also be used as prn but again no more than q3h. The previous opioid prn dose is left for more frequent dosing if required.
8. For a few patients q12h regular dosing may be adequate
9. Methadone breakthrough doses (10% of total 24hr dose) may be given q1h prn from day 7.

b) To commence methadone as a first-line, WHO level 3, opioid, start at a dose of 2.5mg q3h prn with morphine 2.5mg as alternative opioid if >breakthrough= doses are required more frequently than 3hrly. Then follow the above protocol. (In elderly or very frail patients it may be safer to start at a dose of 1mg q3h prn – using 1mg/ml solution)

Precautions

Methadone differs from morphine in that it has a long and unpredictable half-life that can lead to accumulation and side-effects without a change in prescribed dose. Medical and nursing staff caring for patients commencing methadone must therefore be alert to the possibility of accumulation and resultant side effects particularly towards the end of the first week of treatment.

Methadone 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 i-v and ~ 15 mins after s.c. injections.

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

Proposal

In cases of severe methadone toxicity, ie where;

- a) conscious level much decreased
- b) respiratory rate < 8 breaths per minute
- c) oxygen sats < 85%

Then:

1) Give naloxone slowly i.v. 0.2mg if no effect after 5mins repeat and continue to repeat at 5min intervals until effect is achieved (if > 2mg given unlikely that methadone toxicity is cause of clinical picture). Naloxone maybe prescribed in an emergency to be given by nursing staff i-m or s.c (there is apparently little difference in time to onset of activity between these two routes)

2) Be prepared to give a second dose (equal to the total dose given initially to obtain desired effect) after about 30 mins as naloxone is distributed and metabolised.

3) If a third dose is required then at the same time commence continuous infusion of naloxone starting at a dose equivalent to 2/3 of the initial dose over 1 hour. This is described via intravenous infusion (0.9% saline or 5% dextrose as the diluent) but could presumably also be given via s.c. infusion. The infusion should be maintained for 12-24hrs (the time required will vary so be guided clinically ie from reappearance of pain) and the patient monitored carefully after discontinuation. The rate of infusion may need to be decreased over time to maintain reversal of side-effects without reemergence of pain.

4) Methadone may be re-started thereafter at a lower dose or an alternative opioid commenced.

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