The clinical use of methadone in cancer and chronic pain medicine

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Key points

- Methadone is a synthetic opioid used in the management of cancer pain, chronic pain, and opioid addiction.
- It has multiple pharmacological modes of action, but it predominantly works via antagonism of the μ-opioid receptor.
- Conversion to and from methadone and other long-term opioids is problematic, and no universally accepted equianalgesic dosing regimen exists.
- Perioperative management of patients taking long-term methadone is similarly problematic, and is discussed.

Methadone is an opioid invented in Germany during the Second World War. Clinical trials were initiated in the USA in 1947, and methadone was originally marketed as Dolophine, with etymological origins from the Latin words dolor (pain) and fins (end). It was recognized in 1964 that it could be used to diminish or prevent the symptoms of craving and withdrawal in heroin users, and continues to be widely used in the management of opioid addiction. During the last 50 years it has also found a place in the management of cancer and chronic pain.

Pharmacology

Methadone is a synthetic phenylheptylamine μ-opioid agonist with a molecular weight of 345.9. It is lipophilic and has a volume of distribution of 4 l kg⁻¹. It has pKₐ of 9.2, and so at physiological pH only 1% of the drug is ionized. It is presented as a racemic mixture of R- and S-methadone, with the R-enantiomer being primarily accountable for μ-receptor agonism and therefore analgesia. The S-enantiomer is responsible for N-Methyl-D-Aspartate (NMDA) antagonism, having an affinity at the NMDA receptor similar to ketamine, and serotonin and norepinephrine reuptake inhibition. This NMDA antagonism may help to prevent opioid tolerance, withdrawal, and opioid-induced hyperalgesia. Finally, methadone may also interact with Na channels in a similar manner to local anesthetics. A summary of the pharmacokinetic characteristics of the drug are summarized in Table 1. In the UK, methadone is available as 5 mg tablets, and in solutions of 1, 10, and 20 mg ml⁻¹. Methadone is usually administered orally. Parenteral preparations are also available in the UK but are less-commonly used.

Absorption and bioavailability

Methadone has a generally high but variable oral bioavailability of 35–100%, with plasma concentrations peaking 2 h after administration. This large variation is in part explained by genetic polymorphism in the cytochrome p450 3A4 enzyme system, along with the possible auto-induction of hepatic first-pass metabolism with long-term use. Oral absorption is also influenced by gastric motility, gut perfusion and pH.

Rectal administration of methadone results in a bioavailability of 76% but has been associated with proctitis.

Distribution

Methadone binds primarily to α-1 acid glycoprotein and also albumin. In the presence of cancer, debilitating illness and opioid dependency, α-1 acid glycoprotein may be elevated as an acute-phase reactant, so reducing the free fraction of active...
Methadone crosses the placenta with concentrations in amniotic fluid similar to that of maternal plasma.

**Metabolism and elimination**

Methadone is metabolized by oxidative biotransformation to inactive metabolites. It is demethylated to 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine, 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrine, methadole, or normethadole, before renal and faecal excretion. In patients with normal renal function, 20–50% of metabolites are renally excreted, but this proportion diminishes as estimated glomerular filtration rate decreases, and excretion occurs almost entirely via the enteral route in anuric patients. In light of this, there is considerable controversy about whether dosage intervals should be increased in renal failure. Peritoneal dialysis or haemodialysis only removes ~1% of the total daily dose.

Methadone is sequestered in lipid-rich peripheral tissues and released back into the plasma slowly during redistribution and elimination. It therefore exhibits a highly variable half-life depending on the degree of saturation of peripheral tissues, increasing with the length of therapy and cumulative dose. Values of between 5 and 130 h are reported, with a mean of 35. Inter-individual variation of up to 24 h is well recognized. However, it is also possible that, in patients on chronic therapy, hepatic enzyme auto-induction may inconsistently reduce half-life. The unpredictable nature of methadone’s pharmacokinetics implies that caution must be exercised when using this drug in the clinical context.

**Drug interactions**

There is considerable potential for interaction with CYP 3A4 inducers and inhibitors. Inducers, such as carbamazepine, phenytoin, rifampicin, and St John’s Wort have the potential to lower plasma concentrations of methadone. Inhibitors, such as fluoxetine, antifungals, and HIV-1 protease inhibitors may do the opposite. It should be noted that many methadone-related deaths recorded in the literature are due to drug interactions rather than methadone alone. In addition, some antipsychotics may precipitate methadone withdrawal symptoms via an unknown mechanism.

**Precautions and adverse effects**

Methadone has a similar range of side-effects to other opioids. However, when compared with morphine, methadone readily accumulates with repeated dosing, and the development of withdrawal symptoms is more insidious and prolonged. Opioid toxicity develops unpredictably during dose titration and may continue long after the drug is discontinued, requiring several days of naloxone treatment.

**Rationale for use in pain medicine**

Methadone has a number of properties that make it useful in the settings of cancer and chronic non-malignant pain, including long half-life, good oral bioavailability, delayed withdrawal, low cost, and convenient dosing schedule. Its use in the UK is governed by the Misuse of Drugs Act 1971.

However, due to unpredictable pharmacokinetics and dose-response relationship, it tends to be used as a second- or third-line opioid. It may be particularly suited to treatment of mixed nociceptive/neuropathic pain states due to opioid and NMDA receptor antagonism together with catecholamine reuptake inhibition, although such theoretical pharmacodynamic advantages have not been borne out in rigorous empirical studies.

Please see Table 3 for a summary of the advantages and disadvantages of methadone use in cancer and chronic non-malignant pain.

**Practical aspects of methadone prescribing**

**Conversion to methadone in opioid-tolerant patients**

The conversion of methadone from and to other opioids is considerably more complicated than conversions between other opioids. The principles of conversion remain the same, however,
and rely on a series of steps using published opioid equivalence ratios to estimate an appropriate equianalgesic starting dose:

(i) Convert existing opioid to oral morphine equivalent dose (OME) (e.g. oral oxycodone:oral morphine ratio is estimated at 1:2).
(ii) Further convert OME to new opioid (e.g. OME to subcutaneous diamorphine ratio is estimated at 3:1).
(iii) Introduce a safety margin by the reduction of calculated equivalent dosage by 33–50% to allow for inherent inaccuracy in equivalence ratio and unpredictability in patient response to new opioid (due to incomplete cross-tolerance).

It can be seen that each step has the potential to introduce significant inaccuracy, with early inaccuracies becoming amplified by later calculations. Published equianalgesic ratios may vary to some extent, and they are usually derived from single dose studies in healthy, opioid-naïve patients, potentially limiting their applicability in most clinical situations in which they are actually used. For example, to convert a patient taking oxycodone 50 mg bd to a subcutaneous diamorphine infusion, a ratio of 1:2 suggests an OME of 200 mg (24 h)\(^{-1}\). Further, a ratio of 3:1 OME: subcutaneous diamorphine gives an estimated 24 h diamorphine dose of 66 mg. Introducing an appropriate safety margin, it would be reasonable to start an infusion at 1.5 mg h\(^{-1}\) while monitoring the patient for analgesic efficacy, opioid toxicity, and withdrawal symptoms and adjusting infusion rate accordingly.

When converting opioid-tolerant patients to methadone, however, the equianalgesic dose ratio varies depending on current opioid dose, becoming relatively more potent in patients taking larger amounts of existing opioid. This is reflected in published conversion regimes, with, for example, Mercadante reporting a strategy utilizing a 4:1 conversion ratio in patients receiving <90 mg day\(^{-1}\) of OME, 8:1 for 90–300 mg day\(^{-1}\), and 12:1 in >300 mg day\(^{-1}\).\(^{11}\)

Conversion strategies to methadone can be divided into two broad groups: by the clock (Edmonton model) and ad libitum. There are no studies comparing the efficacy of one method with the other. The Edmonton method relies on an overlapping approach with the previous opioid over 3 days, with sequential 30% reductions in existing opioid and replacement with 8 hourly methadone at an OME conversion ratio of 10:1. The ad libitum method involves stopping the previous opioid on Day 1 with replacement by a fixed dose of methadone on a 3 hourly prn basis. This is the most-commonly used method in the UK. Figure 1 gives further details of the ad libitum strategy.

During the first week of therapy it may be necessary to provide other immediate-release short-acting opioids for breakthrough pain, but this should be avoided where possible as it may prolong the titration phase. Other strategies such as non-opioid analgesia and non-pharmacological interventions should be tried first.

At the start of methadone titration, the duration of analgesia may be very short, at ~6 h, despite the prolonged terminal

| Table 3 Advantages and disadvantages of methadone in comparison with other opioids |
|---------------------------------|---------------------------------|
| Advantages                      | Disadvantages                   |
| Inexpensive                     | Unpredictable half life         |
| High oral bioavailability       | QTc prolongation and torsade de pointes in high doses and in risk groups |
| Long acting, with stable interdose plasma levels and slow onset to withdrawal | Interaction with other drugs metabolized by the cytochrome P450 enzyme system |
| Serotonin and norepinephrine reuptake inhibition and NMDA antagonist activity | Potential for accumulation with unpredictable, delayed and prolonged opioid toxicity |
| Lack of active and toxic metabolites | Unpredictable equianalgesic dose conversion with other opioids |
| Little accumulation with renal impairment | Variable protein binding and free levels of drug in illness and addiction |
| Constipation develops slowly and may be less marked than with other opioids | Subcutaneous use can produce local tissue reactions |
|                                | Not cleared by renal replacement therapy |

Fig 1 The ad libitum, UK conversion strategy from other opioids to methadone.
elimination half-life. This is due to rapid redistribution after oral
administration, resulting in plasma levels decreasing below the
minimum effective analgesic concentration. With chronic dos-
ing, peripheral tissues serve to maintain plasma levels and may
prolong analgesic effect.

If an in-progress methadone switch needs to be abandoned
due to e.g. inadequate analgesia or QTc prolongation, the original
opioid should be recommenced at 66% of the previous dose
and retitrated.

Starting methadone in opioid-naïve patients

It is very unusual to administer methadone in opioid-naïve
patients with chronic or cancer pain, but if done, an oral prn 3
hourly dose of 2.5 mg in an adult (less in the elderly) might be
considered a reasonable starting point, with conversion on Day
6 to a bd dose as per the ad libitum regime.

Conversion from methadone to other opioids

The conversion of methadone to other opioids may be more prob-
lematic than the conversion of other opioids to methadone as no
published guidance exists for this. Some authors report success-
ful conversion using a 1:4.7 methadone to OME ratio, but this is
not universally accepted, and others suggest a ratio significantly
lower than this (e.g. 1:3). Pragmatically, it may be necessary to
convert to a relatively low OME (e.g. three times daily methadone
dose) with adequate breakthrough opioid analgesia and prn low-
dose methadone to treat any withdrawal symptoms that do not
respond to the new opioid.

Special populations

Controversy exists as to whether the dose of methadone should
be decreased in renal failure. Maintenance doses do not need to be altered in
patients with stable chronic liver disease. During pregnancy patients may require higher doses and
shorter dosing intervals. This is due to reduced absorption and
increased elimination. Neonatal opioid administration may be
required to prevent opioid withdrawal.

Methadone is permitted in breastfeeding mothers, although
the dose should be as low as possible and the infant monitored
to avoid sedation.

General considerations

In light of the above considerations and pitfalls, methadone ad-
ministration in the context of chronic and cancer pain should
be overseen by clinicians experienced in its use. It is the authors’
opinion that conversion to and from methadone should be done
in an inpatient setting due to the unpredictable nature of its
effects. Serial ECGs should be performed as above, and if QTc pro-
longation is demonstrated, consideration should be given to
reducing methadone dose or converting to an alternative opioid.
Clear and regular communication with other healthcare profes-
sionals in both primary and secondary care is essential.

Managing acute pain in patients on methadone

Anaesthetists may encounter patients on long-term methadone
treatment in the perioperative setting. Here, the goals of treatment
should be to prevent opioid withdrawal and to treat acute pain ef-
effectively. Underlying principles are similar to managing patients
on other long-term opioids in this context. This includes:

(i) adequate explanation and communication with the patient,
including allaying potential fears about long-term opioid
re-escalation when other opioids are given;
(ii) provision of usual maintenance opioid or equivalent
throughout perioperative period; and
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(iii) provision of further analgesia on top of maintenance to treat acute pain, using opioid-sparing techniques where possible, and bearing in mind that higher opioid doses may be necessary to achieve clinical effect.

Many of the characteristics that favour the use of methadone in chronic non-malignant and cancer pain complicate its management and use in the perioperative period. Such characteristics include the high degree of inter-individual variability in dose response, numerous medication interactions and long half-life. In addition, parenteral methadone preparations are not routinely stocked by many UK institutions, and no simple bioequivalent conversion ratio exists as detailed above. This may create significant problems if the enteral route becomes unavailable for more than 2 days perioperatively.

There is no published guidance on the management of methadone in the perioperative period. A suggested algorithm is shown in Figure 2.

It should be remembered that many patients on long-term methadone express their dosage in millilitres rather than milligrams. Some use a fixed, individually prepared volume of 100 ml containing a variable concentration of drug. Where possible, methadone dose should be confirmed with primary care colleagues. A preoperative ECG is warranted to establish the QTc before administration of anaesthesia, and if prolonged, consideration should be given to the avoidance of other QTc prolonging drugs and early correction of relevant electrolyte abnormalities.

Declaration of interest
None declared.

MCQs
The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to BJA Education.

References