comprehensive review

The Role of Methadone in the Treatment of Moderate to Severe Cancer Pain

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Abstract

The World Health Organization recommends a step-by-step approach to the management of chronic cancer pain, called the analgesic ladder. Traditionally, morphine has been the prototypical opioid for chronic cancer pain because there is no ceiling effect or upper limit and it is a naturally occurring pure µ-opioid agonist. Occasionally, there are dose-limiting side effects and/or lack of efficacy. Opioid rotation is important because it improves analgesia and the side effect profile. Two principal reasons for failure of strong opioids are the presence of incident pain and/or neuropathic pain. Incident pain usually occurs in a patient with osseous metastases or another movement-related pain syndrome. Other reasons to rotate opioids are side effects such as intractable nausea and vomiting, sedation, dysphoria, delirium, and constipation, which are unresponsive to simple measures such as retitration, antiemetic agents, antipsychotic agents, psychostimulants, and laxatives. There are recent data that demonstrate that the accumulation of active metabolites in patients receiving common opioids such as morphine and hydromorphone are partly responsible for adverse effects. This premise has prompted clinicians and researchers to consider opioid rotation as a valid tool for cancer pain management to increase the probability of acceptable adverse effects with adequate analgesia. Methadone is an opioid agonist with a lack of known active metabolites, which are known to produce side effects with other opioids. Methadone has excellent bioavailability, making it a desirable analgesic agent for refractory types of cancer pain.

Introduction

Methadone hydrochloride is a synthetic opioid agonist that gained popularity in research starting in the latter part of the 19th century and through the early 20th century, primarily as a maintenance or replacement drug in opioid addiction, mostly as a substitute for heroin. Methadone is widely used in the management of addiction and chronic pain in the United States. There are approximately 180,000 patients receiving methadone maintenance therapy who take a single daily dose < 110 mg. Oral and parenteral methadone formulations are often used at much higher doses as analgesic agents, especially in patients with refractory pain from cancer.

Methadone was initially used to a lesser extent for the treatment of pain.1,2 It was developed in the 1940s as an alternative to morphine when morphine was difficult to obtain as a result of World War II. It is worth mentioning that during World War II, methadone was also used in experimentation.
Pharmacology and Pharmacokinetics

Currently, in the United States and many other countries, methadone is available in parenteral, oral, and rectal preparations for use in clinical practice. Methadone for use in cancer pain is a racemic mixture of L- and D-methadone isomers. The L-methadone isomer has been reported to be 8-50 times more potent than the D-methadone isomer, which has predominantly antitussive properties.

Preclinical studies demonstrate that opioid analgesic agents can act on different receptors or subtype receptors, and there is marked individual variability that may influence the analgesia and adverse effects. In addition, the genetic makeup of a patient can influence the analgesia obtained from different opioids. The unique properties of opioids in analgesia, tolerance, and adverse effects may have to do with the active metabolites of the parent drug and different receptor affinities, leading to incomplete cross-tolerance. Methadone is a desirable alternative µ-opioid when more frequently used opioids fail to provide adequate analgesia in patients with cancer who have complex cancer pain syndromes. Methadone has many positive attributes that lend it to the cancer pain armamentarium; it lacks neuroactive metabolites, clearance is independent of renal function, it has excellent oral bioavailability, and the cost is minimal compared with other opioid analgesic agents. The well-known long half-life of methadone can be considered a benefit in that fewer doses are needed per day and there is potentially a long response time. Additionally, methadone possesses an extra opioid or dual mechanism of action, which is its noncompetitive antagonist activity at the N-methyl-D-aspartate (NMDA) receptors.

It has been hypothesized that methadone also shares δ-activity and potentially prevents monoamine reuptake in the brainstem, producing an effect similar to tricyclic antidepressants, which have had a history of being employed for predominantly neuropathic pain in noncancer pain syndromes. Methadone can produce analgesic activity within 30-60 minutes after oral administration with a duration of action of 4-8 hours, with most patients prescribed 6-hour dosing intervals. Methadone is known for relatively variable absorption and a long half-life, which can make initial dosing somewhat difficult. Many authors now recommend initially dosing as needed and then conferring a continuous dose after establishing the patient’s requirements. Sawa reported on 14 patients who received 10-mg doses of methadone for pain and were allowed to establish their own dosing interval. Interestingly, the first day, the patients dosed themselves with 30-100 mg orally every 3-7 hours; however, on the days following, they tapered off to a lower dosage with longer intervals between dosing. The ranges in this study were 10-40 mg orally every 8-10 hours. Currently, clinical experience and research suggest that dosing every 6-8 hours is analgesic and avoids toxicity.

One strong benefit of methadone is that its incomplete cross-tolerance at the receptor level allows relatively small doses to be analgesic. In addition, the cross-tolerance may be partly a result of the ability of methadone to noncompetitively block NMDA receptors. Although the D-isomer of methadone has less analgesic activity than the L-isomer, it has antagonist activity on the NMDA receptor. Consequently, the properties of methadone can greatly enhance analgesia in patients who are not responsive to other opioids or who have refractory cancer pain syndromes.

Plasma Concentrations, Metabolism, Elimination, and Clearance

Nilsson et al reported a single-dose study in which 8 subjects receiving 20 mg of methadone orally had a bioavailability range of 41%-99%. Several studies show wide variability in concentrations of methadone after gas-liquid chromatography analysis. It is well known that there are unique and unusually high concentrations of methadone in plasma after oral, rectal, and intravenous dosing and that this is partially responsible for its efficacy in the treatment of cancer pain syndromes. Methadone is metabolized by N-demethylation in the liver mainly by the cytochrome P450 3A4 to 2 inactive metabolites. It is subject to minimal first-pass extraction through the liver and demonstrates a biphasic elimination with an α half-life of 2-3 hours and a β half-life of 9-87 hours. Methadone is a highly lipophilic molecule, which allows wide distribution in body tissues, with the highest concentrations being found in the lung. Methadone is excreted in the feces and urine. In a single-dose study by Inturrisi and Verebely, the clearance of methadone after 15 mg was administered orally ranged between 8.3 and 19.2 mL per minute. The same authors reported 40% of the drug was excreted in 24 hours, with 50% of the dose excreted in 96 hours.

Adverse Effects and Drug Interactions

Adverse effects of methadone are similar to all other pure µ-opioids—they are many and very variable, depending on the dose and the patient’s biology. Common adverse effects are constipation, nausea, fatigue, and sedation, with less common side effects being dysphoria or euphoria, antidiuretic effect, pruritus, respiratory depression (more common in opioid-naive patients), sweating, bradycardia, QTc prolongation, headache, urinary retention, and impotence. Methadone is primarily metabolized by CYP450 3A4 and, to a lesser extent, CYP450 1A2 and CYP450 2D6. Inducers and inhibitors of these enzymes are likely to cause drug interactions with methadone. Currently, attention is focused on the interactions between methadone and the antiviral drugs used in the treatment of HIV and AIDS. The nucleoside
Methadone as Cancer Pain Treatment

reverse-transcriptase inhibitors and the non-nucleoside reverse-transcriptase inhibitors have an effect on the bioavailability and efficacy of methadone, and clinicians should be aware of the potential drug interactions to prevent toxicity or subtherapeutic effects. The protease inhibitors have not yet been studied; studies are in progress or being planned. The common enzyme inhibitors that can increase the serum level and/or toxicity of methadone are amiodarone, verapamil, cimetidine, ciprofloxacin, erythromycin, fluconazole, ketocanazole, and fluoxetine.

Enzyme inducers can decrease serum levels and/or effect of methadone. Rifampin has been shown to produce withdrawal symptoms when administered to patients who were taking methadone in a maintenance program for addiction. This occurs because of lowered plasma concentrations of methadone and increased urinary and fecal elimination. Other common enzyme inducers are barbiturates, carbamazepine, phenytoin, and spironolactone. Methadone is generally thought to be a safe and effective medication; recently, however, concerns have arisen about the potential for QTc prolongation. This can lead to life-threatening torsades de pointes. Data are very limited; however, major authors and references disagree about the need to allocate this drug as a risk factor for torsades de pointes. The most common risk factor for torsades de pointes is QT segment prolongation; however, other drugs, especially the antiarrhythmic agents, are the most common culprits. Methadone is not considered to be a high-risk drug for QT segment prolongation.

Clinical Use, Efficacy, and the Role of Opioid Rotation

Opioid rotation is the term given to a switch from one opioid drug to another, the aim of which is to improve analgesia in patients with poorly controlled pain and reduce undesired side effects. In general, absolute cross-tolerance does exist among different types of opioids, and it is usually necessary and recommended that the new opioid dose should be approximately 60% of the normal equivalent analgesic dose when rotating to an alternative pure \(\mu\)-opioid agonist (Table 1). \(^{2,4,12,16}\) Opioid rotation to methadone from other \(\mu\)-opioids may be necessary for unresponsive or refractory cancer pain. However, the ability to dose and titrate methadone must be understood, as its administration can be complicated. Methadone has demonstrated interpatient variability in pharmacokinetics, and its well-described extensive bioavailability and long half-life make accumulation a problem following multiple doses. Some equianalgesic dose charts based largely on single-dose studies recommend a 1:1 to 1:4 ratio when converting morphine to methadone; however, with multiple doses of methadone, higher dose ratios are necessary to prevent adverse effects and toxicities. \(^{14,15,17}\)

A few studies demonstrated that if the dose of the previous opioid was increased over a certain level, a lower methadone dose ratio might be effective because of incomplete cross-tolerance. In fact, it is plausible that the initial opioid(s) revealed resistance or a hyperalgesia syndrome. It is usually safe to commence therapy at 10%-20% of the total morphine dose with a dosing interval of 6-8 hours and then individualize the dose according to patient response. In one retrospective study that looked at dose ratio between morphine and methadone in patients with cancer pain, patients receiving \(> 1165\) mg morphine per day before methadone rotation, a median dose ratio of 16.84 (range, 12.25-87.95) was observed, which was approximately 3 times higher than a median dose ratio of 5.42 (range, 2.95-9.09) for the 50% of patients receiving lower morphine doses. \(^{16}\) This study looked at 14 rotations between morphine and methadone and 6 rotations between methadone and morphine, which confirmed the underestimated potency of methadone. In fact, at high doses of morphine, the median dose ratio could be as high as 11 times higher when switching to methadone. Possible explanations are the dual mechanism of action of methadone, pure \(\mu\)-agonist activity, and NMDA noncompetitive antagonistic behavior of methadone associated with tolerance in animals and humans. \(^{16,18}\)

Several authors suggest ways to rotate from other opioids to methadone, and consequently there are several clinical styles that are acceptable and efficacious. Lawlor et al endorse an initial priming period/gradual conversion; over a period of 3 days, morphine dosage is reduced by approximately 30% of the original dose each day, with a correspondingly increased dose of methadone every 8 hours using a ratio of 10:1. \(^{16}\) Ripamonti and Bruera suggest a similar rotation, but using dose ratios of 4:1 in patients who receive 30-60 mg of daily morphine, 6:1 for patients with a total daily dose of 90-300 mg of morphine, and 8:1 for those who receive \(> 300\) mg of daily morphine. \(^{3}\) Mercadante et al rely on a fixed rotation of 20% of the previous daily dose of morphine divided into 8-hour intervals and an additional dose as needed. \(^{2}\) Conversion strategies seem to work and are determined by the comfort level of the clinician. \(^{19-21}\) Common to all cancer pain treatment are the as-needed or rescue short-acting opioids for the breakthrough pain episodes that can occur when baseline pain is well controlled.

The last important phenomenon in the conversion of opioids is that parenteral opioids are more bioavailable than oral opioids. The ratios commonly used are 1:3 parenteral-to-oral for morphine and 1:2 parenteral-to-oral for methadone. \(^{22}\) With this in mind, opioid rotation, particularly to methadone, can be a useful tool for patients who have cancer pain syndromes that are difficult to manage or have a component of neuropathic pain. \(^{23,24}\) Perhaps because of its lack of known active metabolites, methadone can also be useful in renal-compromised patients. \(^{25,26}\) Fecal excretion accounts for the greater part of the dose, and urinary elimination is a minor pathway.
In addition to these benefits, especially for patients receiving higher-dose opioids, methadone is much less expensive than other opioids; and because of the convenient dosing regimen, outpatient compliance may increase. And although there may be a stigma associated with using this drug because of its role in addiction management, patient education can impact its use significantly.

Conclusion

Methadone offers another modality for the armamentarium of medications used for the management of cancer-related pain. It may offer a better side effect profile as well as provide better analgesia. Its complicated pharmacology deserves more attention and study to lend it to more mainstream use as an agent for cancer pain. Further discussions may be needed to establish the correct conversion ratio, but methadone appears to be more potent than morphine in multiple dosing regimens. Opioid rotation to methadone from other more conventional opioids may have multiple benefits for cancer pain syndromes that are refractory or difficult to manage, and may be used accordingly for this population of patients who might require switching opioids for reasons of inadequate analgesia and/or unmanageable side effects.

References


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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (Oral)</th>
<th>Interval</th>
<th>Rescue (Oral)</th>
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<tbody>
<tr>
<td>Method 1</td>
<td>20% of Morphine, methadone 60 mg</td>
<td>Every 6 hours</td>
<td>Morphine 120 mg every 2 hours as needed</td>
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<td>Mercadante et al2</td>
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<td>Method 2</td>
<td>Gradual reduction of morphine sulfate and titration of methadone Methadone 40 mg, decrease morphine by 30% per day</td>
<td>Every 8 hours</td>
<td>Morphine 120 mg every 2 hours as needed</td>
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<tr>
<td>Lawlor et al16</td>
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<tr>
<td>Method 3</td>
<td>10:1 Ratio, methadone 40 mg</td>
<td>Every 8 hours</td>
<td>Methadone 15-20 mg every 4 hours as needed</td>
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<td>Lawlor et al16 (Variation of Method 2)</td>
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<td>Method 4</td>
<td>20% of Morphine, methadone 60 mg</td>
<td>Every 8 hours</td>
<td>Methadone 60 mg every 4-6 hours as needed</td>
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<td>Method 5</td>
<td>8:1 Ratio, methadone 80 mg</td>
<td>Every 8 hours</td>
<td>Morphine 120 mg every 2 hours as needed</td>
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<tr>
<td>Ripamonti et al4</td>
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Methadone as Cancer Pain Treatment


