Research Article

Early Use of Methadone for Cancer Pain

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Abstract

Methadone has been known since the beginning of the 20th century. Its use for cancer pain is still controverted. Several articles clearly show the benefit of methadone for cancer pain. We attempted to identify the advantages of use of methadone early on in the course of cancer. Methadone is a very interesting molecule for cancer pain treatment because of anti NMDA, SSRI and opioid actions, lack of active metabolite, and cost. Its benefits must be balanced against the potential drug to drug interactions during treatment initiation and interactions with other drugs when methadone doses are stable. As for all opioids, side effects can appear. Ten studies including 706 patients support the use of methadone as first line opioid treatment: 7 are prospective studies (one double-blind randomized with morphine, 4 randomized controlled with morphine or transdermal fentanyl, two open studies) and 3 are retrospective studies. Seven studies support its ambulatory initiation (3 prospective including 2 controlled studies, and 4 retrospective studies) with a total of 845 patients. Methadone could be used with caution early on in cancer pain management.

Keywords: Methadone; Cancer pain; Palliative care; Opioids

1. Introduction

In the early 30s, methadone was discovered by Bockmuhl and Ehrhart at J. G. Farbenindustrie. Morphine had been known for 2 centuries. It had been commercialized for pain in 1947 in the USA but quickly its use switched to illegal usage and addiction in the 60s [1]. In the middle of the 90s, methadone was rediscovered as a painkiller. It has been increasingly investigated, with 10 publications in 1992, but 114 in 2018.

In this article, we attempt to present why methadone might be preferred to other opioids in cancer pain. We then balance its benefits against the risks, and assess whether methadone can be used safely and effectively as a first line treatment for in-house or out-patients.

2. Is Methadone a Different Opioid, Specific to Cancer Pain?

Methadone has unique pharmacological characteristics. It has a complex pharmacology with a half-life that changes with chronic administration on account of tissue storage and interaction with its own metabolism [2]. Methadone induces its own metabolism via CYT3A4 and its clearance increases with time. It inhibits the CYT2D6, which is itself involved in its metabolism. There is therefore a balance between inhibition and induction of methadone. Methadone's half-life varies greatly from one patient to another [3]. This particularity leads to a specific use, for example switching to methadone is governed by different rules than when switching to other opioids. Furthermore methadone features specific painkilling activity. Its mixed activity is unique among opioids. Methadone acts as an N Methyl D Aspartate (NMDA) antagonist, which limits opioid hyperalgesia and tolerance phenomena. It decreases central hypersensitivity. Selective Serotonin Recapture Inhibition is induced by methadone, limiting chronic pain development. As opioid agonist binding to opioid receptors of the mu and kappa class, it is a potent step 3 ladder analgesic [4-5]. Because of SSRI and NMDA actions, methadone has been successful for neuropathic pain. A recent Cochrane review identified 3 strong articles in favor of the use of methadone for neuropathic pain, but bias and selection criteria prevented reviewers to come to a definite conclusion [6]. Therefore, methadone seems to be unique analgesic for nociceptive pain and may be particularly effective for cancer pain because pain is often mixed: nociceptive and neuropathic. Furthermore tolerance phenomena are a frequent indication for opioid switching. The NMDA activity reduces this risk. Methadone also has a different type of prescription. Switching to methadone is specific. Several authors suggested different protocols. All proposals are safe and efficient for pain relief [7-14].

3. Methadone's Advantage and Disadvantage

Methadone, as other opioids, causes side effects such as constipation, nausea, dizziness, delirium, etc. It is subject to induce overdose, so specific attention is needed during instauration. Opioid side effects are sometimes described as less important with methadone [14]. Methadone can prolong QT interval, leading to potential torsade de pointes. This risk seems low: between 1969 and 2002, FDA identified 5503 side effects of methadone (addicted and painful patients), 0.29% were for QT prolongation [15]. Methadone is metabolized by CYP 450 (CYP 3A4 and CYP 1A2, 2D6, 2D8, 2C9/2C8, 2C19 and 2B6). It can influence metabolization of several treatments and several molecules lead to methadone fluctuation (under or over dose) [16]. So great care is needed when methadone is instituted, and when another treatment is added. Methadone instauration is complex. Introduction of methadone and opioid withdrawal can be rapid or progressive, Methadone can be administered at a fixed dose or ad libithum; conversion rate can be either fixed (1:10) or progressive (1: 4 for EMO 60 at 90 mg/d, 1: 6 for EMO 90 to 300 mg/day, 1:8 for EMO greater than 300 mg/d).

Despite this drawback, methadone has strong assets because it has no active metabolite, methadone can be used safely for patients with renal impairment [17]. It is a very cheap strong analgesic. It is very useful for complex situations like mixed pain or tolerance phenomena. Recent results show that methadone has anticancer action, which is the exact opposite of the other opioids [18-19]. This data suggests that early use of methadone to avoid complex opioid switching may be beneficial: it limits hyperalgesia, it is cheap, it does not induce cancer development and it is a very potent opioid.

4. Early use: First line

A recent review by international experts supports the use of methadone as a first line treatment. The authors identified 10 studies including 706 patients in favor of early use. 7 studies were prospective, including one double-blind randomized with morphine, 4 randomized controlled with morphine or fentanyl transdermal, two open studies, and 3 retrospective studies [20]. Bruera (2004) proposed a double-blind, multicenter study with 103 patients. The follow up is 4 weeks for patients requiring strong opioid. One group received morphine and the other methadone. Pain control was comparable. More dropouts were observed in the methadone group. Authors report that "higher methadone-induced toxicity could be explained by the lower dose ratio used in this study (1:2) [21]."

Four studies with strong methodology presented positive perspectives for first line treatment. Two randomized prospective studies compared methadone and morphine, including 54 and 40 patients [22-23]. Both drugs were efficient to control pain with same side effect profile. Morphine escalation was observed in Ventafridda's article [22]. Fentanyl and methadone provided good pain control in first line treatment for neuropathic pain due to head and neck cancer [24]. When comparing methadone with morphine or fentanyl, no difference in pain or symptoms were reported during the four weeks of study [25]. Two studies were open prospective, for 19 and 45 patients respectively. Pain control was good (NS less than 4.5/10 and mean NS 3.4/10 respectively). No relevant side effects were observed [26-27]. Retrospective studies exploring the use of methadone showed that 240 opioid-naive patients or unsuccessful with step 2 ladder, had received methadone for pain relief [28-30].

5. Can we initiate methadone for outpatients?

We found 7 studies supporting the ambulatory initiation, 3 prospective including 2 controlled studies, and 4 retrospective studies, for a total of 845 patients. Mercadante (1998) proposed a prospective randomized study of 40 patients: morphine or methadone as first line strong opioids for outpatients. Pain control and side effects were comparable. There was less dose escalation in the methadone group [23]. One year later, Mercadante (1999) tried to identify the factors that could influence the response to methadone. No confounding factors were identified. The authors describe safe and effective use of methadone with careful titration of 45 opioid-naive patients [27] 2016, Porta Sales publishes a single-center, open-label prospective study of 145 ambulatory patients (evaluation in consultation J7-14-28 and phone call J3-9-21). Pain control was described. Maximal pain intensity with Numeric Scale decreased from 9 to 6/10 [31]. De Conno (1996) proposed a retrospective, single-center study conducted in 196 outpatients. Fifty five percent of patients had improved pain relief. Few dropouts (6.6%) were due to methadone-related side effects (10 patients had drowsiness, 3 severe constipation) [28]. In 1999, Hagen published a retrospective analysis of 29 patients. Outpatient methadone rotation was a success for 18 patients. Only 2 patients had insufficient pain relief, 5 were limited by AEs, and 4 by cancer progression [32]. In 2010, Parson published a retrospective, single-center article on 189 patients receiving methadone: 100 (53%) initiations and 89 (47%) rotations. The success rates were 85/100 (84%) and 82/89 (92%) respectively [29]. Mercadantes (2013) retrospectively explored rotations for 201 outpatients. Fourteen had a rotation on methadone, 10 of which were considered successful [33].

6. Conclusion

Methadone could be considered earlier in the management of cancer pain. It has pharmacological advantages: its opioid, anti NMDA and SSRI activities are very useful for cancer pain; it has no active metabolite; and it may have anticancer activity. In addition its cost is low. It should be used with caution, especially because of interactions. Each methadone initiation should be screened and followed. Several studies highlight the safety and non-inferiority of first line methadone compared to other opioids. Initiation can be implemented safely at home. This treatment could be very useful for developing countries. Nevertheless, long term studies are lacking to recommend methadone as a first line treatment.

Conflict of Interest

The authors declare that they have no conflict of interest.

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