Patient-controlled analgesia with oral methadone in cancer pain: Preliminary report

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Summary

Background: Methadone is a very useful drug in cancer pain because of its low cost, lack of active metabolites, high oral availability, and the rapid onset of its analgesic effect. It seems to be well tolerated in patients with difficult pain syndromes who are receiving high doses of opioids, and it may deter the development of tolerance, but a high individual variation in terminal elimination half-life can result in different rates and extents of drug accumulation. For this reason, oral patient-controlled analgesia with methadone was used in 24 advanced-disease patients with pain.

Patients and methods: A regimen of self-administered oral methadone at fixed doses and flexible patient-controlled dosage intervals to achieve adequate analgesia, while avoiding toxic effects of methadone accumulation, was used in 24 patients requiring opioid therapy. After a priming period of three days with fixed doses of 3–5 mg three times a day for naïve patients and 50% of the morphine equivalent of methadone in patients switched from morphine, patients and relatives were instructed to maintain the night-time dose and to administer a second dose when the pain recurred. When more than four doses of methadone a day were used, an increase of the dosage was prescribed. Continuous pain assessment and monitoring of symptoms were offered.

Results: The majority of patients achieved good pain relief until death, and three were switched to very low doses of subcutaneous morphine in their final days. The methadone escalation index was about 2% a day, with a mean dosage increase of 0.3 mg a day for an average of 60 days of treatment at doses ranging from 9 to 80 mg. The plasma concentration in 14 patients ranged from 0.013 to 0.273 mcg/ml with doses of 20–80 mg during chronic treatment. A mean of 2.4 doses a day was reported, including the fixed night-time dose. The extent of side effects was considered acceptable.

Conclusion: Patient-administered analgesia with oral methadone appears to be a simple, cheap and relatively safe technique for controlling cancer pain, permitting individualization by the patient him- or herself and avoiding the risk of accumulation. Continuous assessment is necessary.

Key words: cancer pain, methadone, patient-controlled analgesia

Introduction

Cancer pain can be adequately controlled with orally-administered opioids in most of the patients most of the time. Oral analgesics are usually provided around the clock, with rescue doses for breakthrough pain [1]. There may be significant side effects of morphine-resistant pain syndromes before an acceptable analgesia is achieved. Asymmetrical patterns of cross-tolerance of opioid agonists have been demonstrated [2–4]. A shift from one opioid to another is recommended when the side effect-analgesic equation is skewed towards the side effect component [5]. Methadone seems to be well tolerated in patients with difficult pain syndromes who are receiving high doses of opioids, and it could be effective as one of a possible sequence of opioids used to restrict the development of tolerance. Methadone has been shown to have several advantages over other opioids [2]: it has high oral bioavailability, a rapid onset and a peak analgesic effect, and a long duration of activity due to its low hepatic clearance, which allows for longer intervals between doses. Moreover, methadone costs very little and has no known active metabolite [6]. Attempts to develop guidelines for its use, however, have been hampered in part by a lack of information about pharmacokinetic-pharmacodynamic relationships. Repeated doses of methadone at fixed intervals may lead to its accumulation and attendant toxic effects [7], but the possibility of the inappropriate use of methadone without adequate clinical supervision should not be an argument against its administration [8]. Severe sedation, respiratory depression and non-cardiogenic pulmonary edema have been reported even after several days of treatment with a low equi-analgesic dose of oral methadone [9]. Substantial inter-individual variation in the relationship between changes in plasma methadone concentration and analgesia has been reported in patients with chronic pain receiving methadone [10]. Information about inter-patient variation in pain perception has led to the concept of an individualization of methadone-dosing in the management of cancer pain. Therefore, high individual variation in bioavailability and the long duration of its activity require highly personalized treatments [11].
In recent years the safety and efficacy of patient-controlled analgesia (PCA) have been recognized. Its advantages over those of conventional administration include the superior pain relief it affords, patient satisfaction, and decreased sedation and anxiety. Subcutaneous and intravenous routes of administration are most commonly employed in patients receiving opioids by PCA. The greatest breakthrough in PCA technology has come with the introduction of devices which render it possible to choose an intermittent bolus, continuous infusion, or both [12]. We treated cancer patients in pain severe enough to require opioids at home with a regimen of self-administered oral methadone, with a fixed bed time dose and flexible patient-controlled dosage intervals in an attempt to achieve adequate analgesia while avoiding the risk of toxic effects of the accumulation of methadone.

**Patients and methods**

Twenty-four patients requiring opioid therapy who had no cognitive problems were included in the study. Some of the patients were naive, while others had been switched from morphine to methadone because they had developed intolerable side effects. Initial doses were chosen according to the previous treatment. Naive patients were given 3 to 5 mg doses three times a day in accord with age, weight and level of pain. Patients on morphine were started with 50% per day of the methadone equivalent of morphine divided into three fixed doses, and was adjusted in the first three days by frequent phone contact or home visit. After achieving a dose of methadone capable of maintaining acceptable pain relief for more than 6–8 hours, the patient and his or her relatives were instructed on the management of pain with rescue doses taken as needed plus a fixed dose at bed time. During the course of the treatment, when more than four administrations of methadone a day were self-administered, including the night-time dose, an increase of the dose was prescribed. The relatives were asked to alert the physician to reassess the clinical situation in instances of excessive drowsiness. All of the patients were examined and treated at the outpatient pain clinic of Bucheri La Ferla Hospital or at home, and followed until death with two or three medical examinations a week and frequent phone contact, by a team of doctors and nurses experienced in palliative care. Evaluation was generally in the afternoon hours.

Symptoms such as nausea and vomiting, drowsiness, confusion, dry mouth and sweating, commonly associated with opioid therapy or present in advanced-cancer patients, were recorded on a scale of 0 to 3 (none, slight, considerable, extreme). Symptoms having a median value of all observations (2–3 a week) of more than 1 were considered. The starting (MSD) and maximum doses of methadone (MMD), the days of methadone treatment and the mean number of doses per day ingested by the patient, the mean pain intensity according to the patient's own assessment (when possible) or a doctor-rated VAS on a 0–10-cm scale, were recorded.

Methadone escalation index percent (MEI%) and methadone escalation index in mg (MEImg) were calculated by the following formula: MEI% = [(MMD-MSD)/MSD] × days × 100; MEImg = (MMD-MSD)/days. Blood samples for methadone analysis were drawn from 14 patients during the treatment (the first 6 hours after the last methadone administration). After centrifugation the plasma was separated and stored frozen at −20 °C until analysis determined by gas chromatography combined with mass spectrometry after a liquid separation procedure [13].

The pain syndromes were assessed according to previous studies on the basis of clinical history, the anatomical site of the primary tumor and distant metastases, physical examination, investigations such as CT-scan, echography, etc., when available [14–16].

**Results**

Data on the patients, including starting, maximum and mean daily doses, total number of treatment days, the symptoms or side effects associated with methadone therapy, the pain mechanisms and the mean VAS are shown in Table 1. All of the patients were opioid-naïve except for five who were switched from morphone because of intolerable drowsiness and confusion.

The median MEI were 1.05% and 0.2 mg per day, respectively. Plasma concentrations in 14 patients for whom blood samples were available during the chronic treatment (at least 1 week after starting methadone) ranged from 0.013 to 0.273 mcg/ml (mean 0.107 mcg/ml) with dosages of 20–80 mg daily. The highest methadone concentration (0.273 mcg/ml) was observed in a patient taking 40 mg daily, but at a dosage of 80 mg lower plasma concentrations were also seen (0.207 mcg/ml), i.e., there was no apparent correlation between daily dose and plasma concentration. Twenty-one patients continued the oral treatment with methadone until death, while three were switched from their last methadone doses, 30, 25 and 15 mg daily, to subcutaneous morphine (less than 10 mg daily) in their final one or two days when they became unable to swallow or were unconscious. Elderly patients (over 70 years) received doses ranging from 11 mg (9–15) at the beginning of treatment to a maximum of 21 mg (14–30). Only one aged patient on a relatively high dosage of methadone presented frequent episodes of confusion which was difficult to manage, and the relief, at a mean VAS of 4.5 (pt no. 24), was considered inadequate.

The most common side effects were constipation (n = 12) and dry mouth (n = 8). About 20% of the patients reported drowsiness (n = 5), sweating (n = 4) and nausea and vomiting (n = 4). One patient with a chronic subobstruction was successfully treated while remaining on the same dosage of methadone over a long period (no. 7). The patients who were switched from morphine achieved adequate pain relief, with different requirements for methadone dosage and different MEI. The starting dose and the maximum dose were 33 mg (15–60) and 56.8 (24–80), respectively. This MEI% was the same as the mean global MEI% (1.88%, range 0–4.44).

**Discussion**

The objective of the regular administration of opioids is to forestall the recurrence of pain. A number of clinical situations, including the presence of incident pain or pain due to activity, neuropathic pain, a genetic difference in opioid receptors, a circadian variation of pain intensity, a small therapeutic window, renal failure, and excessive concern about the toxicity of opioids [17–19] comprise potential hindrances to regular administration. An optimum technique would be one that would
make it possible for patients to be given a dose that would rapidly produce analgesia of several hours’ duration without excessive peaks in the blood concentration, to avoid too-frequent dosing. There have been only a few studies of the PCA technique in cancer pain [17]. Oral PCA may be a simpler method than subcutaneous or intravenous PCA, which is costly and accompanied by technical problems which tend to complicate the approach to cancer patients, especially those followed at home.

In a previous study using fixed doses with the time interval increased during the initial days of treatment, the daily dose decreased from 30–80 mg to 10–40 mg, with individual doses being between 10 and 15 mg after one week of this regimen [20]. Most of the patients reported adequate pain relief and elected to continue the methadone therapy with fixed time intervals set on the basis of the previous patient's requirements. Considerable variation was seen in plasma concentrations (0.074–0.54 mcg/ml), which reached a plateau after 2–3 days regardless of the dose, and this study yielded similar findings. Low methadone plasma concentrations were found during this regimen, uncorrelated to the dosage used, in patients taking 20–80 mg of methadone daily.

No significant differences were reported between methadone and morphine in the duration of analgesia when administered intravenously by PCA to hospitalized patients with severe pain, despite the difference between their serum half-lives [21]. However, the methadone group had more severe pain, and more appropriate dosing would have provided more prolonged analgesia. According to the concept of the minimum effective concentration, when the methadone doses are relatively low, the duration of activity depends on distribution and not on elimination [22]. The patients in this study achieved adequate pain relief for 6–8 hours.

### Table 1. Data regarding the patients treated with oral methadone by patient-controlled analgesia.

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Mean 59.5 | Median 61.5 | Range 45–79

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| Sex | age   | primary tumor (F - farynx, C - colon, S - stomach, B - breast, U - uterus, O - ovary, P - pancreas, Bl - bladder, M - mesothelioma, P - prostate); starting (Start) dose (mg); maximum (Max) dose (mg); days of treatment; mean number of daily administration; mean VAS.
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* Switched from morphine.
with adjustment of the dose during the priming phase before the start of self-administration. When more than four self-administrations a day were necessary, the dosage was increased in order to maintain an appropriate analgesic concentration and a prolonged duration of analgesia. The major drawback of PCA analgesia—the waiting period before pain control is achieved—can be overcome by using fixed doses for priming. It was recommended that methadone be administered frequently during the first three days of treatment [23], as about 48 hours may be required to approach steady-state blood levels [10]. After achieving an adequate level of analgesia, the large initial volume of distribution and long elimination half-life of methadone greatly reduced the need to increase the doses of methadone required to maintain analgesia, expressed by the low values of escalation indexes and the low number of daily doses observed in this study. Over 14 days of treatment a 63% increase in the dose of morphine was reported, while the same dose of methadone was maintained throughout the entire period of study [24]. Although it would be incorrect to conclude that no tolerance to methadone develops, an 'artificial' reduction of tolerance during a treatment with methadone may be assumed. NMDA receptor antagonists would be expected to inhibit opioid tolerance and methadone has been shown to exert some NMDA-antagonist effect [25], which could explain the low doses of methadone required in cancer pain, aside from its well known pharmacokinetic characteristics.

This situation resembles that of a semi-closed system used to deliver inhalation anesthesia. The obligatory night-time dose is an example of 'filling the system'. Thus, the regimen proposed may be considered as equivalent to an intermittent bolus plus continuous infusion. Moreover, it is useful to cover the false episodes of breakthrough pain attributable to frequent decreases of basal analgesia observed with opioids with a short half-life [1, 26].

Higher doses are generally reported before a switch-over is considered. Different environmental and socio-cultural conditions, including early exposure to opioids, have been reported to be the principal causes of these differences [27].

The pattern of methadone side effects appears similar to the one observed for morphine although the occurrence of sweating observed in this study appears to be more specifically associated with the use of methadone. The steady-state plasma methadone concentration required to produce 50% of the maximum pain relief after an intravenous dose of 10 to 30 mg varied from 0.04 to 1.13 mcg/ml (mean 0.29 mcg/ml) in a single-dose study [10]. However, the results are not comparable because of differences in approach in these studies.

The major disadvantages of a PCA regimen with methadone include the risk of an accidental or intentional overdose, but this is a problem with other opioids as well. Another contraindication is the development of cognitive failure. One patient, considered unresponsive to the methadone treatment, had repeated episodes of confusion associated with the highest value of MEI found (13.2%). This approach will probably not be indicated in patients with a history of severe alcoholism or drug addiction, although long-acting methadone may provide an effective analgesia with a lower risk of overuse than the short-acting drugs, such as morphine and hydromorphone [28]. Appropriate supervision is required because of its long and unpredictable half-life and relatively unknown equivalent analgesic dose in comparison to other opioids.

Oral PCA with methadone is a simple, safe and inexpensive method for treating home-care cancer patients. However, the findings of this study should be considered preliminary since equianalgesic dose, ideal dose interval, pain relief and side effects, safety and efficacy of oral PCA with methadone in cancer pain have still to be addressed in controlled double-blind studies.

References


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