Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer

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Abstract  Background: Cancer pain is still inadequately treated in up to 60\% of cancer patients. Based on the additional effect on the N-Methyl-D-Aspartate receptor, we expected that methadone (Met) could provide better pain relief than fentanyl (Fen) in cancer pain with a neuropathic pain component.

Methods: A randomised controlled trial was performed with 52 strong opioids naive patients with head-and-neck cancer with substantial pain (pain Numerical Rating Scale [NRS] $>4$) and a neuropathic pain component (Douleur Neuropathique [DN4] $>4$). Twenty-six patients were treated with Met and 26 with Fen. Patients were evaluated at 1, 3 and 5 weeks. The primary outcomes were reduction in average pain, clinical success (defined as 50\% average pain decrease) and reduction in pain interference. Secondary outcomes were global perceived effect (GPE) and side-effects.

Findings: Reduction in NRS was higher with the use of Met at 1, 3 and 5 weeks (pain change 2.9, 3.1 and 3.1) compared to Fen (1.4, 1.7 and 2.0). This difference was significant at 1 (p = 0.011) and at 3 weeks (p = 0.03). Clinical success (>50\% improvement) was higher with Met at 1 week (15\% versus 50\%, p = 0.012). The change in pain interference, the GPE and side-effect profile were not significantly different between the groups.

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1. Introduction

Up to 60% of patients suffering cancer-related pain are inadequately treated for their pain [1,2]. This prevalence is high and contradicts the statement by Meuser et al [3] that cancer pain could be treated effectively (in 70–86% of patients), if the World Health Organisation (WHO) ladder is used. As numerous studies and meta-analyses up till now show no clear benefit in pain relief for one opioid over the other, there is no consensus on the choice of strong opioid to start with at step 3 of the WHO ladder [4–7]. In order to minimise side-effects and interactions, guidelines advise to prescribe an opioid one has clinical experience with. Other factors to keep in mind are ease of use and cost.

In current pain management, patients with cancer pain are treated with an opioid irrespective of the pain type (neuropathic, nociceptive or mixed). Methadone (Met) is an opioid which has, besides an opioid receptor–mediated effect, an additional effect on the N-Methyl-D-Aspartate (NMDA) receptor [8]. The NMDA receptor is known to be important in central sensitisation (CS) [9]. CS is a process reported to be fundamental in development and maintenance of neuropathic pain. Hence, a combined targeting of the NMDA receptor and the opioid receptors might result in better pain relief in neuropathic pain patients. Currently, limited evidence is reported on the effect of Met over other opioids in treatment of neuropathic pain in both cancer and non-cancer patients [10,11]. To further confirm this, randomised clinical studies are needed. A meta-analysis based on three studies on the effect of Met in neuropathic non-cancer pain was inconclusive as data could not be pooled due to methodological differences [12]. Furthermore, studies were performed with Met as a first-line strong opioid in cancer patients, comparing Met to other opioids but no significant difference in pain reduction or side-effects was noted [13,14]. The latter might be explained due to the fact that these studies did not differentiate between neuropathic, nociceptive or mixed pain types.

Given the dual mechanism of action of Met on both the NMDA receptor and on the opioid receptors, we hypothesise that Met is superior to fentanyl (Fen) in alleviating pain in cancer pain patients with a neuropathic pain component. In order to test this hypothesis, a randomised clinical trial was performed comparing the effect of Met to transdermal Fen in patients with head-and-neck cancer suffering from neuropathic pain.

2. Methods

2.1. Study design

This study is part of a prospective single-centre, open-label, randomised controlled trial (RCT) in which 52 patients were included with head-and-neck cancer pain with a neuropathic pain component and 82 cancer patients with nociceptive pain due to radiotherapy. To answer the research question if Met is superior in pain management for patient with cancer pain with a neuropathic component, data of the 52 neuropathic pain patients were used in the present analysis.

The RCT was approved by the local medical ethics committee of the Maastricht University Medical Center and was registered at clinicaltrials.gov (identifier NCT01317589).

2.2. Patients

Patients were included in the study from May 2011 to July 2015. Patients were recruited at the outpatient clinic of the head-and-neck department of the oncology centre of Academic Hospital Maastricht (MUMC+), a regional oncological centre. Patients with histological proven head-and-neck tumours with moderate to severe neuropathic pain (≥4 on the standard Numerical Rating Scale (NRS), range 0–10, related to tumour or therapy and Douleur Neuropathique [DN4] ≥ 4) were included in the study after screening for eligibility criteria: age >18; naïve to continuous strong opioids. Exclusion criteria were: illiteracy; surgery less than 7 d before the start of the study; pregnancy; contraindications for Fen or Met; myasthenia gravis; and asthma.

All patients gave written informed consent.

2.3. Randomisation and masking

After informed consent patients were randomly assigned to the Fen or Met group. The randomisation was stratified by surgery, chemotherapy, and radiotherapy using software for randomisation of clinical trials ALEA (version 2.2 CTCM/ALEA).

2.4. Procedures

2.4.1. Measurements

After informed consent, patients received a booklet with questions concerning demographics, pain, breakthrough...
medication use, opioid side-effects, the patients' perceived effect of the therapy, depression, anxiety and quality of life.

Pain was measured using the Brief Pain Inventory (BPI), which is a patient completed numeric rating scale that assesses the severity of pain and its impact on daily functioning via the seven-item pain Interference Scale (general activity, mood, walking, relationships, sleep, normal work and enjoyment of life) [15–17].

Daily breakthrough medication: Patients were asked to document their breakthrough medication needed once a day in a diary.

Opioid side-effects: Opioid side-effects (xerostomia, nausea, vomiting, constipation, somnolence and drowsiness) were scored on a four-point scale (1–4), where a score of 1 stands for 'not at all' and 4 stands for 'severe'. Patients were asked if they suffered from a dry mouth, if they felt sleepy or dull, if they felt dizzy or nauseated, and if they vomited, or were constipated. We dichotomised the data for severity. Scores 1 and 2 were referred to as minimal, and scores 3 or 4 were referred to as severe.

Global perceived effect (GPE): GPE reflects a patient’s belief about the efficacy of treatment [18]. GPE is a seven-point scale depicting a patient’s rating of overall improvement. Patients rate their change as ‘complete pain relief’, ‘much improved’, ‘slightly improved’, ‘no change’, ‘slightly worsened’, ‘much worsened’ or ‘worse than ever’.

Depression and anxiety (Hospital Anxiety and Depression Scale): The Dutch translation of the Hospital Anxiety and Depression Scale is validated to be used as a screening tool for depression and anxiety disorders [19,20].

Quality of life (EuroQol 5D): The EuroQol 5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health. It provides a simple descriptive profile and a single index value for health status [21].

The treating physician filled out the medical data form to obtain the following sets of measurements:

Neuropathic pain: Type of pain will be measured by the DN4 questionnaire. The DN4 is a validated questionnaire consisting of 10 yes or no questions. One point is given for each yes. A cutoff value of ≥4 is used to discriminate between patients with and without neuropathic pain. The Dutch translation of the DN4 has been validated [22]. The medical examination part of the DN4 was performed by the physician.

Medical data (medical chart): cancer type and location (lip, oral cavity, nasopharynx, hypopharynx, larynx, salivary glands, sinuses), date of diagnosis, treatment history (radiotherapy, current or more than 4 weeks ago/accelerated radiotherapy yes or no, bilateral radiotherapy yes or no, chemotherapy, current or more than 4 weeks ago), stage of disease (curative treatment, palliative treatment, palliative care), sort of pain (nociceptive, neuropathic, mixed), medication (including but not limited to neuropathic pain medication), possible opioid side-effect symptoms (xerostomia, nausea, vomiting, constipation, somnolence, drowsiness) and grade of mucositis (Common Toxicity Criteria).

2.4.2. Protocol

Follow-up duration was 5 weeks, and patients were seen four times after informed consent was obtained. At baseline, patients provided the demographic variables, the BPI, side-effect questionnaires, HADS, and QoL. Met 2.5 mg twice daily or Fen patch 12 μg/h was prescribed (or the double doses when patients already used weak opioids), as well as Fen nose spray 50 μg or Fen sublingual 100 μg as necessary up to six times per day for breakthrough pain. Due to delivery problems with the Met 2.5 mg tablets, the starting dose was altered to 2 mg twice daily later in the study.

Patients were allowed to take six breakthrough medications per 24 h. They were instructed to take a second dose of the breakthrough medication when no effect was present at 15 min after the first dose. The dose of the ROOs is independent of the basis opioid dose. We titrated the basis opioid on base of the patients story and breakthrough dose by increasing the daily dose with 50%. Because the lowest dose of the Fen patch is 12 μg/h, the dose could only be doubled. The breakthrough medication was titrated conform the instructions belonging to the individual preparations.

We reviewed the patients after 1 week. Met has a long and variable half-life and steady state is to be expected after 4–7 d, so we preferred not increasing the dose within a week. The patients received a 24/7 phone number to contact in case of trouble (side-effects/pain).

At 1, 3 and 5 weeks, patients filled in the BPI, side-effect questionnaires, and GPE. The opioid dose in both groups was decreased with 30% when possible or stopped if medication was at starting dose. Therapy discontinuation due to side-effects was assessed at every visit.

2.5. Outcomes

2.5.1. Primary outcomes

Primary outcome measures are the change in average pain, the proportions of patients reporting clinical success for average pain at 3 weeks defined as a reduction of 50% in average pain score [23], and the change in pain interference after 3 weeks.

2.5.2. Secondary outcomes

Secondary outcomes included the time to achieve significant pain relief and GPE. Furthermore, side-effects and therapy discontinuation due to side-effects, mean increase of opioid dose measured by the opioids escalation index (maximal dose-starting dose/startning dose)
and use of breakthrough medication were used as secondary end-points.

2.6. Statistical analysis

Baseline characteristics are reported as mean and standard deviation or absolute value and percentage. To compare the proportion of patients reporting clinical success at 3 weeks after randomisation between the Met and Fen groups, the Pearson's chi-squared statistic was used. The difference in change in pain interference was tested using the Student t test. In addition to univariable analyses of the primary outcomes, we performed multivariable analyses to correct for potential baseline differences despite randomisation and to increase precision in the estimation by using logistic and linear regression for the proportion of clinical success and change in pain interference, respectively. Missing data were imputed using multiple imputation, and data were analysed on an intention-to-treat basis (J.H., J.W.G., S.M.J.v.K., M.H.J.v.d.B.-v.E.).

2.6.1. Sample size calculation

A difference between the experimental and control means of 2 on the NRS score was considered clinically relevant. The estimated standard deviation of response on the NRS for pain was 3 (based on a pilot study, results not published). We aimed to include at least 48 experimental subjects and 48 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability of (power) 0.9. The type I error probability associated with this test of this null hypothesis was 0.05.

3. Results

3.1. Study population

A total of 52 patients were included in the study. Of the 52 patients, 14 were treated with curative intent (4× surgery, 10× radiotherapy) and had treatment-related neuropathic pain. Fourteen patients received palliative antitumour therapy, and 24 patients had far-advanced disease. The latter two groups had combined nociceptive-neuropathic pain. For these groups, it was not possible to differentiate between treatment-related or tumour-related pain. None of these patients had clinical important mucositis. Patients were treated with Fen (n = 26) or with Met (n = 26) (Fig. 1).

We observed a considerable response loss over the complete follow-up period, which was mostly due to intercurrent diseases and success of treatment (Fig. 1). Eight patients (15%) were lost to follow-up at 3 weeks and 18 patients (34%) at 5 weeks. In the Fen group, 18 patients started with 12 mcg/h patches, and eight started with 25 mcg/h patches. In the Met group, six patients started with a total of 4 mg per day, 16 patients started with 5 mg per day and four patients with 10 mg per day.

The baseline characteristics were balanced between the two groups (Table 1). Especially, the quality of life and the pain scores were equal in both groups. The use of prior opioid exposure, mostly codeine or tramadol, some used Fen spray or oxycodone for breakthrough pain without use of baseline opioids, was balanced as well (42.3% Fen versus 46.2% Met). There were slightly less males in the Fen group as compared to the Met group (62% Fen versus 73% Met).

3.2. Decrease in pain

At the primary end-point of 3 weeks, the average NRS decreased from 6.3 to 4.5 in the Fen group versus from 6.3 to 3.2 in the Met group (p = 0.042). The decrease in average NRS for all time points is shown in Table 2. Pain decrease occurred faster in the Met group (mean NRS = 3.4) than in the Fen group (mean NRS = 4.9) (p = 0.011) in the first week. Based on an average pain of 4.2 (standard error of the mean [SEM], 0.36) in the Fen group and 3.2 (SEM, 0.38) in the Met group, no significant difference (p = 0.11) is noted at week 5.

3.3. Clinical success

Clinical success, defined as a decrease of 50% in average NRS, was noted in 27% of the patients in the Fen group and in 44% in the Met group (p = 0.23) at 3 weeks (Fig. 2). A 50% decrease in average NRS was achieved faster with Met than with Fen. At 1 week, 50% of the patients in the Met group and 15% of the Fen group showed clinical success (p = 0.012). This initial difference between the groups after 1 week diminished over the following weeks, as no significant difference was noted between the Fen and Met groups at 3 and 5 weeks (49% Met versus 33 Fen p = 0.367).

3.4. Interference

The mean decrease in pain interference for patients treated with Fen at 3 weeks was 8.2 versus 15.7 for patients treated with Met (p = 0.29). The decrease in interference was consistent at all time points, and although not statistically significant, the decrease tended to be more prominent in the Met group (Table 2).

3.5. Multivariate analyses

The multivariate analyses did not alter the primary outcomes significantly. No outcomes reached or lost their statistical significance in the multivariate analyses. See Table 2 for adjusted p-values.
3.6. Global perceived effect

The GPE showed that in the Fen group, 27% of patients reported to experience ‘much improvement’ as compared to 56% of patients in the Met group at 3 weeks. Fig. 3 shows the proportion of patients that scored one of the seven items on the GPE scale at 1, 3 and 5 weeks. No statistical significant difference was noticed (p = 0.084, p = 0.428 and p = 0.151, respectively).

3.7. Side-effects

No serious side-effects were noticed in our study population, and deaths were related to normal disease progression. There was no drop out due to intolerable side-effects. There was no significant difference between the groups in percentage of patients with severe side-effects (i.e. score 3 or 4 on a four-point scale of one of the side-effects; dry mouth, sleepiness, dizziness, nausea, vomiting, constipation).
The most common side-effect was dry mouth, 46% of patients in the Fen group reported a dry mouth at 3 weeks and 35% in the Met group. Overall, about 70% of the patients complained about a severe dry mouth at any point in the study.

3.8. Opioid increase ratio

Patients in the Fen group experienced a slightly steeper, albeit not significant, increase in opioid dose over the weeks as compared to patients in the Met group (1.2 versus 1.3 at 1 week, 1.5 versus 1.8 at 3 weeks, and 1.6 versus 2.2 at 5 weeks). The amount of breakthrough medication did not differ between the groups (Figures not shown).

4. Discussion

This RCT is the first to demonstrate that the use of Met results in a better and faster pain relief in the treatment of oncological pain with a neuropathic component as compared with Fen.

The decrease in pain (NRS) in head-and-neck cancer patients with neuropathic pain receiving Met is...
significantly higher at 1 and 3 weeks as compared to Fen treated patients.

Ample preclinical evidence exists that the DNMDA receptor, a glutamate receptor abundantly present in the dorsal horn of the spinal cord, is essential for the development of CS and increased sensitivity in neuropathic pain [24]. Animal studies demonstrate an antihyperalgesic effect of NMDA-receptor blockers in models of inflammatory, neuropathic and ischaemic pain [25]. A systematic review of the use of the selective NMDA-antagonist ketamine for the treatment of intractable chronic pain in cancer (five RCTs, six observational studies and one case series) concluded that ketamine may be an option, although strong evidence was lacking [26]. Furthermore, results from a RCT by Salas et al [27] demonstrated the presence of responders and non-responders to ketamine.

Met is a strong opioid with significant non-competitive NMDA-receptor antagonist qualities [8,28]. It is thus likely that Met modulates the glutamate transmission at the (pain) gate in the spinal cord where nociceptive afferents pass their signal to the dorsal horn pain neurons via the AMPA and NMDA receptors. Hence, Met may not only modulate the opioid receptors known to be involved in neuropathic pain but may affect the increased synaptic plasticity of the NMDA receptor at the glutamatergic synapse or central nervous system during chronic neuropathic pain.

Many small studies and case reports describe the successful rotation from different strong opioids to Met [29–35]. A positive clinical response, better pain control and/or less side-effects is seen in more than 50% of patients after rotation to Met [36,37].

The effect of Met in cancer pain was evaluated in two systematic reviews. The 2007 Cochrane review concluded that the efficacy of Met is similar to morphine and this conclusion was based on nine RCTs [4]. It was then concluded that the efficacy of Met is similar to morphine although a differentiation between nociceptive and neuropathic pain was made in only one study [13]. When no difference between nociceptive and neuropathic pain was made, no difference in pain relief between morphine and Met could be observed. With respect to the latter, it is important to realise that the investigators did not test for differences in patients with neuropathic pain specifically, but only used a subpopulation with a neuropathic component [13].

In a recent systematic review, based on four RCTs published after the 2007 Cochrane review on the effect of Met in cancer pain management was evaluated [38]. Here, no difference in effectiveness between Met compared to other strong opioids was reported in two RCTs [14,39]. It should be noted that these RCTs did not differentiate between cancer patients with neuropathic pain or nociceptive pain. Two other RCTs used in this systematic review evaluated the effect of opioid rotation to Met: in one study, no conclusion on the efficacy of Met in treatment of cancer pain could be presented due to the number of dropouts [40], and the other reported a decrease in pain intensity switching from morphine to Met and a patient preference for Met [41].

No differences in side-effect profiles between Met and other strong opioids were reported [4]. It should be noted that a significant reduction in constipation and xerostomia in most patients was reported 7 d after rotating to Met. From a group of 13 patients rotated from Met to another strong opioid for the study, 12 had to be rotated back because of pain increase and dysphoric effects [42].

Patient selection is of utmost importance in choosing Met as first choice opioid in pain in patients with cancer. On theoretical basis (NMDA-receptor antagonism) is the superiority of Met over other strong opioids only to be expected in continuous and massive nociception.

The unique pharmacological properties make Met a difficult drug in inexperienced hands. There is a large interindividual variability in bioavailability (41–90%), possibly due to gene polymorphisms [43]. Furthermore, Met is known to have along and variable half-life (7–65 h) influenced by urine pH, high protein binding (85–90%) and a distribution volume of 3.6 l/kg [44]. The metabolism of Met by CYP 3A4 and 2B6 implies numerous drug–drug interactions and Met prolongs the QTc time with risk on torsades-de-points [45]. Therefore, the administration and management of Met should be done, preferably in a pain clinic, by experienced pain physicians.

Compared to other studies, we started with a relative low dose of Met which might decrease the risk of severe side-effects. Despite this relative low dose, we observed a good clinical outcome, with a very good patients’ GPE. We therefore advise, based on our results, to start with a low dose in opioid naïve patients and slowly increase the dose if and when necessary.

This study has some limitations. Although most participants were available for the analysis of short-term pain relief, we observed a significant loss to follow-up over the course of 5 weeks, which was in part due to treatment success. To compute unbiased estimates of treatment effects, to obtain the statistical precision that we needed to detect a clinically relevant difference and
to make the intention-to-treat sample available for analysis, we used multiple imputation. As compared to many other frequently used methods of handling missing data, multiple imputation yields correct standard errors and unbiased estimates when data are missing at random [46].

In contrast to the original power calculation, we were unable to include 48 patients in each group. As stated after 4 years, we only included 52 patients. There are different explanations for the relative low accrual: possibly, we overestimated the prevalence of neuropathic pain in patients with head-and-neck cancer, more patients than expected already received strong opioids (mostly via their GPs) and, possible most important, the travelling distant to the university hospital. Our institution is a referral centre for a large region. When patients become palliative, they most often prefer to be referred to a physician in their region.

The power calculation we performed for this study was based on very limited data. Earlier studies comparing Met to other opioids showed no significant differences. Furthermore, as far as we know no RCTs comparing Met to other opioids in neuropathic pain have been published. Therefore, it was impossible to precisely estimate the expected difference. Our power calculation was based on an estimated standard deviation of three which finally proved to be less than two in our study. Despite the fact that the present study is underpowered, we want to emphasise that our findings have significant clinical impact: a decrease in pain, during the first weeks of treatment is expected to result in a better quality of life for patients. In our opinion, the profit of at least 3 weeks better pain relief is important for oncological patients, especially in view of the fact that they have short life expectancy.

It is obvious that our findings need to be further studied in other cancer patients with neuropathic pain. It is not clear if the findings, now restricted to head-and-neck cancer patients with neuropathic pain can be generalised for all cancer patients suffering from neuropathic pain. From a conceptual point of view, as the NMDA receptor is involved in neuropathic pain, it might be expected that Met treatment will result in a better pain relief also in patients with different types of cancer with neuropathic pain.

The largest contribution of our RCT is that this study is the first to proof that the theoretical concept (and clinical experience) of involvement of the NMDA receptor specifically in neuropathic pain in patients with cancer holds through and should be targeted in treatment.

5. Conclusion

Met is significantly better than Fen in the treatment of neuropathic pain in patients with head-and-neck cancer in terms of pain relief and time to achieve pain relief in patients with cancer. In patients with oncological pain due to head-neck cancer with a neuropathic component, Met should be considered.

Contributors


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Conflict of interest statement

None declared.

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