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Original Research

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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Interpretation: This is the first study to compare the effects of Met to Fen in cancer patients with a neuropathic pain component. Based on the results of this study, Met should be considered in the treatment of oncological pain with a neuropathic component.

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 ($\geq$4 on the standard Numerical Rating Scale (NRS), range 0–10, related to tumour or therapy and Douleur Neuropathique [DN4] $\geq$ 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