CLINICS

RAPID COMMUNICATION

Methadone in post-herpetic neuralgia: A pilot proof-of-concept study

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OBJECTIVE: This research was designed as a pilot proof-of-concept study to evaluate the use of low-dose methadone in post-herpetic neuralgia patients who remained refractory after first and second line post-herpetic neuralgia treatments and had indications for adding an opioid agent to their current drug regimens.

METHODS: This cross-over study was double blind and placebo controlled. Ten opioid naïve post-herpetic neuralgia patients received either methadone (5 mg bid) or placebo for three weeks, followed by a 15-day washout period and a second three-week treatment with either methadone or placebo, accordingly. Clinical evaluations were performed four times (before and after each three-week treatment period). The evaluations included the visual analogue scale, verbal category scale, daily activities scale, McGill pain questionnaire, adverse events profile, and evoked pain assessment. All patients provided written informed consent before being included in the study. ClinicalTrials.gov: NCT01752699

RESULTS: Methadone, when compared to placebo, did not significantly affect the intensity of spontaneous pain, as measured by the visual analogue scale. The intensity of spontaneous pain was significantly decreased after the methadone treatment compared to placebo on the category verbal scale (50% improved after the methadone treatment, none after the placebo, $p = 0.031$). Evoked pain was reduced under methadone compared to placebo (50% improved after the methadone treatment, none after the placebo, $p = 0.031$). Allodynia reduction correlated with sleep improvement ($r = 0.67$, $p = 0.030$) during the methadone treatment. The side effects profile was similar between both treatments.

CONCLUSIONS: Methadone seems to be safe and efficacious in post-herpetic neuralgia. It should be tried as an adjunctive treatment for post-herpetic neuralgia in larger prospective studies.

KEYWORDS: Post-Herpetic Neuralgia; Methadone; Neuropathic Pain.

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INTRODUCTION

Methadone was first described over fifty years ago. It is a synthetic opioid agonist that exhibits a potent antagonist effect on glutamate N-methyl-D-aspartate (NMDA) receptors. Methadone is highly bound to proteins (alfa-1-acid-glycoprotein), highly lipophilic and metabolized by the liver (mainly by the cytochrome P450 CYP 3A3/4 isoenzyme); it has no known active metabolites. Methadone has a high intestinal absorption, and its bioavailability is approximately 80%, with much less inter-individual variability compared to other opioids, such as oral morphine. One unique feature of methadone is that is has a robust distribution phase with a short lasting (alpha) half-life of approximately 3 hours, followed by an extended elimination phase (beta) ranging from 12 to 60 hours; it also displays large inter-individual variability. This elimination phase may result in toxicity and drug accumulation. Most of the drug is excreted in feces with no significant accumulation in patients with renal impairment. Despite its long term use in drug addiction and in cancer pain patients, there is a great paucity of studies on methadone in neuropathic pain syndromes. Neuropathic pain is present in 7% of the general population (1) and may represent up to 60% of patients with cancer-related pain. Opioids are effective for neuropathic pain and are used as second and third line treatments in this population. However, most of the available evidence concerns the use of tramadol and extended release oxycodone. Other opioids, such as hydromorphone and methadone, were seldom evaluated for this pain syndrome. Methadone is an inexpensive and widely

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available drug in many countries, but it is also a potent NMDA inhibitor, which could potentially increase its analgesic effects in neuropathic pain patients. The aim of this pilot proof-of-principle study was to evaluate the use of low-dose methadone in refractory post-herpetic neuralgia (PHN) patients who remained refractory after undergoing first and second line treatments and had indications for adding an opioid to their current drug regimen. The main outcome measurement was pain intensity reduction, and the secondary outcomes were patient safety, changes in pain interference in daily life and the different effects of chronic pain.

METHODS

Patients

The aim of this pilot proof-of-concept study was to assess the safety and efficacy of methadone in PHN patients. Patients with chronic (>6 months) symptomatic PHN with visual analogical scale (VAS) scores >40/100 mm despite using first and second line treatment drugs (e.g., tricyclic antidepressants, venlafaxine and gabapentinoids) were recruited from the Pain Center of the Hospital das Clínicas, University of São Paulo, Brazil. All patients were opioid naïve. The PHN diagnosis was based on current diagnostic criteria (2) for defined neuropathic pain. Pain was located in the cervical, dorsal or trigeminal areas.

The study was approved by our local institutional review board and registered at ClinicalTrials.gov (0078/11 and NCT01752699, respectively). All patients provided written informed consent before being included in the study.

Study design

In this crossover, double-blind, randomized trial, all participants received either methadone 5 mg or placebo (bid) for three weeks, followed by a 3-week washout period and then another three-week treatment period with methadone and placebo, according to the randomized treatment sequence. The methadone and placebo pills looked identical.

Clinical assessment

All participants were evaluated before and after each treatment period, for a total of four assessments (two at baseline and two at the end of each three-week treatment period). All clinical assessments were similar and included the following details:

- spontaneous pain (SP) intensity using a VAS;
- evoked pain (EP), dynamic mechanical allodynia intensity in the painful area was used to study EP, and a gentle stroke with a standardized brush (Senselab Brush 05, Somedic AB, Hörby, Skane, Sweden) at a speed of 2 cm/s and covering a 6-cm distance inside the PHN painful area was used; EP was scored as none (=0), mild (=1), moderate (=2), or severe (=3) after three strokes;
- the Category Verbal Scale (CVS) was measured as mild, moderate, and severe pain intensity (3);
- the daily activities scale (AS) (items from the Brief Pain Questionnaire) was used to measure the impact of pain on different activities of daily living and was scored as normal (=0), decreased (=1), or abolished (=2) (4);
- the McGill Pain Questionnaire (MPQ) (5); and
- adverse events were assessed by direct questioning patients on the presence of new symptoms presenting during treatment.

Data analysis

Each participant's baseline characteristics were expressed as descriptive statistics with average ± standard deviation. A non-parametric test for repeated series (the Wilcoxon signed-rank test) was used because the data did not show normal distribution according to the Kolmogorov-Smirnov test. The proportion of responders *vs.* non-responders and the total number of participants with improved or aggravated symptoms (scores) under methadone compared to placebo were compared using Fisher's exact test. Correlation analyses were performed using Spearman's correlation coefficient. Sample size was calculated based on the data available on the effects of methadone in other neuropathic pain syndromes (6,7). Sample size estimation was calculated based on the information available from open-label studies that suggested a responder rate close to 50% under methadone (6,8-10) In all instances, the level of significance was set at $p<0.05$.

RESULTS

Patient characteristics

Ten patients (6 females, mean age 71±21 years) with neuropathic pain secondary to PHN (mean duration of pain

Table 1 - Pain score and questionnaire comparisons between methadone and placebo.

	Response to methadone (n)	Response to placebo (n)	Response to placebo and to methadone	(*p*-value)
Improvement in the Verbal Scale	5	0	5	0.031*
Reduction in the Visual Analogue Scale	5	3	2	0.363
Improvement in Evoked Pain	5	0	5	0.031*
MPQ subscores				
Sensitive	7	3	0	0.172
Affective	3	4	3	0.773
Evaluative	2	4	4	0.890
Miscellaneous	2	6	2	0.964

Total number of responders in each treatment arm (methadone and placebo). The results are expressed as the total number of responders. Improvement in the verbal scale pain score from baseline; VAS, visual analogue scale, ≥30% reduction from baseline; Evoked pain improvement, pain intensity reduction (≥30%) from baseline.
McGill Pain Questionnaire (MPQ), subscores of the different aspects of pain (sensitive, evaluative, affective and miscellany), ≥3 decreases in each domain from baseline. *$p<0.05$.

41 ± 19 months) were included in the study and completed the two treatment phases. They experienced pain in the following dermatomes/areas: cervical n = 3, dorsal n = 4, and trigeminal n = 3.

The treatment had the following effects on the patients' pain and general activity levels.

Methadone did not significantly affect the intensity of spontaneous pain, as measured by the VAS compared to placebo.

The intensity of spontaneous pain was significantly decreased after the methadone treatment compared to placebo on the CVS (50% improved after methadone, none after placebo, $p = 0.031$). EP was reduced with methadone compared to placebo (50% improved after methadone, none after placebo, $p = 0.031$) (Table 1).

The activities of daily living and McGill Pain Questionnaire scores did not significantly change after the active treatment. In particular, methadone did not have any negative impact on daily activities, such as concentration, mood or sleep.

Correlation analyses

Allodynia reduction correlated with sleep improvement ($r = 0.67$, $p = 0.030$) during the methadone treatment. Older age was associated with greater impacts on concentration ($r = -0.69$, $p = 0.024$) and daily activities ($r = 0.69$, $p = 0.025$).

Side effects

The frequency of reported adverse events, such as constipation, nausea and dizziness, did not differ significantly in either treatment period. None of the participants left the study.

DISCUSSION

We have demonstrated that at low doses, methadone decreased the pain intensity scores and evoked pain levels in PHN patients and had a satisfactory safety profile. This controlled study is one of the few to study methadone's effect on neuropathic pain and the only one to evaluate a specific patient group, such as PHN patients.

There is a great paucity of randomized controlled studies of methadone in chronic pain. Note, there are no placebo-controlled studies on the use of this drug in cancer patients, which is understandable because of ethical issues. Case series have suggested that methadone could be used long term in neuropathic pain patients (11,12). Until now, only one placebo controlled study evaluated its efficacy in a small sample of heterogeneous neuropathic pain syndromes (13). In this study, methadone was used in a rather peculiar regimen, taken on alternate days at 10 and 20 mg/day doses. It was found that methadone at 20 mg/day had a significant effect over placebo in each 20-day trial duration (7). An open-label study evaluated the analgesic effect of methadone against morphine in cancer pain patients. The analgesic effects were similar, but methadone was associated with less frequent dry mouth and more frequent headaches, and while the morphine dose had to be significantly titrated during the 14-day trial, the methadone dose remained the same (14). Similar results were reported (15) in a parallel trial comparing methadone and morphine in cancer pain patients. In a more recent study (16), the authors suggested that methadone would be as effective as morphine in cancer pain patients with or without neuropathic pain. However, the external validity of this study remained limited because of the extremely high drop-out rate observed, which was most likely caused by the high dose conversion ratio from morphine to methadone (2:1) and the fixed dose regimen chosen, which would force patients in the methadone group to receive relatively more drug than the morphine arm, with no possibility to decrease it without leaving the study.

The latest study (17) included cancer pain patients in an open-label parallel design trial to receive either methadone, sustained release morphine or transdermal fentanyl. The authors found no difference in pain relief or in the negative impacts of quality of life or adverse events. However, methadone was associated with a substantially lower treatment cost than the other treatments.

Excitatory amino acids have been implicated in the occurrence of neuropathic pain, specifically through NMDA receptors, which have been implicated in the occurrence of opioid tolerance and are considered to play a major role in the central sensitization seen in neuropathic pain patients. Because methadone is a potent opioid agonist and an NMDA antagonist, it has been suggested that it would have efficacy in neuropathic pain. Methadone has been shown to attenuate mechanical and cold allodynia in experimental models of both peripheral and central neuropathic pain (18), exhibiting anti-allodynic affects superior to oxycodone and morphine (19). It has also been shown that the blockade of NMDA receptors plays an important role in the analgesic effects observed in experimental models of peripheral neuropathic pain (20), which may also be related to its norepinephrine and serotonin reuptake blocker properties (21). The preferential effect of methadone in dynamic mechanical allodynia found in the present study and its correlation with sleep improvement is an original finding and confirms the findings from experimental studies. Larger controlled trials of the use of methadone in neuropathic pain must be performed because it is an inexpensive opioid that has pharmacological particularities, such as long half-life and NMDA antagonism that make it an attractive option to opioids currently available for this pain syndrome. Placebo use in pain patients frequently raises ethical concerns. Despite the possible analgesic effect of methadone to treat PHN a priori, it is not currently approved as a treatment option for neuropathic pain, and it is not widely available in Europe or in many Latin American countries for this indication mainly because of the lack of clinical evidence attesting to its efficacy, such as this brief pilot study. Methadone and placebo were added to the current analgesic regimen of patients who were already receiving the best pharmacological treatment available at our institution at the time of the study. Thus, a more effective neuropathic pain treatment was not withheld because of participating in this study protocol; both methadone and placebo were used as an ''add-on'' treatment. As part of our current ethical recommendations, all patients who improved while taking methadone were offered the medication on a long-term treatment basis after the study ended.

AUTHOR CONTRIBUTIONS

All authors read and approved the final version of the manuscript. Andrade DC and Teixeira MJ were responsible for the study design. Galhardoni R, Moscoso ASC, and Puerta MYT were responsible for the data collection; Tengan S and Osaka M were responsible for the data bank feeding. Andrade DC was responsible for the statistical analyses. Osaka M, Puerta

MYT, ASC, and Andrade DC were responsible for the manuscript writing. Teixeira MJ, Yeng LT and Andrade DC were responsible for the manuscript revising.

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