Use of Methadone as First Line Strong Opioid for Moderate-Severe Pain

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The present study evaluates the use of methadone in patients with advanced cancer and moderately-severe pain under palliative care at home over a period of 5 years, from 1996 to 2000. We calculated the index for methadone dosage increase (as a percentage and value in milligrams). Of the 1,079 patients cared for, 247 (22.89%) received methadone treatment: 126 from the very beginning, average dose of 15 mg / day (5- 50), and in 121 patients treatment with methadone was initiated at a later moment during the period they were cared for (5- 40). The median period of time of methadone administration was 27 days (1-416), the median dose of methadone at the moment of treatment discontinuation being 20 mg (5-60). The main reason for methadone treatment discontinuation was impossibility of oral administration (49.8% in terminal stages, 7.3% presenting nausea, vomiting), and 62.3% showed no side effects. Dosage increase index was 0.33 mg, 2.33% respectively. Methadone has been used mainly as a potent first line opioid, and has been shown to be effective and safe.

Keywords: methadone, pain, opioid, palliative care

Pain is defined by the International Association for the Study of Pain (IASP) as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*. It is one of the most common and debilitating symptoms experienced by patients with advanced cancer, with a prevalence of 80% [1]. According to World Health Organization guidelines, opioid analgesics are the mainstay of the treatment of pain associated with cancer [2].

In a global survey conducted by Dickerson in 1999, 38 palliative care specialists from 17 countries on 5 continents were asked to name 20 essential drugs in palliative care: methadone was ranked second after morphine as the opioid of choice for chronic pain in cancer [3, 4].

Methadone is a pure antagonist of μ opioid receptors and is a potent antagonist of NMDA receptors, its affinity for these receptors being nearly as high as that of ketamine [5, 6]. Antagonizing NMDA receptors, methadone may prevent the development of tolerance to opioids and withdrawal syndrome [7-9] and can play an important role in patients experiencing neuropathic type pain [1, 4, 6, 7, 10, 11].

Methadone inhibits the reuptake of norepinephrine and serotonin, two neurotransmitters [12] with an important role in pain transmission, with an effect similar to tricyclic antidepressants, and also acts as an α receptor agonist [13]. It is a basic substance, lipophilic, which makes it possible to obtain central analgesia with a relatively low incidence of peripheral side effects and considerable tissue distribution. The existence of a peripheral reservoir allows maintaining plasma concentration during chronic treatment.

Methadone is almost exclusively metabolized in the liver by CYP450 enzymes group type I. Methadone has no active metabolites. The main enzyme responsible for N-demethylation of methadone is CYP3A4, with the lesser involvement of CYP1A2 and CYP2D6; CYP2B6 may play a part in metabolism as well. Changes in the levels and expression of CYP2D6 and CYP3A4 correlate with large individual variations associated with the pharmacokinetics of methadone [14]. Inducers, inhibitors or substrates of the CYP450 enzyme system may affect the metabolism of methadone.

Most of methadone is excreted through faeces and only a small part through urine. Methadone does not accumulate in renal failure and is not filtered significantly during haemodialysis. Unlike morphine, there is no need to adjust the dose of methadone in patients with impaired renal function.

Methadone has several potential advantages over opioids in terms of side effects. Due to the double effect on opioid and NMDA receptors, methadone can cause tolerance less frequently compared to other opioids. Another possible benefit is that the phenomenon of constipation occurs much more rarely in patients treated with methadone compared to patients treated with other opioid agonists [1, 4, 6, 15-17]. Also, due to the low incidence of xerostomia [18], methadone is the option of choice in patients with moderately-severe pain and cancer of the head and neck with important xerostomia secondary to local radiotherapy. Methadone causes less sedation than morphine [19]. Methadone has been associated with QT prolongation and occurrence of severe ventricular arrhythmias (torsades de pointes). In the patient information leaflet the manufacturer stresses that this adverse effect is more commonly associated (but not limited) to high doses of methadone (>200 mg/day) [20].

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Experimental part

Material and method

This retrospective study aims to explore the way in which methadone was used between 1996-2000 at Casa Sperantei Hospice (CSH), an organization that serves as a pioneer and model for the development of palliative care in Romania. Given the unique qualities of methadone, its many advantages, the experience of CSH in the use of this medicine in a period when methadone was the only step III opioid available in Romania as a substance for oral administration, the present study aims to answer the question: *Is methadone effective and safe as a first-line opioid in the management of moderate/severe pain in patients cared for at home?*

Observation sheets of all patients cared for at CSH over a period of 5 years (1996-2000), years when methadone was the only available oral opioid, were reviewed and demographic and clinical data were retrospectively collected: sex, age, area of residence, diagnosis, number of days of care, longitudinal presence and type of step I, II, or III analgesic drugs over the course of care. Also, for patients under treatment with methadone, detailed data were collected relating to the episode: presence of pain (location, intensity, quality), daily methadone dose and dose / dose at initiation and at the time of discontinuation of methadone treatment, increase rate of dosage, the time period in which methadone was administered, the reason for discontinuation, or adverse reactions encountered. The dosage increase index was calculated, as a percentage and in mg based on the following formulas: increase index (mg): (MMD-MSD)/number of days of treatment and increase index percentage (MMD-MSD)/MSD/number of days of treatment x 100. (MMD = maximum methadone dose, MSD = starting methadone dose). Data analysis was done using SPSS 12.0.

Results and discussions

1,079 patients were cared for at CSH between 1996 and 2000. Of the 1,079 patients, 350 (32.4%) received step I painkiller treatment during the course of the disease (29.6% with NSAIDs), 582 (53.9%) received step II painkiller treatment (coproxamol 20.1%), 641 (59.4%) received step III painkiller treatment (morphine injection 22.7%, followed by methadone 10.7%), and 87 patients (8.06%) received no analgesic treatment at all.

88.78% of all patients required opioid painkiller treatment at some point during care, a percentage that corresponds to literature data [1].

582 patients received minor opioid treatment; of these 134 (23%) received a sequence of 2, 3 or even 4 minor opioids over time and 32 patients (5.5%) received two minor opioids concomitantly. These data reflect the reluctance of patients, and possibly of medical professionals, to make the transition to a major opioid.

59.4% of patients received step III opioids; 40.77% received just one major opioid during care and only 18.62% received a succession of 2, 3 or 4 major opioids, a much lower percentage compared to that expressed by Ripamonti et al [21]. Ripamonti et al point out that about 80% of patients require opioid change once or several times during the course of the disease. The low value of this percentage reflects the lack of opioid diversity on the Romanian market during those years and the possible lack of knowledge in relation to major opioids, rates of equianalgesia, or side effects.

Of the 247 patients methadone treated, 124 were men (50.2%), and 209 patients (84.6%) lived in urban areas. The most common locations for which methadone was used were: first place - breast cancer (17.8%), second place - colorectal cancer (16.6%), third place - lung cancer (14.98%) and places four and five - cancer of the head and neck (8.91%) and metastases with undefined starting point (6.07%).

Three-quarters of patients under methadone treatment showed no significant comorbidities; only 2 patients presented renal failure and 24 patients had heart disease (painful or painless ischemic heart disease, valvular heart disease, etc.).

No patient in whom the protocol was initiated at CSH provided any evidence of a normal / abnormal electrocardiogram in the observation sheet (EKG result or specification in the observation sheet).

Methadone has been used as a potent first choice opioid in 91.39% of cases. Prior to methadone treatment 14.05% had never received opioid treatment, 79.33% had received minor opioid treatment and only 6.61% transitioned from another major opioid to methadone (table 1).

126 of the patients were undergoing methadone treatment at first record with a mean dose of 15.5 mg/day (minimum 5 mg, maximum 50 mg). In the 121 patients in whom methadone treatment was initiated at CSH the median dose of methadone was 10 mg (minimum 5 mg, up to 40 mg), and most commonly the daily dose was administered 12 h apart (43.8%) or 8 h apart (39.67%). There are studies in the medical literature that compare morphine and methadone as a first line treatment for pain associated with cancer [10, 18, 22].

Ripamonti et al [23] recommended, based on their clinical experience, administration of 3 mg every 8 h. Parsons et al [13] used methadone as a first-line treatment in 89 outpatients (5 mg every 12 h, with additional methadone prescription when required) and had an overall success rate of 92%.

The methadone patient instruction leaflet [20, 24] states, as instructions for administration in opioid-naive patients: *The usual starting dose is 2.5 - 10 mg every 8-12 h with slow titration until achievement of the effect. At first more frequent administration of methadone may be required to maintain analgesia; extreme care is mandatory to avoid overdose, considering the long half-life of methadone.*

In the case of the patients studied, only 14.05% received treatment initially every 6 h as required by CSH protocol. There is no correlation between the dose of methadone at initiation of treatment and age or diagnosis. But there is a negative association between initial dose of methadone and area of residence, with high statistical significance ($p = 0.01$, table 2).

Pain intensity		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	absent	5	2.0	2.0	2.0
	mild	3	1.2	1.2	3.2
	moderate	129	52.2	52.2	55.5
	severe	87	35.2	35.2	90.7
	DK/NA	23	9.3	9.3	100.0
	Total	247	100.0	100.0	

Table 1
PAIN INTENSITY IN PATIENTS RECEIVING METHADONE (AT FIRST RECORD WITHIN THE HOSPICE OR AT METHADONE TREATMENT INITIATION)

Correlations: area of residence – total daily methadone dose		area of residence	total daily methadone dose at initiation at CSH
area of residence	Pearson Correlation	1	-.257**
	Sig. (2-tailed)		.004
	N	247	121
total daily methadone dose at initiation at CSH	Pearson Correlation	-.257**	1
	Sig. (2-tailed)	.004	
	N	121	121

Table 2
CORRELATIONS BETWEEN TOTAL DAILY METHADONE DOSE AT INITIATION AND AREA OF RESIDENCE

*** Correlation is significant at the 0.01 level (2-tailed)*

Correlations: final daily dose of methadone – reason for treatment discontinuation		final daily dose of methadone	reason for treatment discontinuation
final daily dose of methadone	Pearson Correlation	1	.263**
	Sig. (2-tailed)		.000
	N	247	247
reason for treatment discontinuation	Pearson Correlation	.263**	1
	Sig. (2-tailed)	.000	
	N	247	247

Table 3
CORRELATIONS BETWEEN FINAL DAILY DOSE OF METHADONE AND REASON FOR TREATMENT DISCONTINUATION

*** Correlation is significant at the 0.01 level (2-tailed)*

Low doses of methadone given when initiating therapy in patients from rural areas are explained by the fact that patients were predominantly opioid-naive and none of these patients had previously received any step III opioid, unlike those from urban areas in whom methadone was used in the rotation of opioids as well.

The 2% per day dosage increase index (about 0.3 mg / day) for the 247 patients reflects the safety and efficacy of methadone, and is similar to that reported in the literature by Mercadante et al [25]. The period of methadone administration ranged widely, with a median of 27 days (minimum 1 day, maximum 416 days). The main reasons for discontinuation of methadone therapy were terminal condition (49.8%) and uncontrolled pain (14.6%). Similar percentages were recorded for noncompliance to treatment (6.9%) and lack of drug availability (6.1%), while the presence of intolerable side effects represented the reason for discontinuation of treatment in only 5.3% cases.

There is a positive correlation between the final dose of methadone and the reason for discontinuation of treatment, correlation with high statistical significance ($p = 0.01$), explained by the fact that the most common cause of discontinuation of methadone treatment was terminal condition, when the oral route of administration becomes unapproachable (table 3). Moreover, inability to administer oral medication led to discontinuation of treatment in 65.2% of cases (terminally ill, nausea / vomiting and dysphagia).

62.3% of the patients experienced side effects, the most frequently were constipation (14.6%) and nausea and vomiting (7.3%); in smaller percentages, somnolence (1.6%), hallucinations/delusions (1.2%), myoclonus (0.8%).

The low percentage of constipation occurring during treatment is due on the one hand to the prophylactic laxative treatment administered, usually, in association with the opioid therapy and, on the other hand, to the lipophilic nature of methadone and / or the different affinity of methadone for ì gastrointestinal receptors, aspects that contribute to the much lower rate of constipation and to less frequent use of laxatives. Nausea and vomiting, commonly encountered in 1/2 - 3/4 of patients on morphine [26], were encountered much less frequently in methadone treatment, although there was no prophylactic use of metoclopramide observed at initiation of treatment with methadone, as specified in the subsequently developed protocol. Reduced rate of somnolence/sedation is consistent with data from the literature [19].

There is no correlation between the dose of methadone at treatment initiation / discontinuation and the adverse reactions encountered during the course of care.

Association with a co-analgesic has not led to an increase in side effects ($r = 0$), supporting the idea that drug interactions are not always clinically significant and depend on wide individual variations associated with the pharmacokinetics of methadone [27].

The methadone dose at the time of discontinuation was low (median 20 mg, module 15 mg, minimum 5 mg, maximum 60 mg), administered at various intervals of time, most frequently every 8 h (51%) or every 12 h (21.9%). Again we encounter an inconsistency in relation to the methadone treatment initiation protocol developed subsequently.

Methadone dose at the end of the treatment depends on the degree of pain (pain intensity was recorded at the

Table 4
CORRELATIONS BETWEEN FINAL DAILY METHADONE DOSE AND PAIN INTENSITY

Correlations: final daily methadone dose – pain intensity		final daily dose of methadone	pain intensity
final daily dose of methadone	Pearson Correlation	1	-.156*
	Sig. (2-tailed)		.014
	N	247	247
pain intensity	Pearson Correlation	-.156*	1
	Sig. (2-tailed)	.014	
	N	247	247

**Correlation is significant at the 0.05 level (2-tailed)*

time of first record/initiation of treatment); ($p = 0.05$) and (table 4). The explanation for the fact that CSH patients required low doses of methadone for pain control is likely that, at that time, regardless of the age of the patients, the population was not exposed to recreational drugs [28] and had limited access to opioid analgesics, thus not developing tolerance to opioids.

Conclusions

Methadone has been used in a large number of patients between 1996 and 2000. Among patients undergoing step III opioid therapy, the most commonly used was morphine injection, followed by methadone (247 patients).

Methadone has been shown to be safe and effective. Side effects were only found in 37.7% of patients and the most common side effects were constipation (14.6%) and nausea and vomiting (7.3%). The main reason for discontinuation of methadone treatment was terminal condition (49.8%), not incomplete control of pain (14.6%) or occurrence of intolerable side effects (5.3%).

The doses used for treatment initiation ranged between 5 mg and 40 mg, and at the time of discontinuation between 5 mg and 60 mg. The small doses required by CSH patients to control pain are probably explained by the existence of a population not exposed to recreational drugs and / or with limited access to opioid analgesics.

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