METHADONE AS AN ALTERNATIVE ANALGESIC FOR PALLIATIVE PATIENTS

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Abstract. Opioid analgesics are medicines of choice for management of moderate and severe chronic pain, which is one of the most common symptoms in 70-80% of patients in terminal stages of life. One of the perspective synthetic opioid is Methadone, which is used as a medicine for substitution maintenance therapy in the treatment of opiate dependence and administered as pain reliever. A systematic review of the comparative clinical trials of the use of Methadone and Morphine in palliative patients found that Methadone is an effective, safe alternative opioid which provides adequate analgesia. This confirms that the therapeutic efficacy of Methadone is not lower than of Morphine, so that Methadone can be allowed for use as an alternative medicine. Using a pharmacoeconomic analysis was established a better ratio of "cost-effectiveness" for Methadone unlike Morphine (1.35 vs 17.57), which points at higher economic availability of Methadone.

Key words: methadone, palliative medicine, analgesic, chronic pain syndrome

Introduction

According to the data of State educational and scientific center of palliative and hospice care (PHC) and Ukrainian Palliative and Hospice Care League (League) over the past 5 years in Ukraine annually at about 600 thousand patients in the final period of life need palliative care (PC) [7].

Chronic pain syndrome (CPS) is one of the most common symptoms in 70-80% of patients in the terminal stages of incurable diseases of cancer genesis [2]. CPS management is carried out according to the WHO's pain relief ladder with the use of analgesics and adjuvants [15]. Opioid analgesics are medicines of choice in pharmacotherapy (PT) of moderate and severe CPS at II and III "step". Among them are widely used oral dosage forms (DF) of Morphine, which is considered the "gold" standard because of therapeutic efficiency and economic availability. However, in 10-30% of patients after increasing of the doses of morphine proper effect of FT was not observed because of serious adverse effects (AE), lack of analgesic effect or neurotoxicity [3, 4]. This determines usage in clinical practice alternative opioids (Omnopon, Trimeperidine, Buprenorphine, Tramadol, Nalbuphine), adjuvant medicines and non-opioid analgesics very important. Opioid rotation is aimed at preventing the development of opioid tolerance and toxicity and is normally carried out when a dose of oral morphine is more than 1 g per day [1].

One of the perspective synthetic opioid is methadone – a partial agonist of μ- and δ-opioid receptor, which is usually used in substitution therapy in the treatment of opiate dependence and less frequently prescribed as analgesic.

The **purpose** of our study was to investigate the possibility of using methadone as an alternative opioid in national practice of CPS management.

Materials and methods

The objects of the study are: databases Cochrane, MEDLINE and Embase; information about prices from «Regional pharmaceutical warehouse» (Lviv) and International Charitable Foundation "International HIV/AIDS Alliance in Ukraine"; texts of instructions for medical use (IMU) for trade marks (TM) of Methadone tablets 10 mg, included in the State Register of medicines as of 26.12.2015 (http://www.drlz.kiev.ua/): Methadone-ZN® (Kharkiv Pharmaceutical company "Zdorovya narodu", Ukraine), Methaddict® (Sandoz Pharmaceuticals GmbH, Slovenia), Methafin® IC ("Interchim", Odesa, Ukraine) and Methadol Pharmascience® (Pharmascience Inc., Canada); IMU of Morphine tablets 10 mg: Morphine-ZN (Kharkiv Pharmaceutical company "Zdorovya narodu", Ukraine) and Morphine sulphate ("Interchim", Odesa, Ukraine). As methods of research were used: bibliographic, statistical, comparative, content analysis, data analysis of clinical trials (CT), the cost-effectiveness analysis. For assessment the effectiveness of compared medicines odds ratio (OR) was calculated using the formula [6, 9]:

$$OR = \frac{a/c}{b/d} = \frac{a \times d}{b \times c}$$

where *a* and *b* – the number of patients with a positive effect respectively the 1st and 2nd medicine;

c and *d* – the number of patients without clinical effect respectively 1st and 2nd medicine.

Results

At the first stage of research was conducted a systematic review of databases Cochrane, MEDLINE and Embase on the effectiveness of Methadone in palliative patients with CPS (Table 1) [5]. Clinical trial (CT) of *Gourlay et al*. [10] showed that the half-life was 30.4 ± 16.3 hours and 2.7 ± 1.2 hours for Methadone and Morphine, respectively. The longer half-life for Methadone was associated with long-term therapeutic effect, which, respectively, was significant for CPS relief. There were also marked differences in the bioavailability (BA) of oral DF: for Methadone - 79 ± 11.7%, and for Morphine - 26 ± 13%.

In the CT conducted by *Grochow et al*. [11] and *Ventafridda et al*. [14] was not found significant difference between clinical efficiency (CE) and pharmacological properties of parenteral DF of Morphine and Methadone, and also shown that greater half-life of Methadone does not lead to a significant prolongation of the therapeutic effect. These studies have shown the possibility of using Methadone as an alternative analgesic.

As a result of the comparative CT *Mercadante* [13] established that opioid escalation index (OEI %) was lower in the group taking Methadone (an oral solution) (1,7 ± 0,4), in comparison with group taking slow release Morphine (3,5 ± 0,5). Seven patients, who used Methadone, did not need to increase the dose throughout the study period, while only 1 patient in the group that took Morphine, did not require dose escalation.

In the CT held by *Bruera et al*. [12] patients were divided into 2 groups, one of which took Methadone, another one - Morphine. Evaluation of CE was performed on the 8th, 14th and 28th study day. Was determined that the proportion of patients whose CE was 20% amounted to 0.49 (95% C 0,34-0,64) for Methadone and 0.56 (95% C, 0,41-0,70) for Morphine. Thus, the CE of both medicines did not significantly differ, which argues about the suitability of Methadone for treatment of CPS.

For the statistical evaluation of the meta-analysis results was taken CT in the report of which were indicated numbers of patients with and without therapeutic effect (*Bruera et al*., 2004). After analysis the odds ratio in the chosen CT it is possible to make a conclusion, that the chances for Methadone are slightly higher than the chances of Morphine because OR = 1,16 (> 1). So, it means that Methadone has a sufficient therapeutic efficacy for using it as an alternative analgesic.

At the next stage of the study was carried out determination of the ratio of "cost-effectiveness" for tablet forms of Morphine (Morphine-ZN) and Methadone (Methadone-ZN) in the treatment of CPS. Thus, the daily dose was took into account, starting from Morphine (60 mg per day), and the daily dose of Methadone was calculated based on equianalgesic dose to 60 mg of morphine (15 mg per day).

As can be seen from Table 2, the ratio of "cost-effectiveness" for Methadone is lower than in Morphine by 4 times, indicating the significant benefits of methadone (showed in therapeutic effects) per paid monetary unit.

Table 1. *The results of experimental comparative trials on the use of Methadone*

Medicine	Dosage regimen (dose ratio)	The number of patients (included / evaluated)	Clinical efficiency (CE)
1	2	3	4
1. Randomized, parallel-group CT (Gourlay et al., 1986) [10]			
Methadone (M)	**Stage 1:** IV M or MO – 15-25 mg **Stage 2:** Oral MO: 15 mg / 4 hours – 150 mg / 3 hours M: - 15 mg 1 time per 2 days – 20 mg / 2 times per day **Stage 3:** Individual selection of doses	**18** (n = 9 (M); n = 9 (MO))	**Stage 1** - VAS ↓ from 55 to 0 mm after 2-5 min; effect – 5 hours; further analgesia – in 7 hours **Stage 2** – VAS ↓ from 65 to 10 mm after 90 min; effect – 9-10 hours BA : oral - 79 ± 11.7 %
Morphine (MO)			**Stage 1** – VAS ↓ from 82 to 0 mm after 5-15 min; effect – 5 hours **Stage 2** - VAS ↓ from 65 to 20 mm after 100 min; effect – 6 hours BA: oral - 26 ±13 %
2. Randomized, parallel-group CT (Ventafridda et al., 1986) [14]			
Methadone (M)	8-28 mg / 6 hours (after 3 days – / 8 hours)	**66/54** (Exclusion: Inefficiency: 1 (MO), 1 (M); SE: 2 (M) Death: 2 (MO), 5 (M)	VAS ↓ 70 to 25 mm
Morphine (MO)	4-24 mg / 4 hours		VAS ↓ 55 to 20 mm
3. Randomized, double-blind, controlled CT (Grochow et al., 1989) [11]			
Methadone IV	344 mg (16 - 960)	**23/18** (n = 10 (MO); n = 8 (M))	There was no significant difference between the CE of both medicines
Morphine IV	128 mg (24 - 456)		
4. Randomized, prospective, parallel CT (Mercadante, 1998) [13]			
Methadone oral liquid 0,1%	13,6 ± 0,7; max 25,2 ± 3,9	**40** (n = 20; n = 20)	VAS 34 ± 1
SR morphine (SR MO)	32,5 ± 2,5; max 109,5 ± 27,7		VAS 33 ± 2
5. Randomized, double-blind CT (Bruera et al., 2004) [12]			
Methadone (M)	7,5 mg / 12 hours (5 mg / 4 hours – if needed)	**103/66** (n = 49/29 (M); n = 54/37 (SR MO))	*% of patients with CE > 20%* 0,49 (95% C, 0,34-0,64)
SR morphine (SR MO)	15 mg / 12 hours (IR MO - 5 mg / 4 hours - if needed)		0,56 (95% C, 0,41-0,70)
OR = 1,16 (95% C, 0,668 - 3,371)			
Notes*: IV – intravenous DF; SR – oral DF with sustained release of medical substance; IR () – oral DF with immediate release of medical substance; BA – bioavailability; SE – side effects of medicines*			

***Table 2.** The ratio of "cost-effectiveness" of Morphine and Methadone tablets in the treatment of CPS*

Medicine	Daily dose, mg	Cost of daily therapy, USD	Clinical efficiency **	Ratio of „cost-effectiveness“
Morphine	60 mg	0,51	0,56	0,91
Methadone	15 mg*	0,11	0,49	0,22
* – equianalgesic dose; ** CE: part of patients with therapeutic effect more than 20%				

The final stage of the study was a comparative analysis of texts of medicines' IMU, which found some differences in them. In particular, in Methadone TM an active ingredient is the same - methadone hydrochloride, active ingredient in Morphine TM is morphine hydrochloride (Morphine-ZN) and morphine sulphate (Morphine sulfate).

As can be seen from Table 3 analyzed medicines also differ by name and number of the inactive drug ingredients (excipients). Totally in Methadone TM were used 8 excipients (3 to 5 in one TM) and the in Morphine TM - 7 at scale variation from 3 to 6. Most often was used microcrystalline cellulose and magnesium stearate (all TM). Excipients not only determine the technological possibility of receiving certain medicines in a particular DF, but also define or regulate their stability and efficiency for a certain time [8]. According to IMU shelf life for Methadone-ZN and Methadol Pharmascience is 5 years and for Methaddict and Methafin IC – 3 years. Shelf life for all Morphine TM is the same – 2 years.

***Table 3.** List of excipients for Methadone and Morphine TM*

Name of excipient	Methadone TM				Total	Morphine TM		Total
	Methadone-ZN	Methaddict®	Methadol Pharmascience®	Methafin® IC		Morphine-ZN	Morphine sulfate	
Magnesium stearate	+	+	+	+	4	+	+	2
Microcrystalline cellulose	+	+	+	+	4	+	+	2
Lactose monohydrate	+	+	-	+	3	-	-	-
Lactose anhydrous	-	-	+	-	1	-	-	-
Corn starch	-	+	-	-	1	+	-	1
Pregelatinized starch	+	-	-	-	1	-	-	-
Cellactose® 80 (mixture of lactose monohydrate and cellulose powder (75:25))	-	-	-	-	-	+	-	1
StarLac® (lactose monohydrate, corn starch)	-	-	-	-	-	-	+	1
Sugar, pressed	-	+	-	-	1	-	-	-
Dye (FD&C Blue No. 1 lacquered 13% (E 133))	-	-	+	-	1	-	-	
Crospovidone	-	-	-	-		+	-	1
Silicon Dioxide Colloidal	-	-	-	-		+	-	
Total	4	5	4	3	x	6	3	x
Shelf life, years	5	3	5	3	x	2	2	x

Table 4. *Indications of Methadone and Morphine TM*

Indications	Methadone TM				Morphine TM	
	Methadone-ZN	Methaddict®	Methadol Pharmascience®	Methafin® IC	Morphine-ZN	Morphine sulfate
Severe pain, including pain during malignant tumors, severe traumas, myocardial infarction, in postoperative period	–	–	–	–	+	+
Moderate to severe pain, which is not eliminated by other narcotic analgesics	+	–	+	+	+	+
For detoxification in the treatment of opiate dependence (heroin and other morphine-like drugs dependence), and for substitution maintenance therapy of opiate addiction	+				–	

Table 5. *Contraindications to use of Methadone and Morphine TM*

Contraindications	Methadone TM				Morphine TM	
	Methadone-ZN	Methaddict®	Methadol Pharmascience®	Methafin® IC	Morphine-ZN	Morphine sulfate
hypersensitivity to the components of medicines; respiratory depression; bronchospasm	+	+	+	+	+	+
exacerbation of bronchial asthma	+	+	+	+	–	–
severe hepatic insufficiency	–	–	–	–	+	+
accumulation in blood of the excess of carbon dioxide (hypercapnia)	+	+	+	+	–	–
diarrhea associated with pseudomembranous colitis caused by cephalosporins, lincomycin, clindamycin, penicillins	+	+	+	+	–	–
diarrhea caused by poisoning	+	+	+	+	–	–
motility disorders of the gastrointestinal tract	–	–	–	–	+	+
abdominal pain of unknown etiology	–	–	–	–	+	+
intestinal obstruction; simultaneous use with MAO inhibitors, and within 2 weeks after their use; intracranial hypertension, head injury	+	+	+	+	+	+
stroke	–	–	–	–	+	+
acute alcohol intoxication	–	–	–	–	+	+
fever	–	–	–	–	+	+
epileptic status	–	–	–	–	+	+
delirium	–	–	–	–	+	+
cachexia	–	–	–	–	+	+
addiction to „light“ drugs (codeine, petydyn and similar agonists of opioid receptors)	+	+	+	+	–	–

The results of further analysis showed some differences in indications and contraindications of Methadone TM. As can be seen from Table 4, indication in all Methadone TM is the treatment of opiate addiction, in Methadone-ZN, Methadol Pharmascience and Methafin IC is also indicated their use in management of pain syndrome. Indications for Morphine TM are identical – severe CPS.

It should be noted that there are no differences between contraindications of Methadone TM (Table 5). In Morphine TM differences between contraindications are absent. Also were found common contraindications between Morphine and Methadone TM: hypersensitivity to the components of medicines, respiratory depression, intestinal obstruction, intracranial hypertension, head injury, the simultaneous use with MAO inhibitors. The main differences were following: Methadone is contraindicated when patients have diarrhea, hypercapnia, weak dependence on opioids, Morphine – for persons with hepatic insufficiency, abdominal pain, stroke, fever, epileptic status, delirium, acute alcohol intoxication, and cachexia.

As for the method of application and doses, the main difference is that for Methadone-ZN, Methadol Pharmascience and Methafin IC are specified doses for the treatment of opiate addiction and pain management, and for Methaddict – only for the treatment of opiate addiction. In Morphine TM dosage and administration are identical and recommended in the treatment of CPS.

It was also established that the texts of analyzed IMU of Methadone TM contain an average of 11 groups of SE (from 9 to 12) (Table 6). As for the number of possible adverse clinical effects, the same number - 90 – is listed in IMU of Methadone-ZN and Methaddict, 89 effects – in Methafin IC and in Methadol Pharmascience is 77. Also it is necessary to note that some of the

Table 6. *Side effects of Methadone and Morphine TM*

Groups of SE	Number of possible adverse clinical effects					
	Methadone-ZN	Methaddict®	Methadol Pharmascience®	Methafin® IC	Morphine-ZN	Morphine sulfate
SE associated with withdrawal syndrome	27	27	24	26	–	–
General effects	–	–	6	–	–	6
Hematologic	3	3	1	3	–	
Mental disorders	5	5	–	5	10	9
Nervous system	9	9	11	9	13	9
Sense organs	1	1	–	1	3	3
Cardiovascular	17	17	13	18	7	6
Respiratory	4	4	2	4	4	4
Gastrointestinal	7	7	8	8	9	12
Hepatobiliary	1	1	–	–	–	–
Skin and subcutaneous tissue	6	6	4	6	–	3
Genitourinary	3	3	4	3	4	5
Metabolism	–	–	4	–	–	–
Immune	–	–	–	–	6	2
Other	7	7	–	6	3	–
Total	90	90	77	89	59	59

clinical effects, which in IMU of Methadone-ZN, Methaddict and Methafin are included in groups "Other", "Nervous system", in IMU of Methadol Pharmascience are included in groups "General effects" and "Metabolism".

Number of clinical effects for Morphine TM is the same – 59, and the content of each group of SE is virtually identical (Morphine sulfate contains more SE groups that is associated with the allocation of some clinical effects in separate groups compared with Morphine-ZN).

Conclusions

1. A systematic review of results of comparative trials on use of Methadone and Morphine in palliative patients' analgesia found that Methadone is an effective, safe alternative opioid, and if dosage is correct it provides adequate pain management. Results of statistical analysis showed that the odds ratio for Methadone compared to morphine is 1.16. The above mentioned suggests that the therapeutic efficacy of Methadone is not lower than in Morphine, which allows its use as an alternative medicine.

2. Pharmacoeconomic analysis found best ratio of "cost-effectiveness" for Methadone unlike Morphine (0,22 to 0,91), point at higher economic availability of therapy by this medicine.

3. Based on a comparative study of instructions for medical use of Methadone and Morphine trademarks were found some differences that particularly concerned the types of excipients, indications, contraindications and side effects. At that, the differences were more characteristic for Methadone trademarks. Also in instructions for medical use Methadone is indicated first of all for opiate dependence treatment (all 4 trademarks) as well as for the pain management (3 trademarks), while Morphine is exclusively painkiller.

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