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Opioid Dependence Treatment: is Levomethadone a New Frontier? A Pilot Study in Italy

Milo Meini[1], Marco Moncini[1], Laura Daini[1], Daniela Scaramelli[1], Marta Milianti[1], Tania Giarratana[1] and Paola Rucci[2]*

[1]Local Health Authority Toscana Nordovest, Drug Addiction Service, Via Fleming 1, 56025 Pontedera (PI), Italy

[2]Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum University of Bologna, Via San Giacomo 12, 40126 Bologna, Italy

***Corresponding author: Paola Rucci,** Email: paola.rucci2@unibo.it

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Abstract

Objective: Methadone is marketed in most of the world as a racemic mixture containing two enantiomers in a 50:50 ratio. Since 2015, the pure R-isoform (levomethadone) has been authorized in Italy for the treatment of opioid addiction in adults.

Aim: The aim of this study is to analyse the safety and the tolerability of levomethadone in adults formerly treated with racemic methadone for opioid dependence or untreated (drug-naïve subjects)

Method: Between June and December 2016, 21 consecutive patients with opioid dependence were treated for 6 months with levomethadone at the Drug Addiction Service of Pontedera (Italy).

Results: Eighteen patients (85.7%) completed the 6-month treatment period and 3 dropped out. No adverse events or side effects were observed and no deaths occurred during treatment. Among those transferred from racemic methadone, the percentage of drug-positive urine screens decreased from 51% to 18% after two months of levomethadone treatment and then to 0% at six months. Withdrawal symptoms, craving and compliance improved significantly after transfer to (R)-methadone.

Conclusion: Transfer from racemic to (R)-methadone is safe and well tolerated.

Keywords: Levomethadone; Safety; Tolerance

Abbreviations: EMIT: Enzyme Multiplied Immunoassay Technique; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; NMDA: N-methyl-D-aspartate

Introduction

Methadone is marketed in most of the world as a racemic mixture containing two enantiomers in a 50:50 ratio; in some European countries, such as Germany and Austria, the pure R-isoform has been available since the past century [1].

In 2015, the pure R-isoform has been authorized in Italy for the treatment of opioid addiction in adults and is currently available as an oral 0.5% solution.

Methadone is a synthetic opioid, μ-receptors agonist, with a pharmacological activity similar to that of morphine. Its molecular structure is characterized by an asymmetric carbon atom, which produces two enantiomers: the R-isomer or levomethadone and the S-isomer or dextromethadone [2].

The stereospecificity of many opioids for μ receptors is well known: it has been demonstrated, for example, that the affinity of the levomethadone on μ receptors is 10 times higher than that of S-isomer and that its analgesic potency, in humans, is about 50 times higher [3-5].

In healthy volunteers 7.5 mg of oral dextromethadone did not produce respiratory depression or pupillary constriction that were observed with an identical amount of levomethadone or with 15 mg of the racemic (R-S) methadone; a mild respiratory depression is observed with dextromethadone in the dosage range of 50 to 100 mg [6,7].

In addition to exerting its action on opioid receptors, methadone acts on glutamatergic receptors, and in particular on the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. It has been hypothesized that the drug's ability to induced less analgesic tolerance is due to the non-competitive antagonist action of S isomer at the NMDA receptors [1,8-12].

Evidence from current international literature indicates that levomethadone is an active ingredient with improved safety profile and more efficacy than racemic; its pharmacodynamics would also allow the use of about half the dose [1,10,13,14].

Given the complete lack of data on the use of R-isomer in Italy, we report the results of the first clinical use of this drug in an Italian Drug Addiction Service.

The Aims of this Study are:

- To analyse the safety and the tolerability of levomethadone in adults formerly treated with racemic methadone for opioid dependence or untreated (drug-naïve subjects).
- To identify patients for whom levomethadone should be preferred over racemate or vice versa.

To this purpose, we examined treatment compliance, craving, use of heroin (or other opiates without medical prescription), side effects, psychiatric comorbidity and the cardiologic safety profile, already described in the literature [12,15-18].

Study Population

Between June and December 2016, 21 consecutive patients were enrolled at the Drug Addiction Service of Pontendera (Italy) and treated for 6 months with levomethadone.

The Drug Addiction Services (DAS) are established in Italy since 1990 for the diagnosis and treatment of substance use disorders. DAS are multi-professional services that deliver pharmacological, psychological and social interventions for the most common substance use disorders treatments according to international guidelines [19] and in relation to clinical experience.

Inclusion Criteria

A. Age ≥18 years.

B. Opioid dependence, diagnosed according to ICD-9-CM criteria [20].

C. Patients already treated with racemic methadone or buprenorphine, or drug-naïve subjects with opioid dependence.

D. Ability to understand the study procedures and to provide a written informed consent to participation.

Abuse or dependence on substances other than opioids did not preclude participation in the study.

Patients underwent a careful physical examination at the beginning of the study and during treatment with levomethadone. Reasons for drop-out, adverse events, withdrawal symptoms and craving were recorded.

Patients already being treated with the racemate were transfered to levomethadone with a starting dosage, whenever possible, of half the racemate dose.

For drug-naïve subjects the initial dose of levomethadone was defined based on the assessment of physical addiction, confirmed by Wang scale score [21].

The levomethadone dosage was then increased in the subsequent days until it reached the appropriate dosage for clinical stabilization [22].

Socio-demographic data, psychiatric comorbidities, information on drug treatment and the results of laboratory tests of enrolled patients were extracted at baseline from the National Information System of Drug Dependence and updated during the study.

Toxicological analyses of urine samples were periodically conducted in direct observation of urination, and/or with closed-circuit camera. Urine specimens were analyzed using the immunoenzymatic procedure EMIT (Enzyme Multiplied Immunoassay Technique) to search for opioids and other illegal substances. Cut-offs for positivity were 300 ng/ml for morphinuria, metadonuria and benzoilecgonine and 50 ng/ml for cannabinoids [23].

Craving was assessed using the Visual Analogue Scale 0-100.

To confirm the lower cardiotoxicity of levomethadone reported in the reported literature and, in particular, its lower interference compared to the racemate on ventricular repolarization (long QT, *torsade de points*, etc.), all study participants underwent electrocardiogram to measure the QTc-QT interval corrected for heart rate [15,24-26]. Cut-offs used for prolonged QTc intervals were ≥430 ms (borderline values) and ≥450 ms (abnormal values) for males, and ≥450 ms (borderline values) and ≥470 ms (abnormal values) for females [27].

All patients signed a written informed consent to participation after receiving an explanation of study procedures and having the opportunity to ask questions.

Statistical Analysis

Data were summarized as percentage frequencies, mean ± standard deviation or median and range. In patients transferred from racemic methadone, craving and the % positive urine samples in the months before and after transfer to levomethadone were compared using Wilcoxon signed-rank test.

Results

Demographic characteristics of the study sample are reported in Table 1. Patients had a mean age of 38 years (SD = 11.6). Fourteen (66.7%) were male, 7 (33.3%) female; 11 (52.4%) were single, 10 (47.6%) married or living with a partner; 12 (57.1%) patients were employed and 9 (42.9%) were unemployed. Thirteen patients (61.9%) had comorbid psychiatric disorder diagnosed using DSM-IV criteria (5 major depression, 4 bipolar disorder, 3 borderline personality disorder, 1 anorexia nervosa).

Twelve patients (57.1%) had been formerly treated with racemic methadone for an average of 25 months (SD = 27.2) the last mean dosage was 80.8 mg/day (SD = 48.1); 1 (4.8%) had received buprenorphine for 132 months and the last dosage was 8 mg/day.

Eight subjects (38.1%) were drug-naïve: 7 were heroin-dependent and 1 was oxycodone-dependent; all patients had a moderate/severe spontaneous withdrawal syndrome with a mean Wang's scale score of 24.3 (DS = 6.1) at baseline. The history of drug treatment and the dosage of levomethadone are reported in Table 2.

Table 1: Demographic characteristics of the sample (*n = 21*).

	***N* (%)**
Gender	
Male	14 (66.7)
Female	7 (33.3)
Marital status	
Married or stable partnership	10 (47.6)
Single	11 (52.4)
With children	9 (42.9)
Without children	12 (57.1)
Working status	
Currently employed	12 (57.1)
Currently unemployed	9 (42.9)
Age (mean and SD)	38 (11.6)

Table 2: History of drug treatment at baseline and dosage of levomethadone.

	Mean (SD)
Patients formerly treated with racemic methadone (N=12)	
Duration of last substitution therapy with racemic methadone (in months)	25.0 (27.2)
Last dosage of racemic methadone (mg/day)	80.8 (48.1)
First dosage of levomethadone (mg/day)	39.7 (23.5)
Stabilization dose of levomethadone (mg/day)	46.7 (25.0)
Patients formerly treated with buprenorphine (N=1)	
Duration of last substitution therapy with buprenorphine (in months)	132
Last dosage of buprenorphine (mg/day)	8
First dosage of levomethadone (mg/day)	15
Stabilization dose of levomethadone (mg/day)	50
Drug-naïve patients (N=8)	
Quantitative assessment of spontaneous withdrawal syndrome according to Wang's scale score*	24.3 (6.1)
First dosage of levomethadone (mg/day)	12.9 (2.5)
Stabilization dose of levomethadone (mg/day)	25.0 (7.8)

*) Severe: 31-45; Moderate: 21-30; Mild: 11-20; Marginal: 5-10; Absent: 0-4

The average initial dose of levomethadone was 39.7 mg / day (SD = 23.5) for patients formerly treated with racemic and 12.9 mg / day (SD = 2.5) for drug-naïve subjects. The dosage prescribed to the only person formerly treated with buprenorphine was 15 mg / day. No withdrawal signs were observed and no patient reported symptoms.

The levomethadone dosage was increased, in agreement with the patient:

1. When laboratory findings indicated the use of other opiates;
2. When it was lower than that the appropriate dosage according to international guidelines;
3. To increase levometadonemia and thus reduce the use of heroin and craving [30];
4. When the patient reported that the dose was insufficient for adequate 24 hours coverage.

Only 2 patients after 57 and 118 days of therapy asked for an increase of dosage because they felt that the current dosage did not

ensure a 24 h coverage; an increase of 10 mg/day was adequate and satisfactory for both patients.

The average stabilization dose of levomethadone was 46.7 mg / day (SD = 25.0) for patients transferred from racemic methadone and 25 mg / day (SD = 7.8) for drug-naïve subjects previously treated with buprenorphine. All patients agreed to increase dosage because of the positive effects experienced with levomethadone. This made it possible to prescribe potentially more effective drug dosages, in line with the international guidelines.

Retention in treatment at 6 months was 85.7%. Two patients discontinued levomethadone after 1 and 9 days, because they did not want to stop using drugs. Another discontinued treatment after 95 days because he was confined in prison where he was treated with racemic due to the unavailability of levomethadone.

No patient experienced side effects from taking levomethadone.

Three patients who had suffered from excessive sweating during racemate treatment reported the disappearance of this side effect; one reported the regularization of bowel previously constipated.

The 12 patients transferred from the racemate reported feelings of general well-being, a higher mental lucidity and more feel like doing; the majority (83.3%) also mentioned a better hold within 24 hours after taking the levomethadone. Craving was assessed in this subgroup at baseline and bimonthly after beginning levomethadone treatment. Craving declined significantly from 30.8 (SD = 21.5) in the last two months of racemate treatment to 6.7 (SD=8.9) in two months of levomethadone and then to 4.2 (SD=5.1) at four months and 1.7 (SD=3.9) at six months (Wilcoxon test, p <0.01 at each time point). Seven patients were offered to be transferred back to the racemate and all refused. Moreover, only 18% of the urine samples collected during the first two months of levomethadone were positive for opioids compared with 51% positive detected in the last two months of treatment with the racemate (Wilcoxon test, p<0.01, Table 3). At the third and fourth months, positive urine samples were 16% and 5% and dropped to 0 at the sixth month.

Table 3: Use of heroin during levomethadone therapy in the patients previously treated with racemic methadone.

	Urine samples (*N.*)	Positive for opioids (*%*)
Last 2 months of treatment with racemic methadone	158	81
First 2 months of treatment with levomethadone	157	27
Third month of treatment with levomethadone	80	16
Fourth month of treatment with levomethadone	75	5
Fifth month of treatment with levomethadone	74	1
Sixth month of treatment with levomethadone	74	0

In the patient formerly treated with buprenorphine the analytical toxicology detected, in the first 2 months of treatment and thereafter approximately 20% reduction in the positivity for opiates. Levomethadone had no effect on the use of other drugs. During the study, psychopathology levels did not worsen among patients with psychiatric comorbidity.

Craving and positivity for opiates declined significantly (p<0.01) in patients with and without psychiatric comorbidity (Figure 1). No significant difference in this trend was found between the two groups.

Ten study participants (47.6%), after a complete abstention from the use of other opioids for at least 3 weeks, underwent ECG. No clinically significant changes were observed in the ECG, including the QTc that was in the normal range for both males (408.4 ± 16.8) and females (444.3 ± 3.2). This result excludes any effect of levomethadone on the electrophysiological measures associated with an increased risk of sudden cardiac death.

Discussion

The present study reports the results of the first use of levomethadone over 6 months for treating opioid dependence in Italy.

After replacing methadone with half-dose levomethadone, no signs or symptoms suggestive of withdrawal syndrome were observed, confirming evidence from the literature [1,28]. All patients formerly treated with racemic methadone were satisfied with the transfer to the new drug, and none of them stopped taking levomethadone.

Participants reported higher physical and mental well-being, a proactive attitude and better hold in the 24 hours between the intake of a dose and the next intake. This is probably the reason why all of them refused to be transfered back to racemate.

We assume that the lack of a non-competitive antagonist action

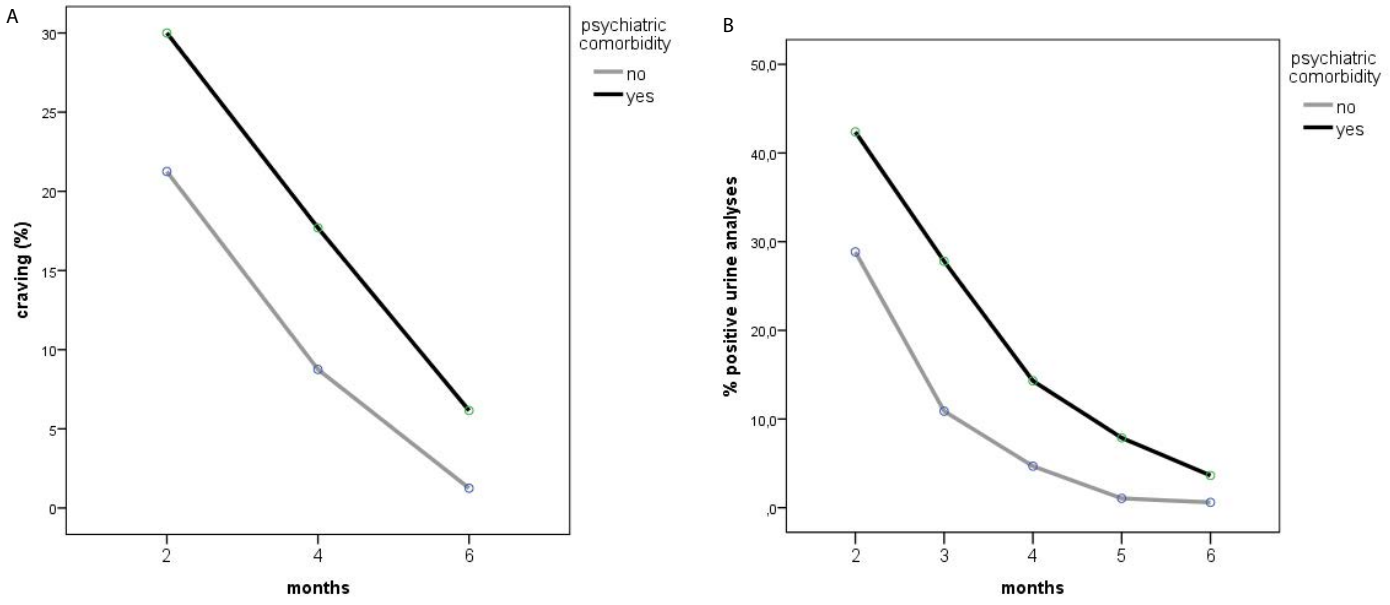

Figure 1: (A) Mean percentage of craving and (B) mean percentage of positive urine analyses in patients with and without psychiatric comorbidity during treatment with levomethadone.

of dextromethadone on NMDA receptors may be the reason for the reduced inhibitory action of the drug toward excitatory brain receptors compared to racemate. On the other hand, as indicated by several authors [3,29], levomethadone has a longer half-life compared to racemate and an increased elimination half-life (also in steady-state conditions), which justifies the better hold reported by our patients.

It was reported in the literature that the lack of action of dextrometadone on NMDA receptors would lead to the development of a greater tolerance for the levomethadone and this, in turn, would result in an increase of maintenance doses [5].

The above observation is not confirmed in our study where an increase in the dosage was required just once and only in two cases; a possible explanation is the low plasma concentration of levomethadone [30].

This is in line with the findings of a retrospective study [31] based on 370 cases treated with racemic and 309 with levomethadone, in which no significant differences in "tolerance index" and dose increase were found between the two treatment groups.

Our results that the QTc interval was in the normal range in all participants confirm the lack of cardiotoxicity of levomethadone and support the notion that it does not interfere with the QTc interval, as already reported in the literature [32,].

It is, however, worth pointing out that in most cases, in the absence of genetic predisposition [23,34] even the effect of the racemate on the QTc interval is not clinically relevant, so that international guidelines for methadone treatment of opioid addiction do not recommend a pre-treatment electrocardiographic screening. On the contrary, ECG screening is required by the guidelines for the treatment of pain in the presence of concomitant risk factors of QTc interval prolongation.

Moreover, a recent study [24] indicated that methadone influences exclusively the interval ranging from the T-wave peak to its end (T_p-T_e), further downsizing its role in the determinism of a pathological prolongation of QTc interval, and underscored the effect on ventricular repolarization of some antipsychotics, antidepressants and mood stabilizers, prescribed for comorbid psychiatric disorders.

In our study side effects were virtually absent, in particular, those involving the CNS (irritability, anxiety) and the gastrointestinal system, differently from the findings of study that indicates a higher frequency of these effects in levomethadone compared to the racemic [12]. Moreover, no changes in the severity of psychopathology were found in patients with psychiatric disorders (61.9% of the sample).

Notably, our results indicate that the common side effects attributable to the racemate (sweating and constipation), reported at baseline by one third of the sample, disappeared during levomethadone treatment, suggesting that this drug is well tolerated by patient suffering from opioid dependence with and without comorbid psychiatric disorders.

Even more clinically relevant are the reduction of craving for heroin and the progressive reduction of positivity for opioids detected with toxicological examinations. This suggests that patients treated with the racemic receive an undoubted benefit from trasfer to levomethadone.

Although our findings are very encouraging, they should be interpreted with caution because of the limited sample size and the possible "novelty effect" that the levomethadone may have produced in our patients, similar to what happened after the introduction of buprenorphine for the treatment of opioid dependence [35]. Thus results should be considered preliminary and warrant confirmation.

Moreover, although our patients with psychiatric disorders did not experience a worsening in psychiatric symptomatology, levomethadone prescription should be carefully considered in patients with other psychiatric comorbidities not present in our sample, in particular anxiety disorders (generalized anxiety, panic, etc.). In fact, the absence of R-methadone and its effects on glutamate receptors could lead to a worsening of anxiety symptom, irritability and sleep disturbances.

Notwithstanding these caveats, some tentative assumptions can be made about patients who would benefit more from levomethadone. The R-isoform, albeit more expensive than the racemic mixture, may be preferred in patients with cardiac diseases, in patients with comorbid psychiatric disorders, with side effects inducted by racemate or in patients for whom intravenous intake of racemate is risky [6]. Levomethadone could also be better tolerated by patients with chronic kidney disease or treated with drugs that inhibit the methadone metabolism [4].

Lastly, when it is necessary to use high racetamate doses to achieve effective levometadonemia (plasma concentrations between 200 and 250 ng/ml) the pure R-isoform is preferable to improve treatment response [30].

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