Effectiveness of melatonin in tardive dyskinesia.

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Abstract. Tardive Dyskinesia (TD) is a movement disorder associated with the clinical administration of antipsychotics. It is believed that TD is due, among other factors, to an increase in the oxidative damage produced by free radicals. Antioxidants, like vitamin E, have been used in the treatment of TD but there is no evidence of their effectiveness. Melatonin (MEL) is 6 to 10 times more effective, as an antioxidant, than vitamin E and it has been used with an apparent higher effectiveness in the treatment of TD, although the results have not been conclusive. A randomized, double blind, placebo controlled design was used to determine the effectiveness of MEL (20mg/day) during 12 weeks in 7 patients with TD. Six patients with TD were treated with placebo. The Abnormal Involuntary Movement Scale (AIMS) was chosen to assess the severity of TD initially and after 4, 8 and 12 weeks. The psychiatric evaluation was done following the Brief Psychiatric Rating Scale. In two patients treated with MEL a significant improvement (more than 60%) of the values of AIMS was detected. In the remainder five, as well as in the patients treated with placebo, no difference was observed during the 12 weeks. When compared the AIMS score in all the MEL-treated patients with the values in the placebo-treated patients, no significant differences were detected during the 12 weeks of the study. However, the significant clinical improvement observed in two patients must be considered before reaching a final conclusion on the usefulness of MEL in TD.

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Efectividad de la melatonina en la discinesia tardía.

Resumen. La Discinesia Tardía (DT) es un trastorno de los movimientos asociado al uso crónico de antipsicóticos que parece producirse, entre otros factores, por un incremento en los procesos oxidativos. La vitamina E se ha utilizado en su tratamiento, pero no hay evidencia de su efectividad. Como la melatonina (MEL) es 6 a 10 veces más efectiva como antioxidante que la vitamina E, se ha utilizado con una aparente mayor efectividad, aunque los resultados no han sido concluyentes. Se realizó un estudio doble ciego, al azar y controlado con placebo, para determinar la efectividad de la administración de la MEL durante 12 semanas en 7 pacientes con DT. Seis pacientes con DT fueron tratados con placebo. La Escala de Movimientos Involuntarios Anormales (AIMS) se usó para evaluar la evolución de los movimientos al inicio y a las 4, 8 y 12 semanas de tratamiento. La evaluación clínica psiquiátrica se hizo con la Escala Breve de Evaluación Psiquiátrica. En dos pacientes tratados con MEL se observó una mejoría clínica superior al 60% pero en los restantes, así como en los tratados con placebo los valores de la AIMS no variaron significativamente en el transcurso de las 12 semanas. Cuando se compararon los valores de la AIMS de la totalidad de los pacientes tratados con MEL, con los del grupo placebo, no se detectó ninguna diferencia significativa. Sin embargo, la mejoría clínica significativa de dos de los pacientes estudiados debe considerarse para llegar a una conclusión sobre la utilidad de la MEL en la DT.

INTRODUCTION

Tardive dyskinesia (TD) is a movement disorder associated with chronic administration of antipsychotics (1, 2). It is a major cause of disability and has a negative impact on the patient's quality of life (3). It has been determined that TD occurs in 3 to 5% of patients treated with antipsychotics during the first 5 years and 68% of patients after 20 to 25 years of exposure to typical antipsychotics (4-6). The introduction of atypical antipsychotics has decreased the risk of TD (7); however, a systematic review of the literature suggests that the annual incidence of TD is 1% with atypical and 5% with typical antipsychotics (8).

Oro-facial TD impairs chewing and swallowing and originates speech disturbances (8, 9). Limb TD, when severe, causes gait disorders that can result in falls (9).

The pathophysiology of TD is not well defined. It has been suggested that it is due to an increase in oxidative damage caused by free radical generation (10, 11), to GABA-ergic hypofunction (12), although the treatment with GABA agonists drugs like baclofen, progabide, sodium valproate and tetrahydroisoxazolopiridine (THIP) has given inconclusive and unconvincing results in neuroleptic-induced TD (13). Post-synaptic changes in striatal cholinergic

interneurons have also been proposed as responsible for TD as well as an increase in sensitivity or prolonged blocking of dopamine receptors (14). In this regard, it has been shown that melatonin (MEL) inhibits dopamine release in specific areas of the mammalian central nervous system (hypothalamus, hippocampus, medulla-pons and retina). Additionally, antidopaminergic activities of MEL have been demonstrated in the striatum and this hormone may modulate dopaminergic pathways involved in movement disorders in humans, including TD (15).

Antioxidants such as vitamin E have been used in the prevention and treatment of TD. However, in a multicenter long-term, well-controlled study, no evidence was found of the effectiveness of vitamin E in the treatment of TD (16). Melatonin, which is 6 to 10 times more effective as an antioxidant than vitamin E (17), neutralizes a variety of free radicals and reactive oxygen intermediates such as hydroxyl radicals, peroxynitrite anion, singlet oxygen and nitrous oxide. Shamir et al (18) were the first to use MEL in the treatment of 19 patients with TD, administered with 2 mg/day controlled release MEL at 8 PM for 4 weeks followed by 2 weeks of drug washout. Then the subjects underwent another treatment (MEL or placebo) for 4 additional weeks. Efficacy was assessed with the Abnormal Involuntary Movement Scale (AIMS). The authors concluded that these doses of MEL were not effective in the treatment of TD. Later, Shamir *et al.* (19) published the first work that demonstrates the effectiveness of the treatment of TD with MEL. Using, again, a double blind, placebo-controlled, crossover study they assessed the effectiveness of the administration of 10 mg/day controlled release MEL for 6 weeks in 22 schizophrenic patients with TD. They found a significant decrease (p <0.01) in the values of AIMS, without adverse events. How-

ever, they concluded that the brevity of the study (6 weeks) did not allow them to speculate that MEL is capable of reversing TD. The latest published reviews agree that, until now, evidence for the efficacy of MEL in TD is not conclusive (20-22).

For these reasons, the aim of this paper was to conduct a longitudinal, double-blind, randomized study, comparing the effect of a higher dose of MEL, administered for 12 weeks, on clinical symptoms of 7 patients with TD.

PATIENTS AND METHODS

This pilot study included 13 patients with neuroleptic-induced TD. Eleven suffered from schizophrenia and two from bipolar disorder; all met the DSM-IV-TR diagnostic criteria for the diagnosis of neuroleptic-induced TD. Three were outpatients, two were hospitalized at the Psychiatric Hospital of Maracaibo and the remainder 8 patients were treated at "Instituto de Resocialización Psiquiátrica La Sierrita", Maracaibo, Venezuela. No recent medication change was done. Most of the patients have been receiving the same antipsychotic treatment for at least 3 years up to 10 years. The mean disease duration was 30.9 ± 1.8 years (mean ± SE), with a range of 20-41 years. Nine patients were male and 4 female. The mean age ± SE of the patients was 59.9 ± 2.7 years, with a range of 46-75 years. Antipsychotics received were levopromazine (9 patients), haloperidol (4), clozapine (2), aripiprazole (2), olanzapine (1), quetiapine (1) and risperidone (1). All individuals who participated faithfully complied with antipsychotic treatment and maintained it throughout the study. The average dose of medication received was 400 mg/day of chlorpromazine equivalents. We excluded patients with organic diseases such as liver or kidney disease, neurological disorders and comorbid substance abusers.

The group of patients treated with MEL received the following antipsychotic treatments: levopromazine (5 patients), olanzapine (1 patient), haloperidol (1 patient), quetiapine (1 patient), aripiprazole (1 patient), clozapine (1 patient) and risperidone (1 patient). The placebo group was treated as follows: levopromazine (4 patients), haloperidol (3 patients), aripiprazole (1 patient) and clozapine (1 patient) (Table I). The treatment with anticholinergics was maintained by ethical reasons. In each of the MEL and placebo groups two patients received biperidine. Other treatments applied were the following: in the MEL group, valproic acid (1 patient), carbamazepine (1 patient), alprazolam (1 patient), indapamide (1 patient). In the placebo group: carbamazepine (2 patients), chlor-

imipramine (2 patients) and lithium carbonate (1 patient). During the study there was no dosage adjustments.

Patients signed a corresponding informed consent before starting the study, which was approved by the Director of the Psychiatric Hospital and the Director of the "Instituto de Resocialización Psiquiátrica La Sierrita" of Maracaibo. The individuals selected were divided randomly into two groups, under double blind pattern: 7 patients received MEL (Allergy Research Group, Alameda, California, USA) at a dose of 20 mg/day, every night for 12 weeks. Of the group of 7 patients who received melatonin two were outpatients (schizophrenia and bipolar disorder), one was hospitalized at the Psychiatric Hospital of Maracaibo and the remainder 4 patients were treated at "Instituto de Resocia-

TABLE I
ANTIPSYCHOTIC TREATMENTS RECEIVED BY TD PATIENTS OF THE MELATONIN
AND PLACEBO GROUPS

Melatonin Group	Antipsychotic treatment	Chlorpromazine equivalent doses (mg/day)
Patient N°		
1	Olanzapine	200
2	Quetiapine + levopromazine	850
3	Aripiprazole + levopromazine	425
4	Risperidone + levopromazine	125
5	Levopromazine	50
6	Clozapine	400
7	Haloperidol + levopromazine	1650
Placebo Group		
Patient N°		
1	Haloperidol + aripiprazole + levopromazine	550
2	Haloperidol + levopromazine	275
3	Haloperidol	275
4	Levopromazine	50
5	Clozapine	300
6	Levopromazine	50

lización Psiquiátrica La Sierrita". Of the latter, two patients were hospitalized for 3 years, one during 4 years and one for 6 years. A group of 6 patients received placebo capsules, identical in appearance, for a similar period. In the placebo group one patient was outpatient, one was hospitalized at the Psychiatric Hospital, and 4 remained at "Instituto de Resocialización Psiquiátrica La Sierrita". Of the latter, one patient was hospitalized for 2 years, two patients have been interns during 4 years and one patient have been hospitalized for 6 years. For our study we selected a higher dose of MEL than that administered by Shamir et al (19) since their results were not conclusive and MEL is a safe compound when used at the dose administered to our patients. In fact, a dose of 300 mg/day of MEL has been administered for 2 years to patients suffering from amyotrophic lateral sclerosis and it was well tolerated (23).

The AIMS scale was used for the evaluation of movements (20, 21) since it demonstrated sufficient psychometric properties (19, 22, 24, 26). AIMS has 12 items and it is the most widely used for the assessment of TD. Items 1 to 7 evaluate the abnormal movements in 3 regions of the body including the orofacial area, trunk and extremities and are expressed in a 5-point Likert scale (0 = none, 4 = severe). Only items 1 to 7 were evaluated in our patients. Item 1: Muscles of facial expression, e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning blinking, smiling, grimacing. Item 2: Lips and perioral area, e.g. puckering, pouting and smacking. Item 3: Jaw, e.g. biting, clenching, chewing, mouth opening, lateral movements. Item 4: Tongue. Rate only increases in movement both in and out of mouth. Not inability to sustain movement. Item 5: Upper (arms, wrists, hands, fingers). Include choreic and athetoid movements. Do not include tremor. Item 6:

Lower (legs, knees, ankles, toes), e.g. lateral knee movements, foot tapping, heel dropping, foot squirming, inversion and aversion of foot. Item 7: Neck, shoulders, hips, e.g. rocking, twisting, squirming, pelvic gyration. The summation of these 7 items can reach a peak value of 28. The other items (8 to 12) on the AIMS determine the overall severity, degree of disability caused by abnormal movements, the awareness that the patient has of the abnormal movements and dental status. We also used the Brief Psychiatric Rating Scale (BPRS) (25) for psychiatric evaluation in both groups (placebo and treated with MEL). No changes were observed in the BPRS during the study. Simultaneously, we evaluated the hepatic and renal function in all patients at the beginning and throughout the study. Only one of the authors (FC) evaluated patients with the AIMS scale.

The two-way analysis of variance (ANOVA), followed by the one-way ANOVA and the Student's t test were used to evaluate changes detected in the AIMS and BPRS scores of the placebo and MEL groups across the treatment time. The significance level was set at 0.05. Data are presented as mean ± standard error.

RESULTS

During treatment with MEL no adverse effects were shown and no patient withdrew from the study due to this cause or to worsening of the disease.

The initial values of BPRS in patients treated with MEL were 21.33 ± 4.88 (mean ± SE), while those treated with placebo were 26.33 ± 1.45. The difference was not significant, confirming that both groups, randomly chosen, had the same degree of psychiatric symptoms.

As for the results of AIMS, there were no significant differences among the values obtained initially. In patients treated with

MEL the values of AIMS were 13.86 ± 5.24 and in patients treated with placebo 15.83±1.64 suggesting a similar state of motor impairment in both groups (Table II). The results of one way ANOVA were $F_{3,24}$=1.313; p=0.2931 for the placebo group; $F_{3,28}$= 1.751; p=0.1794. During the 12 weeks of treatment with MEL or placebo there were no statistically significant differences in AIMS. However, in two patients treated with MEL it was possible to detect a significant decrease in AIMS. In one, the values fell from 13 points at the beginning to 5 points after 12 weeks of treatment. This was a 58 years old male schizophrenic patient with TD of 23 years of evolution, who has been taking risperidone (2 mg/day) and levopromazine (25 mg/day) during the last 4 years. The other was a 65 years old male schizophrenic patient with TD of 29 years of evolution who has been receiving levopromazine (50 mg/day) and biperidine (2 mg/day) for the last 6 years and whose AIMS values fell from 19 points at the beginning to 6 points after 12 weeks of treatment.

DISCUSSION

The use of MEL as adjuvant therapy seems to be well accepted for macular degeneration, glaucoma, protection of the gastric mucosa, irritable bowel syndrome, arterial hypertension, diabetes, side effects of chemotherapy and radiation in cancer patients or hemodyalisis in patients with renal insufficiency and, especially, for sleep disorders of circadian etiology (jet lag, delayed sleep-phase syndrome, sleep deterioration associated with aging) and in those related with neurological degeneration as in Alzheimer´s disease. The utility of MEL in anesthetic procedures has also been confirmed (27). The majority of studies document the very low toxicity of MEL over a wide range. Doses of 2 mg daily (28) for 6 months have been used with no clinically relevant differences in safety between MEL and placebo in vital signs, ECG, physical examination or endocrine functions; these results demonstrated short- and long-term efficacy and safety of MEL in elderly insomnia patients. Higher doses of MEL (21 mg daily) have been used during taxane chemotherapy, preventing or reducing the taxane-induced neuropathy (29). A single oral dose of 300 mg of MEL has also been administered (30) to study the possible mechanism of its radio-protective effect.

In the treatment of TD a result is estimated to be clinically significant when AIMS values are reduced more than 3 points (31, 32). In this study, only two patients treated with MEL showed clinical improvement within 12 weeks of treatment. Despite the interesting results achieved in these two patients, this research is limited by the small sample size. Moreover, the

TABLE II

EFFECT OF MELATONIN TREATMENT (20 mg/day, N=7) AND PLACEBO (N=6) ON THE VALUES OF THE ABNORMAL INVOLUNTARY MOVEMENTS SCALE (AIMS) IN PATIENTS WITH TARDIVE DYSKINESIA

	Weeks			
	0	4	8	12
Placebo	15.83 ± 1.64	13.5 ± 1.06	12.33 ± 1.23	11.67 ± 1.73
Melatonin	13.86 ± 5.24	12.57 ± 5.26	9.71 ± 4.57	9.29 ± 5.35
	NS*	NS	NS	NS

* No significant.

chronicity of the disease in institutionalized patients probably reflects a greater severity of symptoms. In spite of the possibility of having a type 2 error in the statistical analysis, the improvement of the clinical signs observed in these two patients merit a more detailed and extensive investigation on the effect of MEL on TD.

Additionally, unlike the MEL used in this work, in the study of Shamir *et al.* (19), which reported the effectiveness of the hormone (10 mg/day) in TD, the substance administered was a controlled release hormone, similar to the release pattern of endogenous MEL (33). However, the average drop of 2.45 ± 1.92 points on the AIMS, as reported by these authors, is not considered significant unless the abnormal movements are located only in one area (20). Furthermore, the clinical improvement of 30% of TD observed by Shamir *et al.* (19), has been questioned because other studies that evaluated different treatments of TD have shown an improvement higher than 30% (34, 35).

An association has been reported between the ATG haplotype in the gene encoding the receptor for MEL MTNR1A and schizophrenic patients that do not develop TD (36). It is possible that polymorphisms of genes encoding MEL receptors (MTNR1A and MNTR1B) establish significant differences in therapeutic response to MEL. Such genetic variations could be linked to the clinical improvement of over 60% observed in two patients in our study. On the other hand, the low bioavailability (average 18.9%) and large individual variation (average 17.7 fold) may also explain the different responses in subjects who take MEL orally. For some individuals a dose of 3 mg when taken to benefit sleep may induce drowsiness the day after; for others, whose bioavailability is low, this dose may not be sufficient to treat insomnia. Therefore, individualization of dose is suggested based on the serum or salivary MEL levels after MEL administration or adjusting the dose depending on the responses of the subjects. Drug interactions also influence the bioavailability of MEL. Hence, the need to clarify the pharmacokinetics of MEL and its interactions with other substances (37).

Another limiting factor in MEL treatment is the fact that this substance is considered a dietary supplement and therefore is not fully regulated by the Bureau of Food and Drug Administration of the United States, where many brands of MEL are sold (including the one used in this study). Factors such as contamination, adulteration and quantities that do not correspond with what is offered, among others, must be considered before reaching a final conclusion on the usefulness of this compound in the treatment of TD.

It would be necessary to conduct a multicenter, well controlled and long lasting study, with standardized MEL, whose purity leaves no room for doubt. This research should include a greater number of young patients with a shorter evolution of TD, which would be treated for a longer time.

The possibility that MEL is more effective in prevention than in the treatment of TD must be ruled out, due to results of previous experimental studies which suggest that free radical toxicity and oxidative stress play an important role in the pathophysiology of oro-facial dyskinesia induced by neuroleptics and that MEL could be used for prevention or treatment (38).

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