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Improvement of Movement Disorders with Mirtazapine: A Preliminary Open Trial

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SUMMARY: We performed a non-controlled open trial in 22 patients who had movement disorders. Patients received 30 mg of Mirtazapine per day. Twenty patients (90.9%) had a favorable response and their scores on the severity and functional scale improved after treatment. The time needed to control abnormal movements was 30 days in almost 70% of the subjects. Further randomized controlled trials could determine the effectiveness of Mirtazapine for movement disorders.

RESUMEN: Realizamos un estudio no controlado abierto en 22 pacientes, quienes tuvieron desórdenes del movimiento. Los pacientes recibieron 30 mg de Mirtazapina por día. Veinte pacientes (90.9%) tuvieron una respuesta favorable y sus puntajes en la severidad y escala funcional mejoraron después del tratamiento. El tiempo necesario para controlar los movimientos anormales fue 30 días en 70% de los pacientes. Posteriores estudios randomizados y controlados podrían determinar la efectividad de la Mirtazapina para desórdenes del movimiento

Movement disorders tend to be chronic and persistent. Drugs that are available to control and treat movement disorders are generally not very effective. Mirtazapine is an anti-depressant with a mechanism that is different from traditional drugs; that is why it has been referred to as a specific noradrenergic and serotoninergic drug (1-3). Recent reports of isolated cases have indicated that various movement disorders responded to Mirtazapine (4-6). To obtain more data about the potential effectiveness of Mirtazapine for treating movement disorders, we performed a non-controlled open trial on 22 patients.

PATIENTS AND METHODS

Patients who had tremor, dystonia, hemifacial spasms and tardive dyskinesia, with functional disability sufficiently severe to require pharmacological treatment and who came consecutively to our Movement Disorders Unit between January and December 2000 were included. Consent paper was signed previously.

Patients had not taken any treatment for their movement disorders at the moment of recruitment. We excluded patients with infectious or neurological diseases, pregnant women, patients with a clinically significant psychiatric diagnosis, patients who were taking hypnotic, ansiolytic or anti-depressant drugs as well as patients with another relevant disease. We used previously accepted clinical criteria to define the presence of tremor, dystonia, hemifacial spasm and tardive dyskinesia (7-11).

At the start of the study, we performed a complete neurological and general examination, which included complementary and hematological tests. At the time of each evaluation, severity and functional incapacity and response to treatment were evaluated by one of us (FA) on the basis of a modified scale (12) according to the following scoring system: 1 = none; 2 = intermittent, which may interfere only slightly with daily activities; 3 = moderate, present between 50% and 75% of the time, which interferes with several activities that the patient tends to avoid; 4 = severe, present 75% of the time or more, which limits many activities of the patient, who is unable to hold a regular job.

We started treatment with 15 mg of Mirtazapine administered at night; a week later, the dose was increased to 30 mg. Patients were assessed at the start of treatment, every week during the first two months and afterwards at least once a month. The main end-point was an improvement in the severity of the functional incapacity. We determined that therapy failed when patients did not respond favorably to Mirtazapine in 60 days. The secondary end-point was the time (in days) in which the patients reached their highest functional capacity. For the patients who showed adverse effects when the dose was increased, we reduced it to the previous one, and one or two weeks later we increased the dose again and then kept it at that level if it was tolerated by the patient. If they did not respond to treatment in 60 days, we dropped the Mirtazapine and indicated other therapeutic alternatives. The patients with depression could continue taking it.

We analyzed the severity and functional incapacity before and after treatment and the possible difference in time of response with non-parametric tests. The statistically significant level was $p<0.05$.

RESULTS

A total of 8 men and 14 women, with ages ranging from 27 to 89 years (median age: 57.5 years; percentiles 25-75%; 49-65 years) were studied. Tremor (40.9%) and dystonia (36.3%) (Table 1) were the most frequent movement disorders. Patients with hemifacial spasm were the youngest (51 ± 13.9 years). The idiopathic etiology (45.5%) predominated. Four patients had moderate depression. In patients with a vascular etiology, we found a focal motor deficit. Before starting treatment, the abnormal movement was severe in 13 patients (59%) and moderate in 9 patients (40.9%). In all cases, the movement disorder was present for more than four months.

A total of 20 patients (90.9%) responded favorably to treatment and improved their functional capacity by at least one or two points on the scale (Table 2). We found a significant statistical relation ($r_s = 0.96$; $p < 0.05$) between the scores obtained in the scale of severity and functional incapacity before and after treatment. Four patients (18.1%), two with tremor and two with dystonia, experienced complete functional recovery. Fourteen patients (63.6%) improved their condition to mild functional disability, and two (9%) shifted from the severe functional stage to the moderate functional stage. The etiology of these patients was idiopathic (n = 9, 45%), post-stroke (n = 5, 25%), family history (n = 5, 25%) and secondary to drugs in one case.

Two patients did not respond to treatment until two months later: one, the oldest, with idiopathic tremor, and another with dystonia secondary to thalamic infarcts. In both patients, treatment with Mirtazapine was continued for depression. Treatment compliance was good in all patients.

In the first month of treatment, 70% of the patients responded favorably. The abnormal movements of 19 patients (86.3%) improved between 8 and 60 days (median: 30, percentiles 25-75%: 15-30 days). The patient with linguofacial dyskinesia reached his peak improvement in more than 60 days.

The response to treatment was more rapid in the patients with hemifacial spasm (between 8 and 21 days) compared to the group with tremor and dystonia (from 15 to 60 days each) with a statistically significant difference ($p < 0.05$). The calculated probability of a favorable response between 15 and 60 days of treatment with Mirtazapine was 82% for tremor and 79% for dystonia; after 60 days, the functional change could be expected to occur in 0.8% and 13% of the patients, respectively. Meanwhile, the probability of hemifacial spasm responding between 8 to 21 days was estimated to be 69%, and no more than 21% favorable modifications over a greater period of time should be expected (Table 2).

Six patients showed slight adverse events. A patient had somnolence and another developed cramps in the lower limbs. Both effects appeared when the dose of Mirtazapine was increased to 30 mg and disappeared when the dose was reduced. With a new increase the symptoms appeared again and therefore the causal relationship was definitive. We reduced the dose in these cases to 15 mg and kept the dose at this level. Two patients reported increased appetite, and two had dry mouth. None of the patients had increases in their hepatic transaminases or alterations in other hematological tests during the follow-up period.

DISCUSSION

In this study we found that Mirtazapine, used as a single drug, improved the functional condition of 90% of the patients with tremor, dystonia, hemifacial spasm and tardive dyskinesia. The majority of the patients experienced significant control over their involuntary movements, improving their functional capacity in a shorter lapse of time (70% achieved a response within the first 30 days). Although response to treatment was relatively variable between individuals, it was evident that the patients experienced clinically significant improvement, regardless of their age, cause of disorder or initial degree of severity and functional incapacity.

Patients improved without showing any marked sedation and with few adverse events during the follow-up period. Cramps in the lower limbs of one of our patients have not been described before.

Mirtazapine could have a broader biochemical spectrum rather than a narrow effect on serotonin (1). Mirtazapine could have binding sites in the basal ganglia output structures and, through this mechanism, might be improving movement disorders.

The present study, although open and non-controlled, provides more data about the potential benefits of Mirtazapine as treatment for movement disorders. Randomized controlled trials need to be undertaken to determine the effectiveness of the drug and to confirm the preliminary results that we have found in our study.

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