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Increase in Body Weight after Pramipexole Treatment in Parkinson's Disease

Hatice Kumru, MD, Joan Santamaria, MD,* Francesc Valldeoriola, MD, Maria J. Marti, MD, and Eduardo Tolosa, MD

Neurology Service, Hospital Clínic de Barcelona and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

Abstract: **Body weight changes occur during the clinical course of Parkinson's disease (PD) and with surgical treatment, but the effect of dopaminergic treatment on weight is unknown. Body mass index (BMI), Hamilton depression scale score (HDS), and Unified Parkinson's Disease Rating Scale III (UPRS-III) were measured before and 3 months after starting pramipexole in 28 PD patients. Pramipexole produced a significant weight increase, as well as motor and mood improvement ($P < 0.001$). HDS and BMI changes were mildly related ($P = 0.05$). A direct effect of pramipexole on limbic D_3 receptors involved in the control of feeding may be responsible for weight gain in PD.** © 2006 Movement Disorder Society

Key words: Parkinson's disease; pramipexole; weight gain

The cardinal symptoms of Parkinson's disease (PD) include a combination of tremor, bradykinesia, rigidity, and postural instability. Other nonmotor symptoms and signs may complicate its course.[1] Patients with PD, for instance, have lower weights than their matched controls. This decrease in weight starts years before the diagnosis and it is not caused by reduced energy intake.[2] It has been related to increased energy expenditure caused by rigidity or dyskinesia, difficulties in feeding or in access to food.[2–6] On the other hand, an increase in weight occurs in PD patients after pallidotomy,[4,6] after pallidal stimulation,[6] or subthalamic deep brain stimulation (DBS).[3] This weight gain after surgery has been attributed to a decrease in energy expenditure—mainly due to reduction in dyskinesia, tremor, or rigidity, and to a lack of adjustment between decreased energy expenditure and energy intake. The effect of dopaminergic treatment on body weight in PD, however, is not well known. A recent report has described a significant loss of weight 2 years after starting levodopa in previously untreated PD patients.[7] However, because this decrease was not present the first year of treatment, it is unclear if it was related with L-dopa treatment or to progress of the disease itself.

While doing research on the effect of pramipexole on somnolence in patients with PD, we observed that weight gain occurred often in these patients. In this work, we describe the effect of pramipexole on body weight and its relation to the motor and mood changes that occur during treatment.

PATIENTS AND METHODS

A total of 28 patients with PD (8 female, 20 male; mean age, 63.2 ±8.8 yr and mean PD duration, 6.8 ±4.8 yr) being on stable medical treatment and without receiving dopamine agonists at least during the last month and needing additional antiparkinsonian medication were included. Concurrent medications that patients were taking were as follows: L-dopa/carpidopa (number of patients [n] = 27, mean daily dose of 558.8 ±271.4 mg), entacopone (n = 5), selective serotonin reuptake inhibitors (n = 7), amitriptyline (n = 2), clomipramine (n = 2), selegiline hydrochloride (n = 3), amantadine (n = 1), benzodiazepines (n = 3). These drugs were unchanged throughout the study period.

Clinical assessments included the Unified PD Rating Scale (UPDRS) score subscale III for motor evaluation, Hoehn & Yahr scale (H&Y), Schwab &England daily living scale (S&E), and the UPDRS IV for evaluation of dyskinesia. At the same visit, the Hamilton depression scale (HDS) was completed. Because the HDS does not contain a subjective evaluation by the patient of his/her mood state, we also used the ninth question of the Pittsburgh Sleep Quality Index (PSQI)[8] to evaluate possible changes in mood not detected by the HDS: "How much

*Correspondence to: Dr. Joan Santamaria, Neurology Service, Hospital Clinic de Barcelona, c/ Villarroel, 170, Barcelona, 08036 Spain. E-mail: jsantama@clinic.ub.es

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TABLE 1. *BMI of patients pre- and post-pramipexole*

BMI	Number of patients	
	Prepramipexole	Postpramipexole
Underweight (<18.5)	1	0
Normal weight (18.5-24.9)	6	5
Overweight (25-29.9)	17	15
Obese (30 or more)	4	8

BMI, body mass index.

of a problem has it been for you to keep up enough enthusiasm to get things done?": 0 = no problem at all, 1 = only a very slight problem, 2 = somewhat of a problem, 3 = a very big problem.

Body weight in all patients was measured between 8 and 9 AM before breakfast, pre- and postpramipexole. Body mass index (BMI) was calculated and classified as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese (≥30.0).

After the baseline evaluation pramipexole was begun in all patients and gradually increased in 1 month to a mean maintenance daily dose of 2.1 ± 0.3 mg (range, 1.1–3.2 mg). After 2 months of stable pramipexole dose, all the clinical procedure was repeated. We also systematically asked the patients and scored accordingly if, after treatment, they had less, equal, or more hunger than before starting pramipexole. Patients were asked for the presence of side effects such as nausea, vomiting, peripheral edema, changes in behavior, or any other symptoms that appeared during treatment. The protocol was approved by the Institutional Review Board, and all the patients signed an informed consent form.

Statistical Analysis

The results were expressed as mean ± standard deviation. Paired *t* test was performed to evaluate pre- and posttreatment differences on UPDRS, H&Y, S&E, HDS, and body weight parameters, and Wilcoxon *t* test to evaluate answers to the ninth question of PSQI. In addition, Pearson or Spearman rank correlation were used to calculate percentage of changes of BMI, of UPDRS III (motor), of HDS, and UPDRS IV (dyskinesia) changes pre- and postpramipexole and age.

RESULTS

Pramipexole produced motor improvement in all patients: UPDRS III, 16.5 ± 4.5 before versus 8.6 ± 4.5 after treatment ($P < 0.001$); H&Y, 1.9 ± 0.4 versus 1.4 ± 0.4 ($P < 0.001$); and S&E, 85.7 ± 5.7 versus 96.4 ± 4.9, ($P < 0.001$), respectively. There was a mild increase in dyskinesias after treatment (UPDRS-IV, 0.3 ± 0.8 before and 0.7 ± 1.1 after treatment; Wilcoxon test $P = 0.02$).

Body Weight Changes

There was a significant increase in weight after pramipexole (74.8 ± 13.2 kg before vs. 77.4 ± 13.2 kg after, $P < 0.001$; BMI, 27 ± 4 before vs. 28 ± 4.2 after, $P < 0.0001$; Table 1; Fig. 1). Of 28 patients, 22 (7/15 = female/male) increased their weight (range, 0.5–8 kg), whereas the other 6 did not: 2 of them did not change their weight, and 4 lost body weight (range, 0.5–2 kg).

No patient reported dysphagia or difficulty to reach food pre- or postpramipexole. Of 22 patients with weight increase, 12 reported more hunger during treatment but the other 10 did not report any change. We did not assess calorie intake. Nausea was reported by 4 patients but improved spontaneously in less than 2 days in all of them. No one reported vomiting or clinically relevant peripheral edema. Neither patients nor their relatives reported changes in the patients eating behavior during the treatment.

Mood Changes

The HDS score improved with treatment significantly (6.8 ± 4.9 vs. 2.7 ± 3.4; $P < 0.001$), although no patient was considered depressed at any time in the study. The score on the ninth question of the PSQI also improved significantly with treatment (1 ± 1.1 vs. 0.4 ± 0.6, $P = 0.009$, Wilcoxon *t* test).

Relation Between BMI Changes, Mood Changes, Clinical Improvement, Dyskinesia, and Age

There was no relation between changes in BMI and UPDRS III (rho, −0.09; $P = 0.7$); UPDRS IV (dyskinesia; rho, 0.06; $P = 0.8$); age (rho, 0.037; $P = 0.9$), but

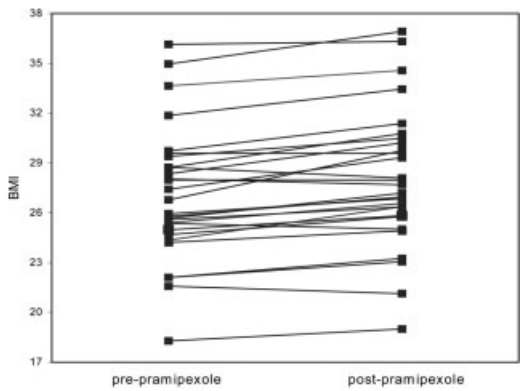

FIG. 1. Body mass index (BMI) of each patient pre- and post-pramipexole.

the relation between the percentage of changes in BMI and HDS was slightly significant (rho, 0.37; $P = 0.05$).

DISCUSSION

We report here that weight gain occurs in patients with PD after treatment with pramipexole. This increase in weight is not related to changes in the motor signs and appears concurrently with a modest improvement in mood. We speculate that a direct or indirect action of pramipexole on the feeding centers of the hypothalamus could be responsible for it. Dopamine is needed to integrate and process the neuronal signals necessary to stimulate and maintain feeding, even in the absence of leptin.[9] It is also associated with pleasurable and rewarding events and may reinforce positive aspects of feeding, facilitating the integration of sensory cues related to hunger, initiating the search for food and its consumption.[9] In addition, dopaminergic neurons in the substantia nigra and ventral tegmental area project to nucleus accumbens and from there to the lateral hypothalamus, an area that regulates feeding.[10] Finally, dopamine-deficient mice are hypophagic and die rapidly of starvation, whereas replacement of DA restores feeding without fully rescuing coordination or initiation of movement.[11] These experimental findings suggest that dopaminergic mechanisms may have a role in the decrease in weight that is observed in untreated PD patients[2] and the weight gain that occurs after DBS,[3,6] pallidotomy,[4] pallidal stimulation,[6] as well as after pramipexole. In opposition to these results, a recent report described a significant loss of weight 2 years after starting L-dopa in previously untreated PD patients.[7] However, because this decrease was not present during the first year of treatment, it is unclear whether or not it was related with L-dopa or with progress of the disease itself. It is also possible that the greater ability of pramipexole to bind D_3 receptors (predominant in the limbic system)[12] compared to L-dopa might explain the different effects of both drugs on weight.

A significant improvement in mood was observed after pramipexole, despite that no patient was considered clinically depressed at any point in the study. Mental depression is associated with loss of food intake and weight loss,[13] and antidepressant treatment (anticholinergic, serotoninergic, and noradrenergic drugs) causes a variable extent of weight gain.[14] During clinical trials, it has been shown that pramipexole has mood-stabilizing or -elevating effects.[15] In this study, many patients and their partners reported a decrease in anxiety and apathy as well as enhanced attention span and interest in daily activity with pramipexole. It could be speculated that this discrete change in mood would produce an increased interest in food and eating. However, the mood change was mild and the correlation with the increase in weight was not strong. In addition, in studies reporting weight gain after surgery for PD mood changes were not related to weight gain.

In conclusion, weight gain may occur in PD patients treated with pramipexole, presumably through a direct effect on D_3 receptors in limbic system.[12] This effect may be relevant and physicians need to be aware of it. Pramipexole, on the other hand, might be of particular help in the treatment of underweight PD patients.

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