Kobe J. Med. Sci., Vol. 56, No. 5, pp. E214-E219, 2010

The Effect of Pramipexole on Depressive Symptoms in Parkinson's Disease.

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Received 8 September 2010/ Accepted 8 October 2010

Key Words: depression, indecisiveness, Parkinson's disease, Self-Rating Depression Scale, Unified Parkinson Disease Rating Scale, pramipexole

ABSTRACT

Depression is a common occurrence in patients with Parkinson's disease (PD). Pramipexole is a dopamine agonist that has been used to treat both motor and non-motor symptoms associated with PD. We conducted a study to elucidate the effect of pramipexole on each of the depressive symptoms as assessed by the Zung Self-Rating Depression Scale (SDS). Twenty patients with PD were treated with pramipexole 1.5-3.0 mg daily for 2-3 months. The SDS and the Unified Parkinson Disease Rating Score (UPDRS) were measured in each subject before and after the treatment. Both the SDS and the UPDRS decreased significantly after treatment with pramipexole. Individual assessment of each item in the SDS indicated that "crying spell", "confusion", "psychomotor retardation", "emptiness", and "dissatisfaction" symptoms improved significantly following treatment, while "depressed affect", "decreased libido", "constipation", and "indecisiveness" symptoms were worse after the treatment. As the symptom of "indecisiveness" did not respond to treatment, it might be an essential symptom in patients with PD.

INTRODUCTION

Psychiatric symptoms, including depression, anxiety, apathy, and anhedonia are known to occur frequently in patients with Parkinson's disease (PD), and recently have attracted considerable attention [1,10]. Although the associated depression is due, at least partly, to the imposed limitations of daily activity, a consistent relationship between the severity of depression and the degree of physical disability from PD has not been identified. As many of the symptoms of depression in patients with PD do not meet the DSM-IV criteria for major depression, the psychiatric problems in individuals with PD should be discussed separately from those in the general population.

Pramipexole, a non-ergot dopamine receptor agonist, has been reported to improve both motor and non-motor symptoms in patients with PD. [11] Although antidepressant effects have been suggested in all types of dopamine agonists, pramipexole has been shown to be more effective than pergolide on the symptoms of depression in patients with PD [11]. Pramipexole has stronger affinity to D3 receptors than do the ergot agonists; thus, the mesolimbic dopamine pathway is thought to be involved in the depression that affects

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patients with PD. [11] However, which of the associated depressive symptoms is most responsive to pramipexole has not been determined. The purpose of this study was to elucidate the effect of pramipexole on each of the depressive symptoms associated with PD.

MATERIALS AND METHODS

Subjects

Subjects consisted of 20 patients (9 men and 11 women) suffering from PD who attended the outpatient clinic of Kobe University Hospital. The mean age of the subjects was 67.3±9.4 years. The diagnosis of PD had been established in all subjects by the presence of Parkinsonism symptoms (i.e., akinesia/bradykinesia, rigidity, resting tremor, and retropulsion). The diagnosis was confirmed by magnetic resonance imaging (MRI) results that revealed no abnormalities such as multiple cerebral infarctions and localized brain atrophy. All subjects were classified as Parkinson Stage II or III, according to the Hoehn and Yahr scale, and had PD an average of 5.9 (±6.4) years. Patients with dementia or severe psychiatric disease were excluded.

Eleven patients had no history of treatment with dopamine agonists prior to study participation ("New" Group, n=11). Pramipexole was started at 0.125 mg once a day, then titrated for less than two months in this group. Nine patients had received pergolide treatment for >3 months prior to study participation ("Change" Group, n=9). Pergolide was replaced by pramipexole (0.75 mg of pergolide to 0.5 mg of pramipexole) in this group.

All participants were treated with 1.5-3.0 mg/day of pramipexole for a period of 2-3 months.

Assessments

The Zung Self-Rating Depression Scale (SDS) was used to assess changes in the affective, psychological, and symptomatic symptoms of depression [13]. Each participant completed this questionnaire before and after the study treatment.

The disabling affects of PD were evaluated using the Unified Parkinson Disease Rating Scale (UPDRS) administered by one of the authors before and after the treatment. Both the UPDRS and the SDS evaluations were performed on the same assessment day pre- and post-treatment.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Kobe University Ethical Committee. All participants provided informed, written consent.

Data analysis

Changes in the SDS and UPDRS scores from baseline to post-treatment were analyzed using paired Student's *t*-test. *p*-values <0.05 were considered to be statistically significant. Comparing between total SDS score and total UPDRS scores, Pearson's correlation coefficients were calculated. Statistic analyses were performed with StatView version 5.0 and SAS version 8.02 (SAS Institute, Cary, NC).

RESULTS

All 20 participants completed the study with no adverse events. The average baseline scores for the UPDRS and the SDS in all participants were 37.9$\pm$14.3, and 46.4$\pm$6.2, respectively. After 2-3 months of pramipexole treatment, both the average UPDRS score and the SDS score decreased significantly (30.0$\pm$14.1, p=0.0003, and 42.3$\pm$7.2, p=0.0005,

respectively). There was no statistical correlation between changes in the UPDRS scores and those in the SDS scores. Individual scores for each of the items in the SDS scores before and after pramipexole treatment are shown in Figure 1. As indicated, the five items, "crying spell", "confusion", "psychomotor retardation", "emptiness", and "dissatisfaction" improved significantly (p <0.05) following pramipexole treatment. Of the remaining 15 items, nine showed slight improvement, two remained essentially unchanged, and four items ("depressed affect", "decreased libido", "constipation", and "indecisiveness") were slightly worse after treatment, although these changes were not statistically significant.

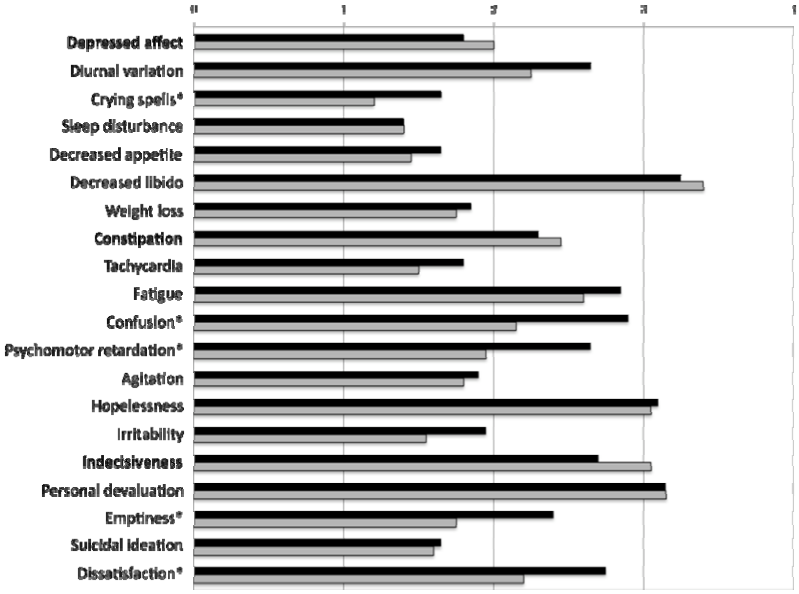

Figure 1. Average scores for each item of the Zung Self-Rating Depressive Scale (SDS) in all participants. (Closed bars: before pramipexole treatment, open bars: after pramipexole treatment, *: p <0.05)

Figure 2 shows changes in the SDS and UPDRS scores in the two study Groups. In the "Change" Group (n=9), the average SDS score improved significantly following pramipexole treatment (47.0 $\pm$ 3.9 to 41.11$\pm$5.9, p=0.001**).** Only slight decreases in the average SDS scores occurred in the "New" Group (n=11) following treatment (45.6$\pm$7.7 to 43.2$\pm$8.3, p=0.086). On the contrary, a significant decrease occurred in the average UPDRS scores of the participants of the "New" Group (37.4$\pm$15.1 to 26.9$\pm$13.1, p=0.002), but not in the "Change" Group (38.6$\pm$14.2 to 33.8$\pm$15.1, p=0.088).

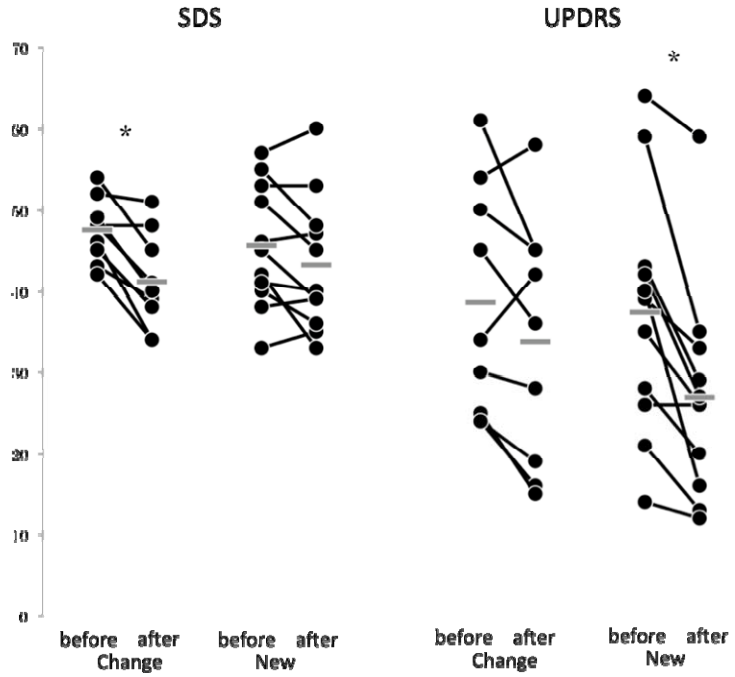

Figure 2. Changes in the Zung Self-Rating Depressive Scale (SDS) and the Unified Parkinson Disease Rating Scale (UPDRS) scores in the "Change" Group and the "New" Group before and after pramipexole treatment. (Grey bar: average group score, *: $p < 0.05$)

DISCUSSION

There are numerous scales used for the evaluation of depression. The Hamilton Depression Scale [4], the Montgomery Asberg Depression Rating Scale, [8] and the Lieberman Lyons Scale [9] have been validated for the assessment of depression in patients with PD. Other scales, such as the Zung Self-Rating Depression Scale (SDS), also have been used to assess depression associated with PD [6,7, 11]. All of these scales are helpful for the screening of depression, but are somewhat problematic for confirming the diagnosis of depression in patients with PD.

In this study, both the UPDRS scores and the SDS scores improved significantly following pramipexole treatment. There was no correlation between the degree of improvement in the UPDRS and the SDS. In our previous study, scores of the UPDRS Part III (motor functions) did not correlate with SDS scores in patients with PD [5]. Improvement in the UPDRS score does not seem to be responsible for the reduction in depressive symptoms. The effects of pramipexole on the assessed symptoms of depression are unlikely to occur as a result in improvement in motor function.

There are three types of depressive conditions that may be present in patients with PD: (1) a major depression that is unrelated to the PD; (2) a reactive depression that is proportional to the disabilities due to PD; and (3) neuropathological changes associated with PD. The first type of depression must be treated as standard depression, while the second type of depression is responsive to treatment of the symptoms of PD. It remains unclear how the third type of depression should be treated. Treatment of the symptoms associated with PD might not be helpful in reducing psychiatric problems, especially in the third type of depression. Presumably, there can be no effective treatment for this type of depression until

treatment targeting the specific neuropathological changes in PD is available. Before initiating treatment for psychiatric symptoms in patients with PD, it is essential to clarify which type of depression is present.

Despite high scores in depression assessment scales, suicidal ideation is rare in patients with PD [1]. Characteristic psychiatric problems among patients with PD are apathy and anhedonia. The anatomical localization of these symptoms is considered to be in the so-called "reward systems", i.e., in the limbic cortex belonging to the mesolimbic system [12]. The D3 dopamine receptors are widely expressed in the mesolimbic pathways from the ventral mesencephalon to the nucleus accumbens and the amygdala [2]. This suggests that the D3 dopamine receptor plays an important role in the psychiatric problems of patients with PD.

Rektorova *et al.* reported that pramipexole was more effective than pergolide in reducing depressive symptoms in patients suffering from PD [11]. As shown in Figure 2, the "Change" (from pergolide to pramipexole) Group showed significant improvement in SDS without changes in UPDRS. On the contrary, the "New" Group showed no remedy in SDS despite of significant amelioration in UPDRS. It is comprehensible that the pramipexole was more effective on motor symptoms in the "New" Group than those in the "Change" Group because pergolide had had anti-parkinsonian effects on the latter. Pergolide has a strong affinity to both D2 and D1 receptors. The anti-parkinsonian effects of a dopamine agonist are displayed through D2 receptors. Pramipexole did not exhibit a greater benefit than pergolide for the treatment of PD via D2 receptors. In SDS, however, pramipexole showed better effect on depressive symptoms than pergolide. Pramipexole has more potent affinity to D3 receptors than does pergolide [3]. Stimulation of the D3 dopamine receptors might be responsible for the antidepressant effect of pramipexole [2]. Thus, pramipexole might improve directly some of the psychiatric symptoms associated with PD.

In this study, although pramipexole decreased the scores of many of the items in the SDS, "depressed affect", "decreased libido", "constipation", and "indecisiveness" items worsened following pramipexole treatment. Both "depressed affect" and "decreased libido" might be related to apathy and anhedonia those are well-known psychological characteristics in PD. "Constipation" is not only a common symptom in patients with PD, but also is an adverse effect of many of the anti-parkinsonian drugs. In our previous study, "indecisiveness" is a characteristic symptom in patients with PD compared to patients with spinocerebellar degeneration that causes similar disabilities in daily life [5]. Although its anatomical localization is unknown, the symptom of "indecisiveness" might be the most common psychiatric manifestation in patients with PD.

Even pramipexole's affinity to D3 receptors appears to have no effect on some psychiatric symptoms, including "indecisiveness". A totally new pharmacologic agent having a unique mechanism to relieve the symptom of mental problems in PD must be required.

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