Hiroshima J. Med. Sci.
Vol. 60, No. 4, 79~82, December, 2011
HIJM 60−15

New Dopamine Agonist Pramipexole Improves Parkinsonism and Depression in Parkinson's Disease

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ABSTRACT

Previous studies have shown that pramipexole might have the potential to improve depressive symptoms in patients with Parkinson's disease. To provide more evidence, in five Japanese patients at Hoehn & Yahr stage 1-3 we evaluated the Unified Parkinson's Disease Rating Scale (UPDRS), Hamilton Depression Rating Scale (HAMD) and Montgomery Åsberg Depression Rating Scale (MADRS) at our hospital. After the pramipexole treatment, each total score of UPDRS, HAMD and MADRS significantly decreased compared with that before the treatment. Our data indicate that pramipexole improves depressive symptoms in patients with Parkinson's disease.

Key words: *Parkinson's disease, Depression, Pramipexole, UPDRS, MADRS, HAMD*

It has been reported that depression is pervasive in cases of Parkinson's disease, and that approximately 40% of patients with Parkinson's disease suffer from depression at least once during the course of their disease[1,3,6,7]. Depression may occur as a result of the monoamine deficiency that characterizes Parkinson's disease. Pramipexole is a new nonergoline dopamine agonist with D2 and preferential D3 dopamine receptor activity[9]. Switching from bromocriptine, pergolide or ropinirole to pramipexole in an overnight schedule is safe. Pramipexole improves depressive symptoms in patients with Parkinson's disease, mainly through a direct antidepressant effect[1]. Kano et al suggested that pramipexole treatment had antidepressant effects in depressive parkinsonian patients and also ameliorates the Hamilton Depression Rating Scale (HAMD) score in nondepressive parkinsonian patients in addition to motor function[8]. However, evidence of the efficacy of antidepressants in this population is still lacking. The aim of this paper is to report the effects of pramipexole on the depressive and functional status of patients with Parkinson's disease, observed in our hospital.

SUBJECTS AND METHOD

The subjects were five patients with Parkinson's disease (Table 1). Mean age at examination was 67.4 ± 14 years (46-82 years in distribution). Mean age at onset of Parkinson's disease was 61.2 ± 14 years (44-77 years in distribution). Mean duration of Parkinson's disease was 6.2 ± 4.2 years (2-12 years in distribution). Mean Hoehn & Yahr (HY) stage was 2.2 ± 1.1 (1-3 in distribution).

Several doses (0.375-1.5 mg/day) of pramipexole were taken for 4 weeks by the 5 patients, respectively. Other anti-parkinsonian drugs (levodopa, selegiline, cabergoline, etc.) and complementary treatments were kept unchanged.

The symptoms of parkinsonism were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), which is composed of four parts. Part 1 evaluates the functions of mentation, behavior and

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mood; part 2 the activities of daily living; part 3 the motor functions; and part 4 evaluates the complications induced by anti-parkinsonian drugs.

The symptoms of depression were evaluated using HAMD and Montgomery Åsberg Depression Rating Scale (MADRS).

RESULTS

Summary of Pramipexole Treatment

Table 1 shows the clinical characteristics and evaluation of UPDRS, HAMD and MADRS before and after the pramipexole treatment.

Precise Case Review

Case 1: A 77-year old female. Her chief complaint was tremor of the left hand. Family history and past history were not significant. Her present illness was resting tremor of the left hand since 2002. She visited a neurologist in our hospital in May 2005. The symptoms were mild resting tremor of her left hand with rigidity and hypokinesia in her left upper extremity, but no disturbance of postural reflex. She was diagnosed with Parkinson's disease at HY stage 1. Total UPDRS, HAMD and MADRS scores were 24, 13, and 10, respectively. Brain Magnetic Resonance Imaging (MRI) was normal. One mg/day of pramipexole was taken for 2 weeks in July 2005. Then 1.5 mg/day of pramipexole was taken for the following 2 weeks in August 2005. As a result of the treatment for 4 weeks, the resting tremor and hypokinesia improved. The total UPDRS, HAMD and MADRS scores became 14, 7, and 3, respectively.

Case 2: An 82-year old female. Her chief complaint was gait disturbance. Family history and past history were not significant. Her gait became slow in 2002. A stooped posture and gait disturbance appeared in 2004. She visited a neurologist in our hospital in June 2005. The symptoms were resting tremor and rigidity in her four extremities (the right side was dominant), hypokinesia, and disturbance of postural reflex, as well as disappearance of arm swing on the right side while walking. She was diagnosed with Parkinson's disease at HY stage 3. Total UPDRS, HAMD and MADRS scores were 48, 22, and 20, respectively. Brain MRI was normal. One mg/day of pramipexole was taken for 2 weeks in July 2005, and then 1.5 mg/day of pramipexole was taken for the following 2 weeks in August 2005. As a result of the treatment for 4 weeks, the resting tremor and hypokinesia of the lower extremities improved. Total UPDRS, HAMD and MADRS scores became 38, 15, and 12, respectively.

Case 3: A 46-year old female. Her chief complaint was hypokinesia of the right upper extremity. Family history and past history were not significant. Hypokinesia and disturbance of elaborate movements in the right extremity appeared in 2003. The symptoms had gradually extended to the right lower extremity. She visited a neurologist at our hospital in May 2005. A masked face and low voice, and mild resting tremor and rigidity in her right extremities with hypokinesia were observed. She

Table 1. Summary of UPDRS, HAMD and MADRS before and after the pramipexole treatment

case	sex	age at exam (years)	age at onset of PD (years)	duration of PD (years)	HY stage	UPDRS A	UPDRS B	HAMD A	HAMD B	MADRS A	MADRS B	dose of PPX (mg/day)
1	female	77	74	3	1	24	14	13	7	10	3	1.5
2	female	82	77	5	3	48	38	22	15	20	12	1.5
3	female	46	44	2	1	9	3	14	6	15	6	0.5
4	male	69	57	12	3	72	61	25	22	32	26	0.5
5	female	63	54	9	3	48	39	8	5	6	1	0.375

UPDRS: Unified Parkinson's Disease Rating Scale
HAMD: Hamilton Depression Rating Scale
MADRS: Montgomery Åsberg Depression Rating Scale
PPX: pramipexole
PD: Parkinson's disease
HY stage: Hoehn & Yahr stage
A: before the PPX treatment, B: after the PPX treatment

was diagnosed with Parkinson's disease at HY stage 1. Brain MRI was normal. One hundred mg/day of levodopa (10 mg/day of carbidopa content) was taken from December, 2004. The symptoms of parkinsonism slightly improved. Two and half mg/day of selegiline, a monoamine oxidase-B inhibitor, was added from January 2005. Then the symptoms of parkinsonism improved further. Neurological and psychological examinations in June 2005 were as follows: total UPDRS score: 9 (Part 1: 2), total HAMD score: 14, and total MADRS score: 15. Half mg/day of pramipexole was added from July 2005. As a result of the pramipexole treatment for 4 weeks, hypokinesia and pain of right extremities and back pain improved. Total UPDRS, HAMD and MADRS scores became 3, 6, and 6, respectively.

Case 4: A 69-year old male. His chief complaint was gait disturbance. Family history and past history were not significant. A stooped posture, walking with short steps, a masked face, hypokinesia, and a low voice appeared in 1993. These symptoms gradually progressed. He visited a neurologist in our hospital in 1996. Neurological findings and examination were as follows: symptoms were cog-wheel rigidity, resting tremor of both hands, hypokinesia, disappearance of arm swing, disturbance of postural reflex, constipation, and pollakiuria during the night. He was diagnosed with Parkinson's disease at HY stage 3. Brain MRI was normal. Clinical course was as follows: anti-parkinsonian therapy began with levodopa from 1996. Anti-parkinsonian drugs such as pergolide, cabergoline, taripexole, and doroxydopa were added with the progress of parkinsonism. Three hundred mg/day of levodopa (75 mg/day of benzeraside content), 300 mg/day of droxydopa, 1.5 mg/day of pergolide, 0.5 mg/day of cabergoline, and 0.4 mg/day of taripexole were being taken at the time of May 2005. Neurological and psychological examinations in May 2005 were as follows: total UPDRS score: 72 (Part 1: 8), total HAMD score: 25, and total MADRS score: 32. Half mg/day of pramipexole was added from June 2005. As a result of the pramipexole treatment for 4 weeks, resting tremor, rigidity and hypokinesia improved slightly. Total UPDRS, HAMD and MADRS scores became 61, 22, and 26, respectively.

Case 5: A 63-year old female. Her chief complaint was resting tremor of the left hand. Family history and past history were not significant. The chief complaint was resting tremor of left hand which had appeared in 1997. The symptom had gradually extended to the entire left upper extremity, and then the lower left extremities. Rigidity of the left upper extremity, slow movement and gait disturbance appeared in 2001. She visited a neurologist at our hospital at that time. Neurological findings and examination were as follows: symptoms were moderate rigidity and resting tremor in the four extremities (the left side was dominant) with tongue tremor, hypokinesia and disturbance of postural reflex. She was diagnosed with Parkinson's disease at HY stage 3. Brain MRI was normal. Her parkinsonism had been well controlled with 200 mg/day of levodopa (20 mg/day of carbidopa content), 3 mg/day of trihexyphenidyl and 0.25 mg/day of cabergoline. Total UPDRS, HAMD and MADRS scores became 48, 8 and 6, respectively. Because rigidity of the left lower extremity and tremor of the left hand were moderate, 0.375 mg/day of pramipexole was added from July 2005. As a result of the pramipexole treatment for 4 weeks, the rigidity and hand tremor slightly improved. Total UPDRS, HAMD and MADRS scores became 39, 5, and 1, respectively.

DISCUSSION

It was reported that pramipexole helped safely alleviate the symptoms of depression and was comparable to fluoxetine, a selective serotonin reuptake inhibitor[4]. In this study, depression was also reported to improve according to the effects of pramipexole on parkinsonism in the patients. The depression rating scales such as HAMD and MADRS were very useful for finding out depression in parkinsonian patients. Examination of their HAMD and MADRS scores showed that all the patients had depression before pramipexole treatment. The UPDRS, HAMD and MADRS total scores after the pramipexole treatment significantly decreased compared with those before the treatment. Therefore, the symptoms of both parkinsonism and depression were improved by the pramipexole treatment. In cases 4 and 5, the HAMD score changes were not so remarkable. A placebo is known to have a large effect in cases of slight depression strikes[4]. For patients in the early stage of Parkinson's disease, treatment with pramipexole is an option[1,2,8,9]. By being treated with pramipexole, they may be able to delay treatment with levodopa[1,2,8,9]. Case 3 is the youngest patient in this trial. She has already begun treatment with levodopa. Pramipexole treatment improved her parkinsonism and depression, and will yield further benefits to her. Pramipexole has its own side effects: headache, hyperalgesia, nausea and vomiting, sedation and somnolence, decreased appetite and subsequent weight loss, orthostatic hypotension, insomnia and hallucinations[1,2,8,9]. In our cases, none of these side effects appeared.

The monoamine deficiency characterizes Parkinson's disease[5]. Not only nigral dopamine neurons (A9 neurons) but also dopamine neurons of the ventral tegmental area (A10 neurons) in the mesolimbocortical system are lacking in Parkinson's disease. It has been suggested that pramipexole, a nonergoline dopamine agonist with D2 and preferential D3 dopamine receptor activity, might improve dysfunction of the mesolimbocortical system related with emotion[2]. In our cases, the pramipexole

trial was just 4 weeks. The new dopamine agonist pramipexole yielded benefits in parkinsonian patients with depression in our hospital. Further long term trial and additional cases are necessary for future research.

(Received August 6, 2010)
(Accepted September 20, 2011)

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