– differential effect on low and high frequency SEPs. Clin Neurophysiol 2006;117:2221–7.
Dum RP, Strick PL. The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci 1991;11:667–89.
Enomoto H, Ugawa Y, Hnanajima K, Yuasa K, Mochizuki H, Terao Y, et al. Decreased sensory cortical excitability after 1 Hz rTMS over the ipsilateral primary motor cortex. Clin Neurophysiol 2001;112:2154–8.
Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE. Multiple non-primary motor areas in the human cortex. J Neurophysiol 1997;77:2164–74.
Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117:845–50.
Gerschlager W, Siebner HR, Rothwell JC. Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 2001;57:379–80.
Hosono Y, Urushihara R, Harada M, Murase N, Kunikane Y, Shimazu H, et al. Comparison of monophasic versus biphasic stimulation in rTMS over premotor cortex: SEP and SPECT studies. Clin Neurophysiol 2008;119:2538–45.
Hummel FC, Heise K, Celnik P, Floel A, Gerloff C, Cohen LG. Facilitating skilled right hand motor function in older subjects by anodal polarization over the left primary motor cortex. Neurobiol Aging, in press.
Ishikawa S, Matsunaga K, Nakanishi R, Kawahira K, Murayama N, Tsuji S, et al. Effect of theta burst stimulation over the human sensorimotor cortex on motor and somatosensory evoked potentials. Clin Neurophysiol 2007;118:1033–43.
Jeffery DT, Norton JA, Roy FD, Gorassini MA. Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. Exp Brain Res 2007;182:281–7.
Kaji R, Urushihara R, Murase N, Shimazu H, Goto S. Abnormal sensory gating in basal ganglia disorders. J Neurol 2005;252:13–6.
Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci 2005;22:495–504.
Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med Phys 1995;22:1997–2005.
Matsunaga K, Nitsche MA, Tsuji S, Rothwell JC. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol 2004;115:456–60.
Matsunaga K, Maruyama A, Fujiwara T, Nakanishi R, Tsuji S, Rothwell JC. Increased corticospianal excitability after 5 Hz rTMS over the human supplementary motor area. J Physiol (Lond) 2005;562:295–306.
Münchau A, Bloem BR, Irlbacher K, Trimble MR, Rothwell JC. Functional connectivity of human premotor and motor cortex explored with repetitive transcranial magnetic stimulation. J Neurosci 2002;22:554–61.
Murase N, Kaji R, Shimazu H, Katayama-Hirota M, Ikeda A, Kohara N, et al. Abnormal premovement gating of somatosensory input in writer's cramp. Brain 2000;123:1813–29.
Mushiake H, Inase M, Tanji J. Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. J Neurophysiol 1991;66:705–18.
Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol (Lond) 2000;527:633–9.
Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulis W, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cogn Neurosci 2003a;15:619–26.
Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003b;114:2220–2.
Nitsche MA, Doemkes S, Karakose T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 2007;97:3109–17.
Okamoto M, Matsunami M, Dan H, Kohata T, Kohyama K, Dan I. Prefrontal activity during taste encoding: an fNIRS study. Neuroimage 2006;31:796–806.
Ogata K, Okamoto T, Yamasaki T, Shigeto H, Tobimatsu S. Pre-movement gating of somatosensory-evoked potentials by self-initiated movements: the effects of aging and its implication. Clin Neurophysiol 2009;120:1143–8.
Pesaran B, Nelson MJ, Andersen RA. Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron 2006;51:125–34.
Raux M, Xie H, Similowski T, Koski L. Facilitatory conditioning of the supplementary motor area in humans enhances the corticophrenic responsiveness to transcranial magnetic stimulation. J Appl Physiol 2010;108:39–46.
Rizzo V, Siebner HR, Modugno N, Pesenti A, Münchau A, Gerschlager W. Shaping the excitability of human motor cortex with premotor rTMS. J Physiol (Lond) 2003;554:483–95.
Rizzolatti G, Arbib MA. Language within our grasp. Trends Neurosci 1998;21:188–94.
Roche N, Lackmy A, Bussel B, Katz R. Impact of transcranial direct current stimulation on spinal network excitability in humans. J Physiol 2010;587:5653–64.
Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. Arch Neurol 2008;65:1571–6.
Schluter ND, Rushworth FS, Passinghaml RE, Mills KR. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements – a study using transcranial magnetic stimulation. Brain 1998;21:785–99.
Shibusawa M, Takeda T, Nakajima K, Ishigami K, Sakatani K. Functional near-infrared spectroscopy study on primary motor and sensory cortex response to clenching. Neurosci Lett 2009;449:98–102.
Stagg CJ, O'Shea J, Kincses ZT, Woolrich M, Matthews PM, Johansen-Berg H. Modulation of movement-associated cortical activation by transcranial direct current stimulation. Eur J Neurosci 2009:1412–23.
Stepniewska I, Preuss TM, Kaas JH. Ipsilateral cortical connections of dorsal and ventral premotor areas in new world owl monkeys. J Comp Neurol 2006;495:691–708.
Tanaka S, Hanakawa T, Honda M, Watanabe K. Enhancement of pinch force on the lower leg by anodal transcranial direct current stimulation. Exp Brain Res 2009;196:459–65.
Taniwaki T, Okayama A, Yoshiura T, Nakamura Y, Goto Y, Kira J, et al. Reappraisal of the motor role of basal ganglia: a functional magnetic resonance image study. J Neurosci 2003;23:3432–8.
Tsuji T, Rothwell JC. Long lasting effects of rTMSand associated peripheral sensory input on MEPs, SEPs and transcortical reflex excitability in humans. J Physiol (Lond) 2002;540:367–76.
Todd G, Butlerb JE, Gandevia SC, Taylor JL. Decreased input to the motor cortex increases motor cortical excitability. Clin Neurophysiol 2006;117:2496–503.
Wolters A, Schmidt A, Schramm A, Zeller D, Naumann M, Kunesch E, et al. Timing-dependent plasticity in human primary somatosensory cortex. J Physiol 2005;565:1039–52.
Zaghi S, Acar M, Hultgren B, Boggio PS, Fregni F. Noninvasive brain stimulation with low-intensity electric currents: putative mechanisms of action for direct and alternating current stimulation. Neuroscientisit 2010;16:285–307.

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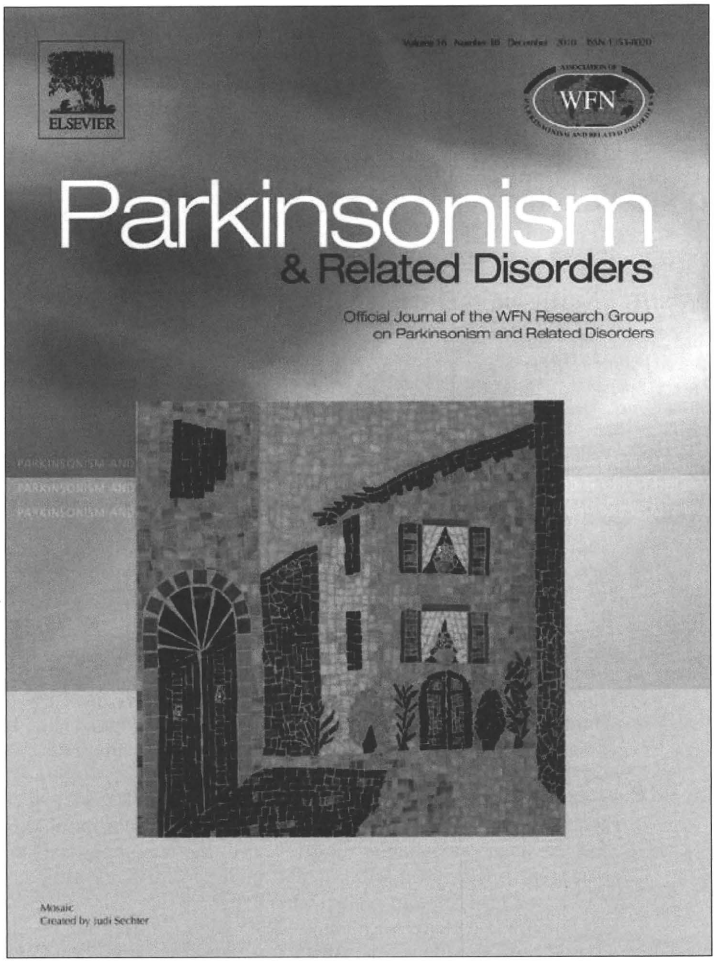

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Short communication

Relationship between ^{123}I-MIBG scintigrams and REM sleep behavior disorder in Parkinson's disease☆

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ABSTRACT

Background: Uptake of ^{123}I-labeled meta-iodobenzylguanidine (MIBG) in myocardial scintigrams has been shown to be as low in patients with idiopathic RBD as in Parkinson's disease (PD) patients.
Aim for study: To clarify whether the existence of RBD accelerates autonomic dysfunction in PD, we investigated the association between MIBG scintigraphic findings and RBD measures among non-dementia PD patients.
Subjects & methods: We conducted clinical interviews to assess REM sleep behavior disorder (RBD) symptoms, and performed polysomnograms (PSG) recordings and MIBG scintigrams on 49 PD patients. The patients were divided into three groups (PD with clinical RBD, PD with subclinical RBD, and PD with normal REM sleep).
Results: PD patients with clinical RBD had reduced MIBG uptake as determined by heart-to-mediastinum ratios of the delayed image compared to those with subclinical RBD and those with normal REM sleep. Multiple linear regression analysis revealed that only the existence of RBD symptoms was significantly associated with reduced MIBG uptake among PD patients without dementia after adjusting for demographic and PD symptom-related variables.
Conclusion: PD patients with clinical RBD might suffer from a wider α-synuclein pathology, including reduced cardiac sympathetic ganglia function as reflected by a lowered MIBG uptake.

1. Introduction

REM sleep behavior disorder (RBD) is characterized by vigorous and injurious behaviors related to vivid, action-filled, and violent dreams in nocturnal REM sleep. RBD is diagnosed when a patient has both violent dream enactment behavior and REM sleep without atonia (RWA) on polysomnograms (PSG). RBD has been widely accepted as one of the important co-morbidities of PD [1] and has been proposed to be one of the risk factors for developing hallucinations [2] [3] in PD patients. Moreover, orthostatic abnormalities were found to be more frequent in PD patients having RBD compared to those without these symptoms [3].

Cardiac uptake of ^{123}I-labeled meta-iodobenzylguanidine (MIBG) on scintigrams is known to be reduced in PD patients [4]. Notably, reduced MIBG uptake on scintigrams in patients with idiopathic RBD is quite similar to that of PD patients [5]. However, it has not been determined whether reductions in MIBG uptake are lower in PD patients with RBD versus those without RBD. To clarify this issue, we investigated the association between MIBG scintigraphic findings and RBD measures among PD patients.

2. Methods

This study was approved by the ethics committees of Tottori University, and all patients gave informed consent to take part in it. Patients with PD who had been hospitalized in the Department of Neurology at the University Hospital from July 2004 to June 2008 were targeted for this study, and forty-nine PD patients agreed to participate. The mean follow-up period on the subject patients was 6.3 ± 5.1 years. They had been receiving oral dopaminergic agents [levodopa dose equivalents

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(LDEs) [6] PD: 371 ± 214 mg/day]. We excluded patients from this study who were taking selegiline or antidepressants and those having suffered from heart failure and/or diabetes mellitus since these factors might have affected the MIBG scintigraphic findings.

Overnight PSG recordings were performed by standardized methods [6]. During REM stage sleep, submental phasic EMG activity (defined as 3-s mini-epochs containing phasic twitches which are at least four times higher than the background EMG activity) or submental tonic EMG activity with durations of more than half of a 30-s epoch was scored as RWA [7].

All the PD patients and their bed partners were also systematically interviewed regarding their sleep problems by a physician specializing in sleep disorders. Interviews especially focused on dream enactment behavior or vocalization while dreaming within one month before the PSG. In line with criteria from the second edition of the International Classification of Sleep Disorders [1], we diagnosed clinical RBD when a patient had both RWA on PSG and the experience of dream enactment behaviors associated with uncomfortable dream content during the preceding year, and included not only violent cases but also non-violent cases. This last criterion was included according to the suggestion by Oudiette et al. [8] that non-violent symptoms might represent the first step in the neurodegenerative process of the disorder. We also defined patients with RWA but without RBD symptoms as subclinical RBD. Finally, we categorized the patients into three groups: PD group with clinical RBD, PD group with subclinical RBD, and PD group with normal REM sleep.

Patients received an intravenous injection of 111-mBq of ^{123}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan). A single photon emission computed tomography (SPECT) image was obtained in an anterior view after 30 min for the early image and after 3.5 h for the delayed one. Average counts per pixel in the heart and mediastinum were used to calculate the heart-to-mediastinum (H/M) ratio. In this study, the H/M ratio of the delayed images, which display the neuronal uptake of MIBG scintigrams more explicitly than those of the early image [9], were used for the analysis.

We compared the continuous variables, including MIBG scintigraphic findings, among the above three groups by using an analysis of variance (ANOVA) followed by *post hoc* testing with Bonferroni correlation. A χ^2-test was also used to compare the categorical variables. Finally, multiple linear regression analysis was performed to explore the risk model of reduced MIBG uptake among the PD patients. The independent variables included age, gender, PD symptom-related variables (duration of morbidity, Hoehn & Yahr stages, and LDEs), and RBD measures (RBD symptoms and RWA on PSGs). Statistical significance was defined as $p < 0.05$ (SPSS, ver. 15.0J, SPSS Japan, 2006).

3. Results

Twenty-six of the 49 PD patients without dementia had RWA on PSG (53.1%); 18 patients were classified as having clinical RBD (36.7%), including 8 with violent behavior and 10 with non-violent behavior. Eight patients were classified as displaying subclinical RBD (16.3%). The other 23 patients had normal REM sleep (46.9%). There were no significant differences in any of the above descriptive parameters among the three PD groups (Table 1).

There was a significant difference in H/M ratios on the MIBG scintigrams among the three groups [$F_{3,54} = 6.33$, $p = 0.001$]. *Post hoc* tests revealed that the PD group with clinical RBD had significantly lower values compared to both the group with subclinical RBD ($p < 0.01$) and the group with normal REM sleep ($p < 0.01$). However, there were no significant differences in H/M ratios between the PD group with subclinical RBD and the group with normal REM sleep (Fig. 1). Within the PD group exhibiting clinical RBD, there was no significant difference in the ratio between patients with violent behavior and those with non-violent behavior (patients with violent behavior: 1.18 ± 0.24, those with non-violent behavior: 1.16 ± 0.09).

Multiple linear regression analysis revealed that the existence of RBD ($\beta = -0.511$, $p = 0.002$) appeared to be the only significantly associated factor among the studied independent variables for reduced MIBG uptake in the final model ($R^2 = 0.314$, $p = 0.006$; Table 2).

4. Discussion

Our results confirmed that MIBG uptake is decreased in non-dementia PD patients with clinical RBD. Moreover, among the studied variables, the existence of RBD symptoms alone was associated with reduced MIBG uptake among PD patients. Interestingly, our results indicate that patients with subclinical RBD do not show significantly reduced MIBG uptake. This finding raises the possibility that neuronal loss and inclusion of Lewy bodies in the sympathetic ganglia as reflected by the reduced MIBG uptake is marked, especially in PD patients having clinical RBD symptoms. PD patients experiencing hallucinations are likely to have more reduced MIBG uptake compared to those that do not [10]. Therefore, our results may corroborate the idea that the existence of RBD symptoms in PD is one of the risk factors for developing hallucinations [2].

As mentioned above, patients with idiopathic RBD have reduced MIBG uptake [5]. Moreover, they have been characterized as likely to have autonomic symptoms including orthostatic hypotension [3] and cardiac dysfunction during both wakefulness and sleep [11,12]. As for PD patients, orthostatic abnormalities have been reported to be more frequent in patients with RBD [3]. Taking this finding and the present MIBG results together, it is possible that the existence of RBD symptoms accelerates autonomic dysfunction in PD patients. Considering that patients with non-violent behaviors showed MIBG findings similar to those with violent behaviors in the present study, it appears that the existence (but not the severity) of RBD symptoms might be related with reduced MIBG uptake. From this finding, we speculate that patients with α-synuclein pathology expanding into the limbic system, resulting in the occurrence of uncomfortable dreams associated with RBD symptoms, might simultaneously have lesions of cardiac sympathetic ganglia.

Our study has several limitations. First, our study did not include normal age-matched control subjects or patients with idiopathic RBD. Although our results show a clear difference in MIBG uptake between PD patients with and without clinical RBD, further study including these two control groups is necessary for drawing definitive conclusions. Second, the existence of RBD symptoms was investigated by retrospective interviews of the subjects and their bed partners. For this reason, we may have been unable to detect the existence of mild RBD symptoms in our subjects.

In conclusion, reduced MIBG uptake on scintigrams could be observed in PD patients with RBD symptoms. Although definitive

Table 1
Comparison of descriptive variables among the three subject groups.

	Groups with clinical RBD ($n = 18$)	Groups with subclinical RBD ($n = 8$)	Groups with Normal REM sleep ($n = 23$)	Significance
Age	71.3 ± 8.3	65.4 ± 8.6	71.5 ± 7.2	n.s.
Gender (Male/Female)	5/13	3/5	10/13	n.s.
Length of PD morbidity	9.0 ± 4.7	3.6 ± 2.6	5.3 ± 4.8	n.s.
Hoehn &Yahr Stages	3.0 ± 0.9	2.5 ± 0.5	2.7 ± 0.9	n.s.
Levodopa dose Equivalents (mg/day)	408 ± 214	283 ± 193	347 ± 199	n.s.
MMSE	25.6 ± 3.9	26.8 ± 2.3	26.3 ± 3.2	n.s.

RBD: REM sleep behavior disorders; MMSE: Mini Mental State Examination.
The values are expressed as mean ± SD. n.s.: not significant.

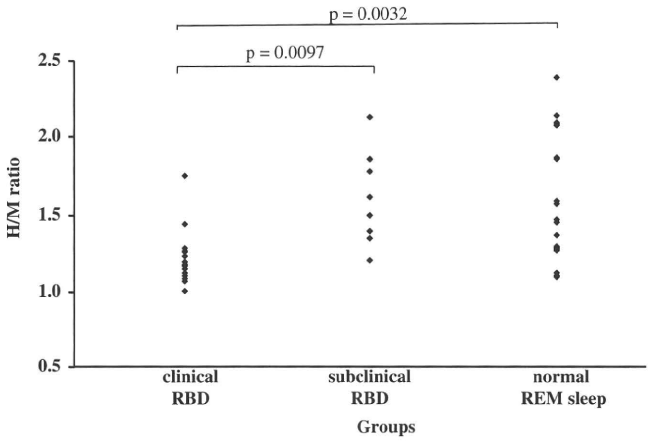

Fig. 1. Comparison of delayed image on MIBG scintigraphic findings among the three groups. ◆ symbols indicate the H/M ratios on MIBG scintigrams for each patient among the three groups (clinical RBD, subclinical RBD, and normal REM sleep).

Table 2
Multiple regression analysis on factors associated with H/M ratio on MIBG scintigrams among the total PD patients.

Model	β	t	p
Age	−0.243	−1.831	0.074
Duration of PD morbidity	0.75	0.488	0.628
Hoehn & Yahr stages	−0.104	−0.721	0.475
The existence of RBD symptoms	−0.511	−3.267	0.002
The existence of RWA on PSG	0.61	0.410	0.684

H/M: heart-to-mediastinum, MIBG: meta-iodobenzylguanidine.
RBD: REM sleep behavior disorders, RWA: REM sleep without atonia.

conclusions cannot be obtained from the results of this study, RBD symptoms might be associated with wider α-synuclein pathology as reflected by cardiac autonomic dysfunction.

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References

[1] American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic and coding manual. 2nd ed.; 2005. Westchester p. 148–52.
[2] Nomura T, Inoue Y, Mitani H, Kawahara R, Miyake M, Nakashima K. Visual hallucinations as REM sleep behavior disorders in patients with Parkinson's disease. Mov Disord 2003;18:812–7.
[3] Postuma RB, Gagnon JF, Vendette M, Charland K, Montplasir JY. Manifestations of Parkinson disease differ in association with REM sleep behavior disorder. Mov Disord 2008;23:1665–72.
[4] Braune S, Reinhardt M, Schnitzer R, Riedel A, Lucking CH. Cardiac uptake of [^{123}I]MIBG separates Parkinson's disease from multiple system atrophy. Neurology 1999;53:1020–5.
[5] Miyamoto T, Miyamoto M, Inoue Y, Usui Y, Suzuki K, Hirata K. Reduced cardiac ^{123}I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. Neurology 2006;67:2236–8.
[6] Uemura Y, Nomura T, Inoue Y, Yamawaki M, Yasui K, Nakashima K. Validation of the Parkinson's disease sleep scale in Japanese patients: a comparison study using the Pittsburgh sleep quality index, the Epworth sleepiness scale and polysomnography. J Neurol Sci 2009;287:36–40.
[7] American Sleep Disorders Association. Manuals of the scoring of sleep and associated events. Rules, technology, and technical specifications; 2007. p. 42–43.
[8] Oudiette M, de Cock VC, Lavault S, Leu S, Vidaihet M, Arnulf I. Nonviolent elaborate behavior may also occur in REM sleep behavior disorder. Neurology 2009;72:551–7.
[9] Hanyu H, Shimizu S, Hirao K, Sakurai H, Iwamoto T, Chikamori T, et al. The role of ^{123}I-Metaiodobenzylguanidine myocardial scintigraphy in the diagnosis of Lewy body disease in patients with Dementia in a memory clinic. Dement Geriatr Cogn Disord 2006;22:379–84.
[10] Kitayama M, Wada-Isoe K, Irizawa Y, Nakashima K. Association of visual hallucinations with reduction of MIBG cardiac uptake in Parkinson's disease. J Neurol Sci 2008;264:22–6.
[11] Ferini-Strambi L, Oldani A, Zucconi M, Smirne S. Cardiac autonomic activity during wakefulness and sleep in REM sleep behavior disorder. Sleep 1996;19:367–9.
[12] Lanfranchi PA, Fradette L, Gagnon JF, Colombo R, Montplaisir J. Cardiac autonomic regulation during sleep in idiopathic REM sleep behavior disorder. Sleep 2007;30:1019–25.

NEUROLOGY

Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease

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Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease

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ABSTRACT

Objectives: The basal ganglia (BG) play an important role in controlling saccades. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely used as a treatment of Parkinson disease (PD) by altering the function of the BG. Nevertheless, the effects of STN DBS on saccade performance are not fully clarified in a systematic manner. In this study, we examined the effects of bilateral STN DBS on both the initiation and inhibition of saccades in PD.

Methods: Thirty-two patients with PD performed 4 oculomotor tasks. Two tasks (visually guided saccades and gap saccades) were reflexive and 2 (memory-guided saccades [MGS] and antisaccades) were volitional. While taking their regular doses of antiparkinsonian drugs, patients performed these tasks under 2 conditions: during DBS (DBS-on condition) and without DBS (DBS-off condition). Fifty-one age-matched subjects served as controls.

Results: In the DBS-on condition, parameters of saccade initiation were improved in all tasks, with shorter latencies and increased amplitudes, except for MGS latency. STN DBS improved the ability to suppress unwanted saccades to the cue stimulus in the MGS task. However, it did not suppress prosaccades during the antisaccade task.

Conclusions: These results suggest that deep brain stimulation (DBS) of the subthalamic nucleus (STN) affects the neural pathway common to both reflexive and volitional saccades, possibly by acting on the STN–substantia nigra pars reticulata–superior colliculi pathway. STN DBS may set the functional level of the superior colliculi appropriate for both saccade initiation and inhibition through this pathway. These findings provide novel insights into the pathophysiology of Parkinson disease and may yield better treatment strategies. ***Neurology*® 2010;74:743–748**

GLOSSARY

AS = antisaccades; **BG** = basal ganglia; **DBS** = deep brain stimulation; **EOG** = electro-oculography; **GS** = gap saccade; **MGS** = memory-guided saccades; **PD** = Parkinson disease; **RT** = reaction time; **SC** = superior colliculus; **SNr** = substantia nigra pars reticulata; **STN** = subthalamic nucleus; **UPDRS** = Unified Parkinson's Disease Rating Scale; **VGS** = visually guided saccades.

The basal ganglia (BG) have 2 output pathways implicated in the control of movements: the thalamocortical parallel pathways[1] and the brainstem motor networks.[2] The oculomotor circuit of the former projects back to the frontal eye field and supplementary eye field, although little is known about its physiologic and pharmacologic aspects. The role of the latter on saccadic eye movement has been demonstrated not only anatomically but also physiologically and pharmacologically.[2,3] Through the BG–superior colliculus (SC) pathway and the corticotectal pathways, the SC is the common terminal for controlling saccadic eye movements. Therefore, saccades reflect the output of the BG, and can be a good indicator of BG function.

Supplemental data at www.neurology.org

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Parkinson disease (PD) impairs not only somatomotor functions but also oculomotor functions. Patients with PD have difficulty in initiating voluntary saccades. Memory-guided saccades (MGS) are hypometric,[4-6] and latencies and error rates of antisaccades (AS) are increased.[7-10] In contrast, reflexive saccades to visual targets such as visually guided saccades (VGS) are relatively spared.[11-14] The preferential impairment of voluntary saccades as compared with reflexive saccades has been explained by the fact that the BG are more involved in voluntary saccades such as MGS.[9,15-17] In addition to the difficulty in initiating saccades, patients with PD have difficulty in suppressing unwanted saccades to cues in the MGS task.[2] Nevertheless, it remains unclear how the impairment of initiation and inhibition of saccades can coexist.

Today, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a common treatment for advanced PD. DBS is believed to interfere with increased output from the BG and improve the functions of its target structures including the thalamus, a component of the BG-thalamocortical circuits, and the SC, which is the output center of ocular movement.[2,18-20] Based on these observations, we considered that STN DBS will affect saccade performance as well as motor functions in PD, and we predicted that voluntary saccades would be more improved by STN DBS than reflexive saccades.

There are some recent reports on the effects of STN stimulation on saccades in patients with PD. STN DBS decreases latencies of reflexive saccades,[21,22] increases amplitudes of reflexive saccades,[21] and increases gains of memory-guided saccades.[23] In addition, it reduces interruptive saccades during fixation.[24] However, the pathophysiology underlying effects of STN DBS on saccade performance are not fully clarified. Our study was designed to investigate the effect of STN DBS on the performance of several kinds of saccades in a large group of patients with PD. Our results show that performances of both reflexive and voluntary saccades are affected by STN DBS. Along with the effect of STN DBS on initiation and inhibition of saccades, our findings provide novel insights into the function of the BG and the pathophysiology of PD.

METHODS

Subjects. The subjects were 32 patients with PD undergoing bilateral STN DBS (15 men and 17 women; age 58.3 ± 7.9 [mean ± SD]; Hoehn & Yahr stage 2–4 [while medicated, but with DBS off]) (table e-1 on the *Neurology*® Web site at www.neurology.org). Their Unified Parkinson's Disease Rating Scale (UPDRS) part III scores were 6–44 in the DBS-off condition. Their mean levodopa equivalent dose[25] was 528.4 ± 397.2 mg. For ethical reasons, subjects continued to take their antiparkinsonian drugs as usual. We also collected control data from 51 age-matched normal subjects (20 men and 31 women; age 57.1 ± 8.3) for comparison with the patients' results (table e-1).

The study was approved by the Ethics Committee of Tokyo Metropolitan Neurological Hospital and the University of Tokyo. A written informed consent was obtained from all participants in the study. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Experimental setup. We used the experimental system developed by Kato et al.[26] and Hikosaka et al.[27] The head was immobilized and DC electro-oculography (EOG) was recorded with 5 Ag-AgCl gel electrodes (bilateral outer canthi for horizontal eye movement, upper and lower edges of the right eye for vertical eye movements, and one ground on the forehead), with low-pass filtering at 20 Hz and digitizing at a sampling rate of 500 Hz. The calibration of EOG gain was adjusted to a target point at 20 degrees left or right. The subjects held a microswitch button and could start and terminate a trial by pressing and releasing it.

Experimental procedures. Four oculomotor tasks—the VGS, gap saccade (GS), MGS, and AS tasks—and the visual detection task surveying the manual reaction time (RT)[27] were performed in the DBS-on state. Two hours after turning off DBS, the same tasks were performed in the DBS-off state in 26 of the 32 subjects. To exclude order effects, the on and off experiments were reversed in the remainder of the subjects. UPDRS part III was also measured in the DBS-on and DBS-off states. All experiments were performed 90–120 minutes after the intake of antiparkinsonian drugs.

Visually guided saccade task. A fixation point was turned on, and the subjects had to fixate on this point. It was turned off after an arbitrary period of 1,500–2,000 msec, and simultaneously the target point was turned on at 5, 10, 20, or 30 degrees to the left or right randomly, and the subjects had to make a saccade quickly to the new position (figure e-1A).

Gap saccade task. The GS task was identical to that of the VGS, except that the target was turned on 200 msec after the fixation point was turned off (figure e-1B). During the GS task, we occasionally noted inappropriate saccades in the opposite direction of the target immediately before initiating a correctly directed saccade. We termed such saccades premature saccades.

Memory-guided saccade task. A fixation point was turned on and while the subject gazed at it a cue was flashed for 50 msec at the future location of the saccade target. The subject had to memorize the position of the cue while looking at the fixation point without making a saccade toward the flash. After 2,000–3,000 msec, the fixation point was turned off and the subject had to quickly make a saccade to the remembered location of the target. The target point was turned on again 600 msec after the fixation point was turned off (figure e-1C). Saccades erroneously

made to the flash cue stimulus during fixation were termed saccades to cue.

Antisaccade task. A fixation point and a cue point were turned on and off in the same way as in the VGS task, but the subject had to make a saccade toward the opposite location of the cue point (figure e-1D). In other words, the actual target point for the saccade was a point opposite to where the cue stimuli appeared. Saccades erroneously made toward the cue point were termed prosaccades.

Visual detection task. This is not an eye movement task but a kind of attention and hand movement task. A central fixation point was turned on and left on throughout each trial. After an arbitrary period of 2,000–2,500 msec, a target point was turned on randomly 5, 10, 20, or 30 degrees to the left or right. The subject had to release the button as soon as the target appeared, without making a saccade toward it.

In all the tasks, subjects were asked to alternate between the left and right hands in consecutive sessions to exclude possible effects of response hand.

Data analysis and statistical assessment. We judged that an eye movement (candidate of a saccade) occurred if velocity and acceleration exceeded threshold values (28 deg/s and 90 deg/s^2 respectively). Eye movement was assessed as a saccade based on its velocity and duration: after the onset, the velocity had to exceed 88 deg/s, this suprathreshold velocity had to be maintained for at least 10 msec, the end of the eye movement was defined as the moment when the velocity decreased to less than 40 deg/s, and the total duration time had to be more than 30 msec. However, EOG signals could contain a significant amount of noise. Small, slow saccades could be omitted whereas large fluctuations due to body movements could be judged to be a saccade. The final judgment was made by visually inspecting whether the eye movement was a saccade or not. Saccades with latency of less than 60 msec were classified as anticipatory and were excluded from analyses. Saccades with onset latency greater than 660 msec in the MGS task were classified as a kind of visually guided saccade which directed to the target after a time lag. These were excluded from the analysis of MGS.

The saccade accuracy was calculated as the ratio of the amplitude of the first saccade to the target presented at 20 and 30 degrees. We counted the frequency of premature saccades in the GS task, saccades to cue in the MGS task, and prosaccades in the AS task.

To assess the effect of STN DBS, the patients' performance on the individual task, the results on the tasks were compared using the 2-tailed paired Student's t test. Furthermore, the results of 3 groups (the control subjects, patients with PD in DBS-on state, and patients with PD in DBS-off state) were compared using the Tukey-Kramer multiple comparison test.

RESULTS Saccade traces of one patient in the DBS-on and DBS-off states (figure e-2) shows that saccades were often hypometric without DBS, but became less hypometric during DBS. Their latencies became shorter and varied less during DBS. Saccades to the cue in the MGS task were less common during DBS. Similar changes were detected in other patients (table e-2), which we describe in the following sections.

Effects on saccade initiation. With or without DBS, the latencies of saccades in the patients were longer than those in the control subjects (Tukey-Kramer multiple comparison test; $p < 0.001$ for VGS, GS, and AS, $p < 0.006$ for MGS) (table e-2). DBS significantly reduced the latencies in all types of saccade except MGS (figure, A).

Without DBS, saccades of all types were more hypometric in the patients than in the controls. The accuracies of these saccades were improved significantly by DBS (figure, B), but the accuracy was still more hypometric than that of the controls, with the exception of the AS task ($p < 0.001$ for VGS, GS, and MGS; $p = 0.280$ for AS).

The improvement of UPDRS part III score correlated with the improvement of VGS accuracy ($r = 0.483$, $p = 0.005$) and GS latency ($r = -0.407$, $p = 0.021$) (figure e-3).

Effects on saccade inhibition. Without DBS, the patients made saccades to cues in the MGS task more often than the controls ($p < 0.001$). DBS made such saccades significantly less frequent (figure, C).

Without DBS, the patients made prosaccades in the AS task more often than the controls ($p < 0.001$). The frequency of such prosaccades was not affected by DBS (figure, C).

Without DBS, the patients with PD made premature saccades in the GS task as often as the control subjects ($p > 0.980$ both for DBS). The premature saccades were not influenced by DBS (table e-2).

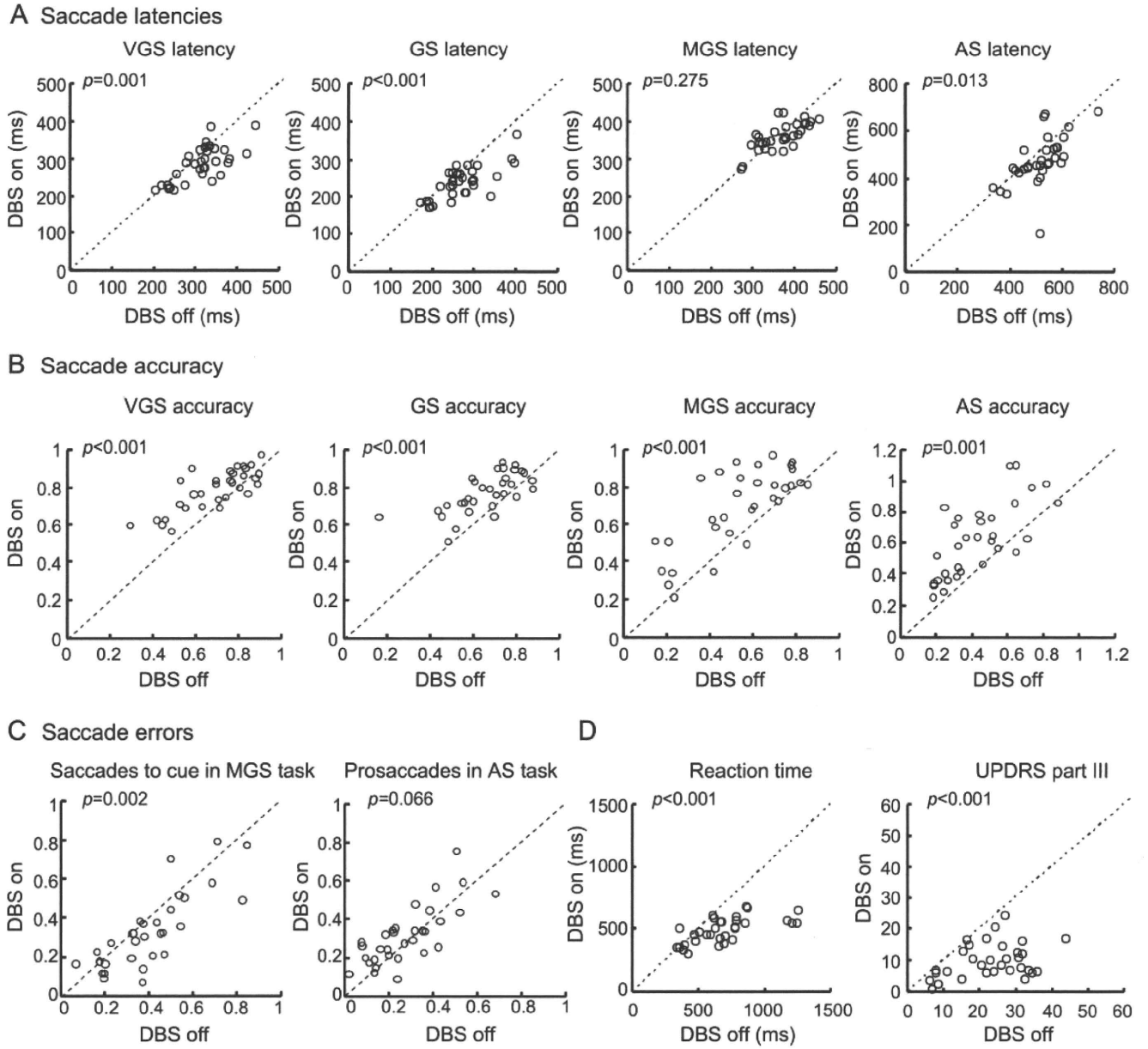
No parameters of saccade inhibition correlated with the improvement of UPDRS part III score (figure e-3).

Effects on the visual detection task. Without DBS, RT was longer in the patients than in the controls ($p < 0.001$). RT was significantly shortened by DBS in almost all the patients (figure, D). The UPDRS part III scores were significantly improved by DBS in all the patients (figure, D). The improvement of RT significantly correlated with the improvement of UPDRS part III score ($r = 0.595$, $p < 0.001$) (figure e-3).

DISCUSSION In this study, we found that in patients with PD undergoing levodopa therapy, STN DBS improves performances of volitional saccades; memory-guided saccades and antisaccades, as well as those of reflexive saccades; visually guided saccades; and gap saccades. In addition, STN DBS improved the inhibitory control of saccades; STN DBS decreased the saccades to cue in MGS, but did not affect the frequency of prosaccades in AS. The improvement of the accuracy of VGS amplitude, the latency of GS, and the RT correlated with the improvement of UPDRS part III score.

The BG are thought to play an important role in the inhibitory control of saccades.[20] In PD, both the initia-

Figure Saccade results with deep brain stimulation (DBS) on and off



The figures show how the saccade latency (A), saccade amplitude (B), and frequency of saccade errors (C) changed when DBS was turned on. The horizontal axis shows the DBS-off condition and the vertical axis shows the DBS-on condition. The plot falls on a line of unison, as indicated by the dashed line running through the origin, if the saccade parameter is identical under subthalamic nucleus (STN) DBS-on and DBS-off conditions. Plots under this line show that the parameter under the DBS-off condition is larger than that under the DBS-on condition, and vice versa. Reaction time (RT) was significantly shortened by DBS in almost all the patients (D). Unified Parkinson's Disease Rating Scale (UPDRS) part III scores were significantly improved by DBS in all the patients. AS = antisaccades; GS = gap saccade; MGS = memory-guided saccades; VGS = visually guided saccades.

tion and the inhibition of nontarget saccades are impaired. In a previous study, the frequency of saccades to cue in MGS was found to be increased in patients with PD, suggesting impaired inhibitory control of unwanted saccades.[2] Excessive inhibition of the SC, as postulated in the rate model of the BG circuit, would actually prevent direct visuomotor execution in response to the cue stimulus. This would be expected to decrease the frequency of saccades to cue, which conflicts with the results of the present study.

STN DBS decreased the frequency of saccades to cue, suggesting that DBS restored the inhibitory control of reflexive saccades. This restorative effect indicates that STN DBS normalizes the inhibitory function of the BG, setting the excitability of SC at an appropriate level, both for initiating and inhibiting saccades. This result seems consistent with the suggestion that the STN plays an important role in keeping the eye position fixed.[28] Our results are better explained by the oscillation model of the BG circuit[29-32] than by the rate

model of the BG circuit. The rate model predicts that if DBS simply restored the firing rate of STN and reduced the excessive inhibitory output through the STN-substantia nigra pars reticulata (SNr) circuit, STN DBS would not only facilitate initiation of saccades but also increase the frequency of unwanted saccades to cue in MGS task. In fact, STN DBS improved saccade initiation but reduced unwanted saccade to cue. Recent studies take into account the oscillation in the BG.[29-32] Beta band oscillations in BG are abnormally enhanced in PD, and the desynchronization in beta band is required to fulfill motor commands to override the elevated threshold for saccade generation. STN DBS would decrease the pathologic oscillations and facilitate motor commands in PD by decreasing the beta band and enhancing the gamma band, while reducing the BG output and lowering the threshold. Reduction in the oscillatory activities by DBS would help maintain the appropriate SC excitability required for saccade initiation and inhibition by normalizing the "leaky" suppression exerted by the BG and decrease the emergence of unwanted saccades to cue. Therefore, STN DBS facilitates the initiation commands and also normalizes inhibition commands. Furthermore, such oscillatory activities might also spread "noisy input" throughout the BG-thalamocortical pathway[33] and disrupt processing involved in saccade inhibition at the cortical and subcortical regions. STN DBS would occlude this noisy input and enable the effective function of neural processing to be issued within the relevant neural structures.

Our results indicate that STN DBS (in addition to levodopa) causes a decrease in saccades to cue. A candidate locus explaining the improvement of inhibitory control is the STN-SNr-SC circuit. This direct projection to the SC appears to play a more important role in suppressing unwanted saccades than the BG-thalamocortical pathway. STN DBS may thus improve the function not only of the BG-thalamocortical pathway, but also of the STN-SNr-SC circuit, although we have to admit the limitation of this study; since we investigated the effects of STN DBS while the patients were taking levodopa, the effects of levodopa may be included in the baseline DBS-off state.

To date, inhibitory control of saccades has been studied mostly using the AS task. In our study, the frequency of prosaccades in the AS task was higher in patients with PD than in controls, which is consistent with previous reports.[8-10] On the other hand, STN DBS caused no change in the frequency of directional errors in the AS task, suggesting that the inhibitory mechanism involved in the AS task may be distinct from that for inhibiting saccades to cue. The occurrence of prosaccades in the AS task has been explained by the failure of the prefrontal cortex to inhibit the SC directly via the descending pathway[16,17,34] although some involvement of the BG (i.e., the caudate nucleus) has also been suggested for AS.[35-37] Therefore, STN DBS might specifically affect the inhibitory mechanism of saccades mediated by the STN-SNr circuit rather than that mediated by the frontal cortex, leaving the frequency of prosaccades unaffected.

The present results showed that both reflexive and voluntary saccades are impaired in PD, consistent with results of our previous study.[38] As mentioned in the Introduction, we predicted that MGS would be more improved by STN DBS than VGS; however, we found that saccades of both types were improved by STN DBS. This suggests that STN DBS improves the function of the neural structures involved in saccades of both types. The simplest explanation is that STN DBS improves the function of the SC. If STN DBS works by interfering with the overactivity of the STN-SNr circuit and reversing the excessive inhibition of the SC, it would engender decreased latency and increased saccade amplitude for both reflexive and voluntary saccades. This is because SC comprises the final common pathway for saccades of both types.

An alternative explanation, but not a mutually exclusive one, is that STN DBS normalizes the activity of the BG-thalamocortical circuits including the motor and oculomotor loops. STN comprises part of this circuit. Therefore, STN DBS might induce functional changes in the entire loop. Both volitional and reflexive saccades would be affected by such functional changes because the oculomotor cortical regions are directly or indirectly connected with this circuit.

DISCLOSURE

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REFERENCES

1. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.

2. Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev 2000;80:953–978.
3. Fawcett AP, Dostrovsky JO, Lozano AM, Hutchison WD. Eye movement-related responses of neurons in human subthalamic nucleus. Exp Brain Res 2005;162:357–365.
4. Crawford TJ, Henderson L, Kennard C. Abnormalities of nonvisually-guided eye movements in Parkinson's disease. Brain 1989;112:1573–1586.
5. Nakamura T, Bronstein AM, Lueck C, Marsden CD, Rudge P. Vestibular, cervical and visual remembered saccades in Parkinson's disease. Brain 1994;117:1423–1432.
6. Vermersch AI, Rivaud S, Vidailhet M, et al. Sequences of memory-guided saccades in Parkinson's disease. Ann Neurol 1994;35:487–490.
7. Lueck CJ, Tanyeri S, Crawford TJ, Henderson L, Kennard C. Antisaccades and remembered saccades in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:284–288.
8. Kitagawa M, Fukushima J, Tashiro K. Relationship between antisaccades and the clinical symptoms in Parkinson's disease. Neurology 1994;44:2285–2289.
9. Briand KA, Strallow D, Hening W, Poizner H, Sereno AB. Control of voluntary and reflexive saccades in Parkinson's disease. Exp Brain Res 1999;129:38–48.
10. Chan F, Armstrong IT, Pari G, Riopelle RJ, Munoz DP. Deficits in saccadic eye-movement control in Parkinson's disease. Neuropsychologia 2005;43:784–796.
11. White OB, Saint-Cyr JA, Tomlinson RD, Sharpe JA. Ocular motor deficits in Parkinson's disease. II. Control of the saccadic and smooth pursuit systems. Brain 1983;106:571–587.
12. Rascol O, Clanet M, Montastruc JL, et al. Abnormal ocular movements in Parkinson's disease: evidence for involvement of dopaminergic systems. Brain 1989;112:1193–1214.
13. Vidailhet M, Rivaud S, Gouider-Khouja N, et al. Eye movements in parkinsonian syndromes. Ann Neurol 1994;35:420–426.
14. Briand KA, Hening W, Poizner H, Sereno AB. Automatic orienting of visuospatial attention in Parkinson's disease. Neuropsychologia 2001;39:1240–1249.
15. Kori A, Miyashita N, Kato M, Hikosaka O, Usui S, Matsumura M. Eye movements in monkeys with local dopamine depletion in the caudate nucleus: II: deficits in voluntary saccades. J Neurosci 1995;15:928–941.
16. Fukushima J, Fukushima K, Miyasaka K, Yamashita I. Voluntary control of saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. Biol Psychiatry 1994;36:21–30.
17. Pierrot-Deseilligny C, Milea D, Müri RM. Eye movement control by the cerebral cortex. Curr Opin Neurol 2004;17:17–25.
18. Wurtz RH, Goldberg ME. Superior colliculus cell response related to eye movement in awake monkeys. Science 1971;171:82–84.
19. Sparks DL. Functional properties of neurons in the monkey superior colliculus: coupling of neuronal activity and saccade onset. Brain Res 1978;156:1–16.
20. Hikosaka O, Wurtz RH. Visual and oculomotor functions of monkey substantia nigra pars reticulata: IV: relation of substantia nigra to superior colliculus. J Neurophysiol 1983;49:1285–1301.
21. Sauleau P, Pollak P, Krack P, et al. Subthalamic stimulation improves orienting gaze movements in Parkinson's disease. Clin Neurophysiol 2008;119:1857–1863.
22. Temel Y, Visser-Vandewalle V, Carpenter RH. Saccadometry: a novel clinical tool for quantification of the motor effects of subthalamic nucleus stimulation in Parkinson's disease. Exp Neurol 2009;216:481–489.
23. Rivaud-Péchoux S, Vermersch AI, Gaymard B, et al. Improvement of memory guided saccades in parkinsonian patients by high frequency subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry 2000;68:381–384.
24. Wark HA, Garell PC, Walker AL, Basso MA. A case report on fixation instability in Parkinson's disease with bilateral deep brain stimulation implants. J Neurol Neurosurg Psychiatry 2008;79:443–447.
25. Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 1995;346:1383–1387.
26. Kato M, Miyashita N, Hikosaka O, Matsumura M, Usui S, Kori A. Eye movements in monkeys with local dopamine depletion in the caudate nucleus: I: deficits in spontaneous saccades. J Neurosci 1995;15:912–927.
27. Hikosaka O, Fukuda H, Kato M, Uetake K, Nomura Y, Segawa M. Deficits in saccadic eye movements in hereditary progressive dystonia with marked diurnal fluctuation. In: Segawa M, ed. Hereditary Progressive Dystonia With Marked Diurnal Fluctuation. New York: The Parthenon Publishing Group; 1993:159–177.
28. Matsumura M, Kojima J, Gardiner TW, Hikosaka O. Visual and oculomotor functions of monkey subthalamic nucleus. J Neurophysiol 1992;67:1615–1632.
29. Boraud T, Bezard E, Bioulac B, Gross C. High frequency stimulation of the internal globus pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neurosci Lett 1996;215:17–20.
30. Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. J Neurosci 2000;20:8559–8571.
31. Wichmann T, Bergman H, Starr PA, Subramanian T, Watts RL, DeLong MR. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. Exp Brain Res 1999;125:397–409.
32. Brown P, Williams D. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol 2005;116:2510–2519.
33. Murer MG, Tseng KY, Kasanetz F, Belluscio M, Riquelme LA. Brain oscillations, medium spiny neurons, and dopamine. Cell Mol Neurobiol 2002;22:611–632.
34. Condy C, Rivaud-Péchoux S, Ostendorf F, Ploner CJ, Gaymard B. Neural substrate of antisaccades: role of subcortical structures. Neurology 2004;63:1571–1578.
35. Lasker AG, Zee DS, Hain TC, Folstein SE, Singer HS. Saccades in Huntington's disease: initiation defects and distractibility. Neurology 1987;37:364–370.
36. Everling S, Fischer B. The antisaccade: a review of basic research and clinical studies. Neuropsychologia 1998;36:885–899.
37. Peltsch A, Hoffman A, Armstrong I, Pari G, Munoz DP. Saccadic impairments in Huntington's disease. Exp Brain Res 2008;186:457–469.
38. Terao Y, Fukuda H, Ugawa Y, Yugeta A, Nomura Y, Segawa M. Saccade abnormalities in Parkinson's disease made toward targets of different eccentricities. Mov Disord 2006;21:S564.

Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease

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Clinical Efficacy of Istradefylline (KW-6002) in Parkinson's Disease: A Randomized, Controlled Study

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Abstract: The objectives of this study were to evaluate the efficacy of istradefylline at an oral dose of 20 mg or 40 mg once daily for 12 weeks in Parkinson's disease (PD) patients with motor complications on levodopa therapy based on the change in the daily OFF time compared with placebo and to assess the safety at these doses. A total of 363 subjects were randomly assigned to receive 20 mg/day istradefylline (n = 119), 40 mg/day istradefylline (n = 125), or placebo (n = 119). The primary outcome variable was the change from baseline at endpoint in daily OFF time based on patients' ON/OFF diaries. At endpoint, the daily OFF time reduced from baseline by 1.31 hours for 20 mg/day istradefylline ($P = 0.013$ as compared to the placebo), 1.58 hours for 40 mg/day istradefylline ($P < 0.001$), and 0.66 hours for placebo; istradefylline significantly reduced the daily OFF time compared with placebo. The UPDRS Part III subscale score (ON state) reduced by 5.7 at endpoint in both istradefylline groups and 3.7 in the placebo group ($P = 0.006$ for 20 mg/day and $P = 0.006$ for 40 mg/day group as compared with placebo). The most commonly reported drug-related treatment emergent adverse event (TEAE) was dyskinesia, which occurred in 2.5% (3/119) of subjects receiving placebo, 8.5% (10/118) receiving 20 mg/day istradefylline, and 6.4% (8/125) receiving 40 mg/day istradefylline. We conclude that istradefylline at 20 mg and 40 mg once daily is effective in relieving wearing-off fluctuations of PD patients. In addition, istradefylline was well tolerated at both doses. © 2010 Movement Disorder Society

Key words: adenosine antagonists; istradefylline; Parkinson's disease; levodopa; randomized controlled trial

Parkinson's disease (PD) is characterized by tremor, rigidity, bradykinesia, and postural instability[1] mainly caused by degeneration of dopaminergic neurons in the substantia nigra.[2–4] Current treatments of PD focusing on symptomatic management with dopaminergic therapies, such as levodopa (L-dopa) and dopamine agonists, are highly effective in controlling motor symptoms in patients with early-stage disease.[5,6] However, motor fluctuations, such as wearing-off and dyskinesia, limit pharmacological intervention.[7,8] Treatment of response fluctuations currently involves combinations of regular and controlled release L-dopa with the addition of a catechol-*O*-methyl-transferase (COMT) inhibitor or a monoamine oxidase B inhibitor, or use of a long-acting dopamine agonist or high dose amantadine HCl.[9]

The motor symptoms observed in PD are physiologically postulated to result from an imbalance between the activities in the γ-aminobutyric acid mediated (GABAergic) striatonigral and GABAergic striato-external pallidal output pathways, with the striato-external pallidal pathway becoming excessively activated in PD[10–12] Adenosine receptors are classified into four subtypes, A_1, A_{2A}, A_{2B}, and A_3. Adenosine A_{2A} receptors are predominantly expressed in the GABAergic striato-external pallidal output neurons.[13,14] Adenosine A_{2A} receptor activation increases the excitability of the

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Members of the Japanese Istradefylline Study Group are listed as an Appendix

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GABAergic striato-external pallidal output neurons via adenosine A_{2A} receptors in the striatum and external globus pallidus.[15,16] Thus, blockade of adenosine A_{2A} receptors would result in a decrease in excessive activation of the striato-external pallidal output pathway, restore the balance in the basal ganglia-thalamocortical circuit and provide an alternative, nondopaminergic approach to symptomatic relief of PD. Moreover, overexpression of pallidal adenosine A_{2A} receptors in PD patients was reported using postmortem brain tissue,[17] suggesting a rationale for using an adenosine A_{2A} receptor antagonist in the treatment of PD.

Istradefylline (KW-6002; (*E*)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro- 1*H*-purine-2,6-dione) is a selective A_{2A} adenosine receptor antagonist, which has a 12 nmol/L human binding affinity constant (K_i).[14,16] Istradefylline reverses motor impairments in neurotoxin-induced experimental models of parkinsonism in rodents and in non-human primates.[18,19] This compound restored motor activity into the normal range in a non-human primate model of PD,[19] whereas L-dopa induced locomotor hyperactivity. In L-dopa-primed non-human primate model of PD, coadministration of istradefylline with a suboptimal dose of L-dopa improved the motor response.[20] Istradefylline improved impaired mobility of dopamine D2 receptor-deficient mice suggesting that this improvement was independent of dopaminergic system.[21] These preclinical studies suggest that istradefylline may provide an antiparkinson effect as monotherapy in PD, and may provide additional efficacy as an adjunct to L-dopa in patients with motor complications. The potential for istradefylline as an adjunct to L-dopa was demonstrated in PD patients with wearing-off fluctuations.[22] Istradefylline was reported to have reduced the daily OFF time, without an increase in ON time with troublesome dyskinesia.[23–25] However, the potential for istradefylline as an adjunct to L-dopa on motor symptoms themselves remains to be explored. This study was conducted to examine the efficacy of istradefylline as an adjunct therapy to L-dopa in Japanese patients with advanced PD.

PATIENTS AND METHODS

The study protocol was approved by the institutional review boards at each of the 47 participating centers. The study was conducted between March 2007 and August 2008 according to the principles of the Declaration of Helsinki and national regulations.

Patients

Informed consent was obtained from 423 patients with PD, of whom 363 were randomized and received double-blind treatment.

To be eligible for enrollment, subjects were required to be receiving at least three doses of L-dopa/decarboxylase inhibitor (DCI) per day with a daily dosage of at least 300 mg; to have been on a stable regimen of all antiparkinsonian drugs for at least 4 weeks before randomization; to have an average of at least 2 hours of OFF time per day as calculated from patients' ON/OFF diaries; and to have PD in Stages 2 to 4 while in the OFF state on the Modified Hoehn and Yahr Scale. Subjects were 20 years of age or older at the time of consent and all of them provided written consent themselves.

Main exclusion criteria included a history of neurosurgical operation for PD; transcranial magnetic stimulation (TMS) within 6 months before randomization, dementia or a Mini-Mental State Examination (MMSE) score of 25 or less, and pregnant women.

Study Design

The enrolled subjects completed diary training and entered the 12-week double-blind treatment period. At the start of double-blind treatment, subjects were randomly assigned to receive 20 mg/day istradefylline, 40 mg/day istradefylline, or placebo. At each postbaseline visit, they were assessed for diary data, UPDRS Parts I to IV, body weight, vital signs, and laboratory parameters. The Modified Hoehn and Yahr stage and Clinical Global Impression-Global Improvement (CGI-I) were evaluated at the end of double-blind treatment, and an ECG was recorded every 4 weeks during the treatment period.

The dosage and dosing regimen of antiparkinsonian drugs were maintained constant as far as possible within 4 weeks before randomization and during the treatment period. In the case of a TEAE most probably related to a specific antiparkinsonian drug, a reduction in the dosage of such antiparkinsonian drug was permitted.

Outcome Variables

The primary outcome variable was the change in the daily OFF time calculated from patients' ON/OFF diaries, which were developed by Hauser et al.[26] One diary consisted of 30-minute time periods for 24 hours beginning at 6:00 a.m. Each period was classified into the following five categories of the subject's condition: Asleep, OFF state, ON state without dyskinesia, ON state with nontroublesome dyskinesia, and ON state

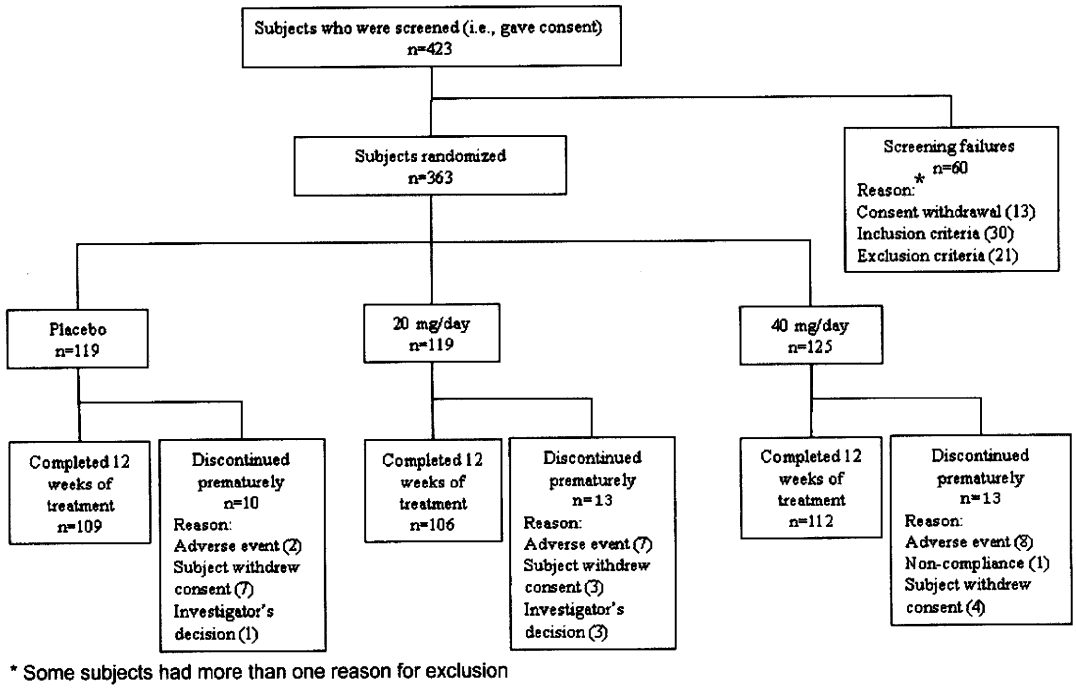

FIG. 1. Patients flow through the trial.

with troublesome dyskinesia. Missing values at week 12 or early termination were imputed using the last observation carried forward (LOCF) approach. The secondary outcome variables included the changes in the percentage of OFF period during awake time per day, the UPDRS Part I to III total score and the score of each Part, and CGI-I. The safety variable was TEAEs, which were determined by the investigator at each postbaseline visit based on symptoms, body weight, vital signs, laboratory results, ECG, and other data. A drug-related TEAE was defined as a sign, symptom or disease considered possibly, probably, or definitely related to the study drug.

Statistical Methods

Subjects who received at least one dose of study drug and who submitted at least one set of diaries were included in the full analysis set. The primary outcome variable was the change in the daily OFF time analyzed using an analysis of covariance (ANCOVA) model with the baseline OFF time as a covariate. Furthermore, the differences in the mean OFF time reduction between 40 mg/day istradefylline and placebo, and that between 20 mg/day istradefylline and placebo were statistically analyzed using Williams' test[27] based on ANCOVA model. The secondary outcome variables were analyzed in a manner similar to that for the primary one. In terms of CGI-I, the difference from placebo for 20 mg/day and 40 mg/day istradefylline will be analyzed by the Wilcoxon two-sample test.

Subjects who received at least one dose of study drug and in whom any postbaseline safety data available were included in the Safety Set. All TEAEs that occurred after the start of double-blind treatment were evaluated.

RESULTS

Population

Of the 363 subjects who received double-blind treatment, 357 subjects (placebo, 118; 20 mg/day istradefylline, 115; 40 mg/day istradefylline, 124) were included in the full analysis set, excluding 6 subjects who failed to submit at least one set of diaries, and 362 subjects (placebo, 119; 20 mg/day istradefylline, 118; 40 mg/day istradefylline, 125) were included in the Safety Set, excluding one subject who was withdrawn from the study without taking any dose of study drug (Fig. 1).

No significant difference was noted in the demographic or baseline characteristics among the three treatment groups (Table 1).

The Primary Outcome Variable

The daily OFF time changes from baseline at endpoint were −0.66 hours for placebo, −1.31 hours for 20 mg/day istradefylline, and −1.58 hours for 40 mg/

TABLE 1. *Demographic and baseline characteristics–full analysis set*

Variable	Placebo 118	20 mg/day 115	40 mg/day 124	*P*-value*
Age (yr)	65.0 ± 7.6	65.1 ± 7.2	63.7 ± 8.6	[a]0.417
Gender (n)				
Male	45 (38.1%)	50 (43.5%)	55 (44.4%)	[b]0.574
Female	73 (61.9%)	65 (56.5%)	69 (55.6%)	
BMI(kg/m^2)	21.82 ± 3.55	21.84 ± 3.19	21.96 ± 3.61	[a]0.984
Time since Diagnosis (yr)	8.338 ± 4.826	8.037 ± 4.076	8.089 ± 4.048	[a]0.977
Time since onset of motor complications (yr)	3.506 ± 3.015	3.167 ± 2.499	3.126 ± 2.884	[a]0.555
The daily OFF time per day (hr)	6.43 ± 2.71	6.79 ± 2.86	6.55 ± 2.48	[a]0.598
UPDRS Part III subscale score (ON state)	20.6 ± 9.2	21.0 ± 10.6	21.1 ± 11.0	[a]0.972
Daily dosage of prior L-dopa (mg)	426.3 ± 143.0	407.0 ± 113.1	415.3 ± 159.2	[a]0.726
Concomitant medications(n)				
Dopamine agonists	105 (89.0%)	110 (95.7%)	114 (91.9%)	[b]0.166
Anticholinergic agents	23 (19.5%)	18 (15.7%)	23 (18.5%)	[b]0.729
Selegiline	62 (52.5%)	57 (49.6%)	67 (54.0%)	[b]0.782
Entacapone	15 (12.7%)	22 (19.1%)	16 (12.9%)	[b]0.292
Amantadine	45 (38.1%)	43 (37.4%)	39 (31.5%)	[b]0.491

*$P < 0.15$
[a]Kruskal–Wallis test
[b]Chi-square test

day istradefylline. The differences from placebo were −0.65 hours for 20 mg/day istradefylline ($P = 0.013$) and −0.92 hours for 40 mg/day istradefylline ($P < 0.001$) (*P*-values by Williams' test) (Table 2). The effect of the baseline OFF time in the ANCOVA model was highly significant (t test, $P < 0.001$).

The Secondary Variables

The UPDRS part III changes from baseline at endpoint were −3.7 for placebo, −5.7 for 20 mg/day istradefylline, and −5.7 for 40 mg/day istradefylline. The differences from placebo were −2.0 for 20 mg/day istradefylline ($P = 0.006$) and −2.0 for 40 mg/day istradefylline ($P = 0.006$) (*P*-values by Williams' test) (Table 3).

The percentages of subjects in the "much improved" or better CGI-I category at endpoint were 14.4% (17/118) for placebo, 20.9% (24/115) for 20 mg/day istradefylline, and 23.4% (29/124) for 40 mg/day istradefylline. The percentages of subjects in the "minimally improved" or better categories were 46.6% (55/118), 56.5% (65/115), and 56.5% (70/124), respectively. There was a tendency for larger numbers of subjects in better improved ranks in istradefylline treated groups. However, in the comparison of distribution of 7 ranks of improvement between placebo and each istradefylline treated group, the differences did not quite reach the statistical significance ($P = 0.074$ for 20 mg/day istradefylline and $P = 0.096$ for 40 mg/day istradefylline by Wilcoxon two-sample test).

The changes from baseline in the ON time with the dyskinesia (nontroublesome and troublesome combined) at endpoint were −0.09 hours for placebo, +0.14 hours for 20 mg/day istradefylline, and +0.32

TABLE 2. *Daily OFF time based on patients' ON/OFF diaries–actual and change from baseline values–full analysis set*

	Placebo 118	20 mg/day 115	40 mg/day 124
Baseline (hr)[a]	6.43 ± 2.71	6.79 ± 2.86	6.55 ± 2.48
Endpoint (hr)[a]	5.80 ± 3.27	5.42 ± 3.37	4.99 ± 2.68
Change from Baseline at end point (hr)[b]			
LS mean	−0.66	−1.31	−1.58
LS mean(vs. placebo)	–	−0.65	−0.92
P-value[c]	–	0.013[d]	<0.001[d]

[a]Mean ±SD
[b]LS (least squares) mean and *P*-value are based on the main effects ANCOVA with terms for baseline, investigator and treatment.
[c]*P*-value by Williams' test.
[d]$P < 0.025$, NS: not significant.

TABLE 3. *UPDRS part III subscale score (ON state)–actual and change from baseline values–Full Analysis Set*

	Placebo 118	20 mg/day 115	40 mg/day 124
Baseline[a]	20.6 ± 9.2	21.0 ± 10.6	21.1 ± 11.0
Endpoint[a]	16.7 ± 9.4	14.9 ± 10.1	15.2 ± 11.1
Change from Baseline at end point[b]			
LS mean	−3.7	−5.7	−5.7
LS mean(vs. placebo)	–	−2.0	−2.0
P-value[c]	–	0.006[d]	0.006[d]

[a]Mean ±SD
[b]LS (least squares) mean and *P*-value are based on the main effects ANCOVA with terms for baseline, investigator and treatment.
[c]*P*-value by Williams' test.
[d]$P < 0.025$, NS: not significant.

hours for 40 mg/day istradefylline. There were no significant differences for both 20 mg/day and 40 mg/day istradefylline versus placebo. Regarding the troublesome dyskinesia, the changes in ON time with troublesome dyskinesia were −0.10 hours for placebo, +0.07 hours for 20 mg/day istradefylline and +0.25 hours for 40 mg/day istradefylline. ON time with troublesome dyskinesia was slightly but significantly longer in 40 mg/day istradefylline compared with placebo (Williams' test, $P = 0.011$). No significant difference was observed between 20 mg/day istradefylline and placebo.

Safety

The incidences of TEAEs were 58.0% (69/119) in the placebo group, 59.3% (70/118) in the 20 mg/day istradefylline group, and 59.2% (74/125) in the 40 mg/day istradefylline group. The most commonly reported TEAE was nasopharyngitis, which occurred in 4.2% (5/119) of subjects receiving placebo, 5.9% (7/118) receiving 20 mg/day istradefylline, and 8.8% (11/125) receiving 40 mg/day istradefylline. The common TEAEs are summarized in Table 4. Dyskinesia, reported as a drug-related TEAE, occurred in 2.5% (3/119) of subjects receiving placebo, 8.5% (10/118) receiving 20 mg/day istradefylline, and 6.4% (8/125) receiving 40 mg/day istradefylline.

No deaths were reported in the study. Serious adverse events were observed in two subjects receiving placebo (three events; external injury of head, CPK increased and transient ischaemic attack), in three subjects receiving 20 mg/day istradefylline (four events; worsening of lumbago and compression fracture at L2, systemic contusion due to a fall, and multiple gastric ulcers (active stage)), and in 6 subjects receiving 40 mg/day istradefylline (eight events; emphysema, CK increased and right upper limb peripheral nerve disorder of right upper limb, cough, hypertension, cholecystitis, and depression aggravated and persecutory delusion). There were no differences in TEAEs between the istradefylline group and the placebo group.

DISCUSSION

We evaluated the efficacy and safety of istradefylline in Japanese patients with PD in this study.

In the primary outcome variable, the changes in the daily OFF time from baseline at endpoint were −0.66 hours for placebo, −1.31 hours for 20 mg/day istradefylline, and −1.58 hours for 40 mg/day istradefylline.

TABLE 4. *Treatment emergent adverse events (those reported for 3% or more of subjects)–Safety Set*

[System organ class] preferred term	Placebo (n = 119)		20 mg/day (n = 118)		40 mg/day (n = 125)	
	n	(%)	n	(%)	n	(%)
Subjects with any TEAE	69	58.0	70	59.3	74	59.2
Nasopharyngitis	5	4.2	7	5.9	11	8.8
Constipation	7	5.9	6	5.1	8	6.4
Dyskinesia	3	2.5	10	8.5	8	6.4
Blood creatine phosphokinase increased	4	3.4	8	6.8	6	4.8
Blood trypsin increased	6	5.0	2	1.7	5	4.0
Protein urine present	3	2.5	2	1.7	8	6.4
Upper respiratory tract inflammation	1	0.8	4	3.4	7	5.6
Blood urine present	1	0.8	7	5.9	3	2.4
Contusion	3	2.5	3	2.5	4	3.2
Lipase increased	5	4.2	1	0.8	4	3.2
Blood urea increased	1	0.8	2	1.7	5	4.0
Nausea	2	1.7	4	3.4	2	1.6
Somnolence	2	1.7	4	3.4	1	0.8
Hallucination	0	0.0	2	1.7	4	3.2
Back pain	1	0.8	4	3.4	0	0.0
Glucose urine present	0	0.0	4	3.4	1	0.8

The differences from placebo were −0.65 hours for 20 mg/day istradefylline (ANCOVA, $P = 0.013$) and −0.92 hours for 40 mg/day istradefylline (ANCOVA, $P < 0.001$). Istradefylline was shown to significantly reduce the daily OFF time in Japanese PD patients compared with placebo.

The duration of the baseline OFF time appeared to be an important prognostic factor as we found a strong positive correlation between the duration of the baseline OFF time and the magnitude of reduction in OFF time at endpoint. Among other clinical variables studied [age, gender, body mass index (BMI), time since diagnosis, time since onset of motor complications, Modified Hoehn and Yahr Scale in the OFF state, daily L-dopa dosage, and combined antiparkisonian drugs], only the age of the patients and the BMI showed positive correlations (F test, $P = 0.002$ for age, $P = 0.042$ for BMI).

Three studies conducted in North America in a similar design to this study proved the effect of istradefylline reducing the daily OFF time at 3 dose levels (20 mg/day, 40 mg/day, and 60 mg/day).[23–25] The reductions from placebo in the daily OFF time were −0.39 and −0.73 hours for 20 mg/day istradefylline (2 studies) (ANCOVA, $P = 0.055$ and $P = 0.033$), −1.16 hours for 40 mg/day istradefylline (ANCOVA, $P = 0.006$) and −0.77 hours for 60 mg/day istradefylline (ANCOVA, $P = 0.023$), whereas reductions from placebo in this study were similar between 20 mg/day and 40 mg/day istradefylline. The reductions at each dose were almost same in 3 clinical studies in North America and this study. This study supported the results of clinical studies conducted in North America.

In the secondary outcome variables, these clinical studies in North America could not prove the reduction of the UPDRS Part III subscale (ON state) score from baseline at endpoint. Whereas istradefylline at 20 mg/day and 40 mg/day significantly reduced the UPDRS Part III subscale score (ON state) compared with placebo in this study. Istradefylline was shown to be effective in improving the UPDRS Part III subscale score (ON state) as well as in reducing the daily OFF time in Japanese PD patients.

In terms of safety, the most commonly reported TEAE in this study was nasopharyngitis (placebo, 4.2%; 20 mg/day istradefylline, 5.9%; 40 mg/day istradefylline, 8.8%), which was considered by investigators to be unrelated to istradefylline in all cases. The most commonly reported drug-related TEAE was dyskinesia (placebo, 2.5%; 20 mg/day istradefylline, 8.5%; 40 mg/day istradefylline, 6.4%) in this study. No dose-dependent increase was found in the incidence of dyskinesia. The intensity was mild to moderate in all cases and no subjects experienced severe dyskinesia. Based on these results, it was found that istradefylline is well tolerated in Japanese PD patients.

In the studies conducted in North America, the most frequently reported drug-related TEAE was also dyskinesia and the intensity was similar to that in this study. There were no great differences between the studies conducted in North America and this study in the incidences of other drug-related TEAEs or the values of laboratory or other test results.

In conclusion, istradefylline at 20 mg and 40 mg once daily is effective in relieving wearing-off fluctuations (as measured by reductions in OFF time) and improving motor function during ON state (as measured by reductions in the UPDRS Part III subscale score) in Japanese PD patients with motor complications on L-dopa therapy. Moreover, istradefylline was well tolerated at both doses.

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Author Roles: Yoshikuni Mizuno participated in study design and interpretation of data, wrote the first draft and revised it based on critical review by coauthors. Kazuko Hasegawa participated in study design, acquisition of data, and critically revised the draft. Tomoyoshi Kondo participated in study design and interpretation of data, performed statistical analyses, and critically revised the draft. Sadako Kuno participated in study design, acquisition of data, and critically revised the draft. Mitsutoshi Yamamoto participated in study design, acquisition of data, and critically revised the draft. There were no ghost writers and this manuscript complies with the *Movement Disorders* policy on ghost writing.

REFERENCES

1. Fahn S. Description of Parkinson's disease as a clinical syndrome. Ann NY Acad Sci 2003;991:1–14.
2. Barzilai A, Melamed E. Molecular mechanisms of selective dopaminergic neuronal death in Parkinson's disease. Trends Mol Med 2003;9:126–132.
3. Dauer W, Przedborski S. Parkinson's disease mechanisms and models. Neuron 2003;39:889–909.
4. Hunot S, Hirsch E. Neuroinflammatory processes in Parkinson's disease. Ann Neurol 2003;53(Suppl 3):S49–S58; discussion S58–S60.
5. Bonuccelli U. Comparing dopamine agonists in Parkinson's disease. Curr Opin Neurol 2003;16(Suppl 1):S13–S19.
6. Jenner P. Dopamine agonists, receptor selectivity and dyskinesia induction in Parkinson's disease. Curr Opin Neurol 2003; 16(Suppl 1):S3–S7.
7. Jenner P. A2A antagonists as novel non-dopaminergic therapy for motor dysfunction in PD. Neurology 2003;61(11 Suppl 6):S32–S38.
8. Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. Limitations of current Parkinson's disease therapy. Ann Neurol 2003;53(Suppl 3):S3–S12.

9. DeLong MR. Primate models of movement disorders of basal ganglia origins. Trends Neurosci 1990;13:281–285.
10. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001;56(Suppl 5):S1–S88.
11. Obeso JA, Rodriguez MC, DeLong MR. Basal ganglia pathophysiology. A critical review. Adv Neurol 1997;74:3–18.
12. Gatev P, Darbin O, Wichmann T. Oscillations in the basal ganglia under normal conditions and in movement disorders. Mov Disord 2006;21:1566–1577.
13. Popoli P, Blum D, Pintor A. The controversial role of adenosine A2A receptor antagonists as neuroprotective agents. Curr Med Chem Cent Nerv Syst Agents 2004;4:35–45.
14. Jenner P. Istradefylline, a novel adenosine A2A receptor antagonist, for the treatment of Parkinson's disease. Exp Opin Investig Drugs 2005;14:729–738.
15. Mori A, Shindou T. Modulation of GABAergic transmission in the striatopallidal system by adenosine A2A antagonists. Neurology 2003;61(Suppl 6):S44–S48.
16. Kase H. Progress in pursuit of therapeutic A2A antagonists: the adenosine A2A receptor selective antagonist KW-6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease. Neurology 2003;61(Suppl 6):S97–S100.
17. Calon F, Dridi M, Hornykiewicz O, Bedard PJ Rajput AH, Di Paolo T. Increased adenosine A2A receptors in the brain of Parkinson's disease patients with dyskinesia. Brain 2004;127:1075–1084.
18. Lundblad M, Vaudano E, Cenci MA. Cellular and behavioural effects of the adenosine A2A receptor antagonist KW-6002 in a rat model of L-DOPA-induced dyskinesia. J Neurochem 2003;84:1398–1410.
19. Kanda T, Jackson MJ, Smith LA, et al. Combined use of the adenosine A2A antagonist KW-6002 with L-DOPA or with selective D1 or D2 dopamine agonists increases antiparkinsonian activity but not dyskinesia in MPTP-treated monkeys. Exp Neurol 2000;162:321–327.
20. Kanda T, Tashiro T, Kuwana Y, Jenner P. Adenosine A2A receptors modify motor function in MPTP-treated common marmosets. Neuroreport 1998;9:2857–2860.
21. Aoyama S, Kase H, Borrelli E. Rescue of locomotor impairment in dopamine D2 receptor-deficient mice by an adenosine A2A receptor antagonist. J Neurosci 2000;20:5848–5852.
22. Hauser RA, Hubble JP, Truong DD, Istradefylline US-,001 Study Group. Randomized trial of the adenosine A2A receptor antagonist istradefylline in advanced PD. Neurology 2003;61:297–303.
23. Stacy M, Silver D, Mendis T, Sutton J, Mori A, Chaikin P, Sussman NM. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. Neurology 2008;70:2233–2240.
24. LeWitt PA, Guttman M, Tetrud JW, Tuite PJ, Mori A, Chaikin P, Sussman NM. Adenosine A2A receptor antagonist Istradefylline (KW-6002) reduces "Off" time in Parkinson's disease: a double- blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol 2008;63:295–302.
25. Hauser RA, Shulman LM, Trugman JM, Roberts JW, Mori A, Ballerini R, Sussman NM. Study of istradefylline in patients with Parkinson's disease on L-dopa with motor fluctuations. Mov Disord 2008;23:2177–2185.
26. Hauser RA, Deckers F, Lehert P. Parkinson's disease home diary: further validation and implications for clinical trials. Mov Disord 2004;19:1409–1413.
27. Williams DA. A test for differences between treatment means when several dose levels are compared with a zero dose control. Biometrics 1971;27:103–117.

APPENDIX

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