

Zolpidem Improves Neuropsychiatric Symptoms and Motor Dysfunction in A Patient with Parkinson's Disease after Deep Brain Stimulation

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Abstract-

Purpose: To illustrate the beneficial effect of zolpidem on the neuropsychiatric and motor symptoms in a patient with Parkinson disease (PD) after bilateral subthalamic nucleus deep brain stimulation.

Case Report: The 61-year-old housewife was diagnosed to have PD for 12 years with initial presentation of clumsiness and rest tremor of right limbs. She was referred to our hospital in March 2009 due to shortening of drug beneficial period since 3 years ago and on-phase dyskinesia in recent 2 years. Bilateral STN DBS was conducted on 18 June, 2009. Fluctuating spells of mental confusion were developed on the next day after surgery. Electric stimuli via DBS electrodes were delivered with parameters of 2 volts, 60 μ s, 130 Hz on bilateral STN 32 days after DBS. The incoherent behaviors and motor fluctuation remained to occur. The beneficial effect of zolpidem on her neuropsychiatric and motor symptoms was detected incidentally in early July 2009. She could chat normally with her caregiver and walk with assistance after taking zolpidem. The beneficial period may last for 2 hours. Zolpidem was then given in dosage of 10 mg three times per day. The neuropsychiatric inventory was scored 56 during zolpidem 'off' and 30 during zolpidem 'on'. To understand the intriguing feature, we conducted FDG-PET during 'off' and 'on' zolpidem conditions. The results revealed that the metabolism was decreased in the right frontal, parietal cortex and caudate nucleus during zolpidem 'off'. These cool spots can be partially restored by zolpidem.

Conclusion: Zolpidem ameliorated the neuropsychiatric and parkinsonian motor symptom in the PD patient. Since GABAA benzodiazepine receptors are widely distributed throughout the central nervous system, zolpidem probably acts via modulating structures lying within the cortico-subcortical loop or by direct effect on these cortical regions.

Key words: Parkinson's disease, zolpidem, neuropsychiatry, subthalamic nucleus

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INTRODUCTION

Zolpidem has been reported to have unexpected benefits on motor disorders in patients with PD⁽¹⁾. However, the mechanism underlying this phenomenon is uncertain. We herein report a case with PD who developed fluctuating neuropsychiatric and motor symptoms after bilateral subthalamic nucleus (STN) deep brain stimulation (DBS). In addition to motor deficits, the neuropsychiatric symptoms were ameliorated by zolpidem. FDG-PET was conducted to illustrate the situation of cerebral metabolism altered by zolpidem.

CASE REPORT

The 61-year-old housewife was diagnosed to have PD for 12 years with initial presentation of clumsiness and rest tremor of right limbs. She was referred to our hospital in March 2009 due to shortening of drug beneficial period since 3 years ago and on-phase dyskinesia in recent 2 years. The medications at the time of referral included levodopa (1000 mg/day), biperdin (8 mg/day), selegiline (10 mg/day) and zolpidem 10 mg at bedtime. Bilateral STN DBS was conducted on 18 June, 2009. Levodopa (750 mg/day), selegiline and zolpidem were maintained during admission. Fluctuating spells of mental confusion were developed on the next day after surgery. She might sometimes be inertia for several hours and then shifted into confusion state with incoherent speech and fearing of being killed in another few

hours. Electric stimuli via DBS electrodes were delivered with parameters of [2 volts, 60 μ s, 130 Hz] on bilateral STN 32 days after DBS. The incoherent behaviors and motor fluctuation remained to occur. Zolpidem was administrated as a hypnotic agent since the third day after surgery. The beneficial effect of zolpidem on her neuropsychiatric and motor symptoms was detected incidentally in early July 2009. She could chat normally with her caregiver and walk with assistance after taking zolpidem. The beneficial period may last for 2 hours. (Figure 1) Zolpidem was then given in dosage of 10 mg three times per day. The Neuropsychiatric Inventory⁽²⁾

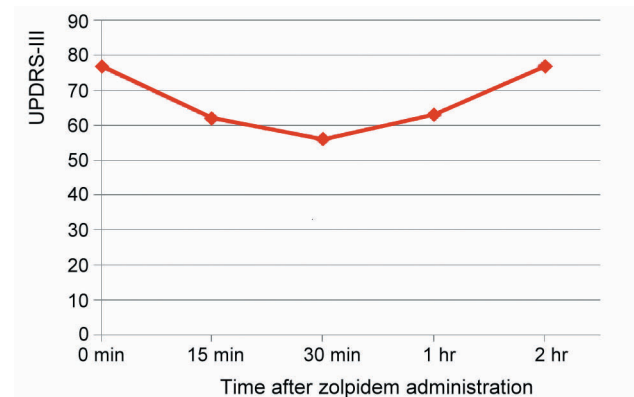


Figure 1. Time course of zolpidem effect during ‘DBS off’ and ‘dopaminergic agents off’ states. Motor function is improved about 5 minutes after the administration of zolpidem and the beneficial effect lasts for 2 hours. Her cognition is ameliorated during this period. The UPDRS-III was evaluated at 15 minutes, 30 minutes, 1 hour, and 2 hours after zolpidem administration.

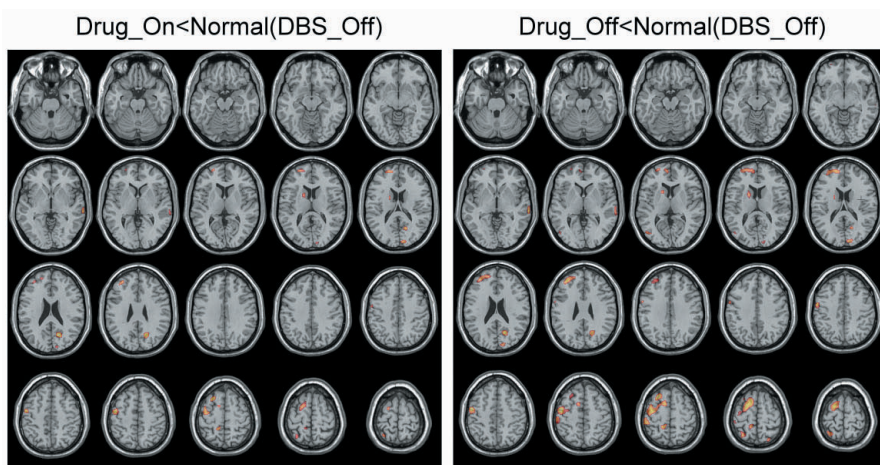


Figure 2. The results of FDG PET/CT during zolpidem ‘on’ (left panel) and ‘off’ phase (right panel).

was scored 56 during zolpidem 'off' and 30 during zolpidem 'on'. FDG-PET was conducted 15 minutes after zolpidem on the 80th day and during off- zolpidem phase on the 83rd day after surgery in DBS switching off state. (Figure 2)

DISCUSSION

It is well known that DBS can improve the motor function of patients with advanced PD. However, around 4% of these patients may develop neuropsychiatric symptoms⁽³⁾. This may be related to the functional perturbation of the STN limbic component caused by electrode implantation or afterward high frequency electric stimulation⁽³⁾. Unlike our patient, most of the neuropsychiatric symptoms were transient in previous reports⁽⁴⁾. The beneficial effect of zolpidem to PD is intriguing. Zolpidem is a hypnotic drug acting as GABA_A agonist. In animal models, it had been reported that zolpidem may quench the STN overactivities by binding to GABA_A receptor in STN and then improve the parkinsonian motor dysfunction⁽⁵⁾. However, the model cannot explain how the neuropsychiatric symptoms can also be ameliorated. Furthermore, the clinical situations of the current patient were not overcome by STN DBS suggesting that the zolpidem effect may involve other mechanisms. In order to further understand the intriguing feature, we conducted FDG-PET during her 'off' and 'on' zolpidem conditions. Statistical parametric mapping was used for analyzing FDG-PET results before and after zolpidem administration. The results revealed that the metabolism was decreased mainly in the right frontal, parietal cortex and caudate nucleus during zolpidem 'off'. (Figure 2) These cool spots can be partially restored by the administration of zolpidem. (Figure 2) The imaging features resembled previous voxel based morphometry MRI and FDG-PET in dementia patients with behavioral disorders⁽⁶⁾. The findings suggest that these regions are

crucial for the regulation of human emotional behaviors. Since GABA_A 1 subunits /1 benzodiazepine receptors are widely distributed throughout the central nervous system⁽⁵⁾, the diminution of metabolism can be temporally restored by zolpidem probably via modulating structures lying within the cortico-subcortical loop or by direct effect on these cortical regions.

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REFERENCES

1. Chen YY, Sy HN, Wu SL. Zolpidem improves akinesia, dystonia and dyskinesia in advanced Parkinson's disease. *J Clin Neurosci* 2008;15:955-956.
2. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308-2314.
3. Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser Vandewalle V. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat Disord* 2006;12: 265-272.
4. Kulisevsky J, Berthier ML, Gironell A, Pascual-Sedano B, Molet J, Pares P. Mania following deep brain stimulation for Parkinson's disease. *Neurology* 2002;59:1421-1424.
5. Chen L, Xie JX, Fung KS, Yung WH. Zolpidem modulates GABA(A) receptor function in subthalamic nucleus. *Neurosci Res* 2007;58:77-85.
6. Zahn R, Moll J, Iyengar V, Huev ED, Tierner M, Krueger F, Grafman J. Social conceptual impairments in frontotemporal lobar degeneration with right anterior temporal hypometabolism. *Brain* 2009;132:604-616.