

Improvement in Parkinsonism with zonisamide treatment in a patient with dementia with lewy bodies

Abstract

Here, I report the case of a 70-year-old man with dementia with Lewy bodies (DLB) who experienced an improvement in Parkinsonism with zonisamide treatment without worsening of visual hallucinations or induction of orthostatic hypotension. The patient was initially medicated with levodopa, ropinirole and donepezil to treat Parkinsonism and dementia, as well as visual hallucinations. Selegiline was later added to help manage a subsequent aggravation of his Parkinsonism. Under this treatment regimen, motor symptoms improved, but adverse effects such as visual hallucinations, orthostatic hypotension and syncopal attacks appeared. Therefore, selegiline was replaced with zonisamide at a dose of 25 mg per day. Subsequently, the visual hallucinations and orthostatic hypotension rapidly improved and, 3 months later, the severity of his short steppage gait was alleviated. This case report describes a patient with DLB who experienced improvement in motor symptoms by incorporating zonisamide into the treatment regimen without deterioration of visual hallucinations or orthostatic hypotension. If adverse effects such as visual hallucinations and orthostatic hypotension are seen in patients with DLB following the use of dopamine agents, zonisamide might be a good alternative therapeutic option. Proper clinical trials need to be done to validate a therapeutic potential of zonisamide in DLB.

Keywords: dementia with lewy bodies, zonisamide, parkinsonism, dementia, visual hallucination, orthostatic hypotension

Volume 1 Issue 3 - 2014

Yoshiharu Taguchi, Shutaro Takashima,
Kortaro Tanaka

Department of Neurology, Toyama University Hospital, Japan

Correspondence: Yoshiharu Taguchi, Department of Neurology, Toyama University Hospital, 263 Sugitani, Toyama 93-194, Japan, Tel +81-76-434-7309, Email ytagu@med.u-toyama.ac.jp

Received: June 26, 2014 | **Published:** July 25, 2014

Abbreviations: DLB, dementia with lewy bodies; PD, parkinson's disease; ADL, activities of daily living; TH, tyrosine hydroxylase; MAO-B, monoamine oxidase-B

Introduction

Dementia with Lewy bodies (DLB) is the second common dementia after Alzheimer's disease, accounting for approximately a quarter of all cases of dementia. It is associated with a progressive decline in cognitive abilities, which interferes with social and occupational function. The clinical features of DLB appear with disease progression, beginning with visual hallucinations and fluctuations in cognitive ability, Parkinsonism, and finally autonomic symptoms.¹ The recommended options for specifically treating cognitive impairments are currently cholinesterase inhibitors such as rivastigmine, donepezil and galantamine.² For patients with DLB, however, the combination of medications required to treat the constellation of symptoms exhibited in this form of dementia can counter each other's therapeutic effects. Anti-parkinsonian agents are used for improving motor symptoms, but have the potential to lead to psychotic problems such as hallucinations and confusion, while anti-psychotic agents are used for improving psychotic symptoms, but can potentially lead motor problem.³ In addition, DLB patients often exhibit drug hypersensitivity,⁴ and therefore cannot be fully medicated.

Zonisamide, which has been identified as an anti-epileptic drug, was approved in Japan for the treatment of motor dysfunctions and for alleviating symptoms in Parkinson's disease (PD) at doses of 25-50mg per day. This report demonstrates that incorporating zonisamide

into the treatment regimen improved Parkinsonism in a patient having DLB without producing any deterioration of visual hallucinations and orthostatic hypotension.

Case report

A 70-year-old man with a history of diabetes came to our hospital for a work-up in July 2010 and was diagnosed with DLB. The patient had already been experiencing bradykinesia and a frozen gait in the last 5 months period, and progressive memory loss and recurrent visual hallucinations of insects within the last month prior to the first hospital visit. Our clinical diagnosis indicated that the patient had rigidity, resting tremors, and postural instability (Hoehn-Yahr stage: 3.0), as well as visual hallucinations and cognitive impairment with loss of short-term memory (MMSE score: 19). Brain MRI showed mild but widespread atrophy. Based on progressive memory loss, recurrent visual hallucinations and Parkinsonism, we diagnosed this patient as probable DLB, according to the consensus guidelines for the clinical diagnosis of the DLB.¹ This patient was not examined for dopamine transporter, because ¹²³I-FP-CIP SPECT tracer binding to the dopamine transporter was not approved in Japan in that time. The patient was medicated with levodopa (300mg a day) on the first hospital visit which led to improvements in rigidity, bradykinesia, and short steppage gait (modified Hoehn-Yahr stage: 3.0 to 2.5). A month later, donepezil was added to the treatment regimen at a dose of 5mg per day for management of dementia and visual hallucinations. Addition of donepezil mildly improved the visual hallucinations. However, on this treatment regimen the patient fell frequently while walking. As a result, ropinirole was also prescribed, and the dosage was gradually increased to 6mg per day. For the next several months,

the patient successfully maintained his activities of daily living (ADL) without his partner's assistance. In February 2011, however, due to exacerbation of bradykinesia, rigidity and short steppage gait (modified Hoehn-Yahr stage: 4.0), selegiline was prescribed at a dose of 2.5mg per day. While an improvement of motor symptoms was achieved, visual hallucinations and orthostatic hypotension (supine blood pressure: 110/66mmHg/ standing blood pressure: 82/48mmHg) reappeared, and syncopal attacks emerged. Taking into account that the combination of medications in the current treatment regimen may be underlying the deterioration of visual hallucinations and orthostatic hypotension, selegiline was switched to zonisamide at a dose of 25mg per day for treatment of Parkinsonism. Under this new treatment regimen, visual hallucinations and orthostatic hypotension were rapidly improved, and 3months later, the relief of bradykinesia and short steppage gait was observed (modified Hoehn-Yahr stage: 3.0) without deterioration of psychotic manifestations such as visual hallucinations and cognitive dysfunctions (Figure 1).

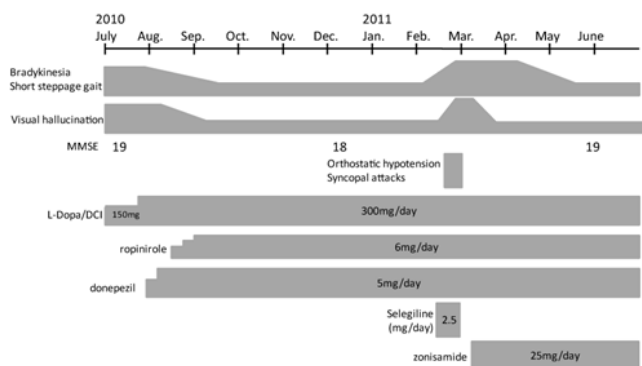


Figure 1 Clinical course.

Discussion

In this case report of a patient with DLB, I observed that zonisamide improved the visual hallucinations and orthostatic hypotension that coincided with initiation of selegiline treatment, while relieving Parkinsonism. Similar results were also observed in other case reports; motor dysfunction in patients having DLB was relieved by zonisamide without causing a deterioration of psychotic symptoms or cognitive function.^{5,6}

Patients with DLB generally experience visual hallucinations and fluctuations in cognitive fluctuation along with orthostatic hypotension with a high incidence rate. Patients having DLB also exhibit drug-hypersensitivity. In DLB, Parkinsonism, autonomic nervous system dysfunction, and psychological disturbances appear with disease progression. Therefore, the required drug therapies are conflicting, often requiring concomitant treatment of both motor and psychotic symptoms. This results in the fact that the patients often cannot be fully medicated. The visual hallucinations and orthostatic hypotension observed with a high incidence rate in patients with DLB are reported to be worsened by L-Dopa medication. Selegiline is a non-reversible monoamine oxidase (MAO-B) inhibitor, which increases dopamine transmission by inhibiting dopamine metabolism in the synaptic cleft, and therefore might possibly increase the adverse events induced by L-dopa. Indeed, the patient experienced a worsening of visual hallucinations and orthostatic hypotension along with an improvement in motor symptoms after addition of selegiline therapy.

Zonisamide has been approved as an anti-parkinsonian drug in Japan and has been available since 2009. However, their mechanisms actions in alleviating Parkinsonism have not yet been fully characterized. Studies suggest that zonisamide may increase dopamine transmission by activating tyrosine hydroxylase (TH) and inhibiting MAO-B activity.⁷ In a study conducted in rats, zonisamide increased intra- and extra-cellular levels of dopamine in the striatum.⁸ In addition, non-dopaminergic effects of zonisamide have also been reported recently. Zonisamide can block T-type calcium-channels and regulate the indirect pathway of basal ganglia. Zonisamide was reported to be efficacious for several kinds of tremors in a drug-induced tremor model in rats through the inhibition of T-type calcium channel.^{9,10} Furthermore, zonisamide was found to have agonist-like activities via opioid δ_1 -receptors expressed in rat striato-pallidal GABA neurons, thereby decreasing GABA release.¹¹ Recently, it was reported that zonisamide may interact with metabotropic glutamate-receptor (mGluR) groups II and III through direct and/or indirect mechanism in rats.¹² These multiple mechanisms of action of zonisamide are all believed to contribute to the relief of Parkinsonism, without worsening L-Dopa-induced dyskinesia and psychotic symptoms. Consistent with this, a clinical trial of zonisamide showed that the incidence of dyskinesia and hallucinations in a group given 100mg of the agent per day is almost the same as that in the placebo group.⁷

Conclusion

In this case report, I described a patient with DLB who experienced an improvement in motor symptoms by the addition of zonisamide to the treatment regimen, without deterioration of psychotic manifestations such as visual hallucinations and cognitive dysfunctions, or orthostatic hypotension. If adverse effects such as visual hallucinations and orthostatic hypotension are seen in patients with DLB following the use of dopamine agents, zonisamide might be a good alternative therapeutic option. Proper clinical trials need to be done to validate a therapeutic potential of zonisamide in DLB.

Acknowledgments

None.

Conflicts of interest

The authors declare there are no conflicts of interest related to the article.

References

- McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies:third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872.
- Beyer K, Ariza A. The therapeutical potential of alpha-synuclein antiaggregatory agents for dementia with Lewy bodies. *Curr Med Chem*. 2008;15(26):2748–2759.
- Rolinski M, Fox C, Maidment I, et al. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Chchran Database Syst Rev*. 2012;3:CD006504.
- Henriksen AL, St Dennis C, Setter SM, et al. Dementia with lewy bodies:therapeutic opportunities and pitfalls. *Consult Pharm*. 2006;21(7):563–575.

5. Odawara T, Shiozaki K, Togo T, et al. Administration of zonisamide in three cases of dementia with Lewy bodies. *Psychiatry and Clin Neurosci*. 2010;64(3):327–329.
6. Sato S, Mizukami K, Asada T. Successful treatment of extra pyramidal and psychotic symptoms with zonisamide in a patient with dementia with Lewy bodies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6):1130–1131.
7. Murata M, Hasegawa K, Kanazawa I, et al. Zonisamide improves motor function in Parkinson disease:a randomized, double-blind study. *Neurology*. 2007;68(1):45–50.
8. Okada M, Kaneko S, Hirano T, et al. Effects of zonisamide on dopaminergic system. *Epilepsy Res*. 1995;22(3):93–205.
9. Miwa H, Hama K, Kajimoto Y, et al. Effects of zonisamide on experimental tremors in rats. *Parkinsonism Relat Disord*. 2008;14(1):3–36.
10. Miwa H, Kubo T, Suzuki A, et al. Effects of zonisamide on c-Fos expression under conditions of tacrine-induced tremulous jaw movements in rats:A potential mechanism underlying its anti-parkinsonian tremor effect. *Parkinsonism Relat Disord*. 2009;15(1):30–35.
11. Yamamura S, Ohoyama K, Nagase H, et al. Zonisamide enhances delta receptor-associated neurotransmitter release in striato-pallidal pathway. *Neuropharmacology*. 2009;57(3):322–331.
12. Fukuyama K, Tanahashi S, Hoshikawa M, et al. Zonisamide regulates basal ganglia transmission via astroglial kynurenine pathway. *Neuropharmacology*. 2014;76(Pt A):137–145.