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. 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 step 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

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 25-50 mg 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 (300 mg 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 5 mg 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 6 mg 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 2.5 mg per day. While an improvement of motor symptoms was achieved, visual hallucinations and orthostatic hypotension (supine blood pressure: 110/66 mmHg/ standing blood pressure: 82/48 mmHg) 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 25 mg per day for treatment of Parkinsonism. Under this new treatment regimen, visual hallucinations and orthostatic hypotension were rapidly improved, and 3 months 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).

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.

Figure 1: Clinical course.
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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-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].

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 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.

References

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