Case Report

The use of zolpidem in the treatment of progressive supranuclear palsy

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1. Introduction

Progressive supranuclear palsy (PSP) is a debilitating progressive neurodegenerative disorder for which there is no proven pharmacological treatment. Zolpidem immediate release formulation has been reported to show short-term improvements in motor function and voluntary saccadic eye movements, but the benefits were not sustained. A 61-year-old man with a 4-year history of PSP was observed over 6 months to have sustained improvement in motor function, pseudobulbar symptoms and ocular motility 2 months after commencing zolpidem controlled release (CR) formulation. He was admitted to hospital and a detailed neurological and functional assessment recorded on video after withdrawal of zolpidem CR, and again following re-introduction of the medication. Within 1 hour of administration of 25 mg zolpidem CR the patient had a dramatic improvement in fine motor skills, dexterity, speed and fluidity of movement, facial and vocal expression, oropharyngeal coordination and function and pursuit, and voluntary saccadic eye movements. These improvements were observed for 4 hours to 5 hours post-dose and were reproducible on subsequent withdrawal and re-challenging. We found that zolpidem CR, a gamma aminobutyric acid (GABA)ergic agonist of the benzodiazepine type 1 receptor, caused sustained improvement in motor and ocular symptoms in a patient with PSP over 6 months. Further studies are needed to determine the potential roles of GABA neurotransmission in PSP.

Zolpidem is not routinely recommended for patients with PSP. However, a subsequent case report documented similar improvements but the effect only lasted for 4 weeks and was not repeatable 2 months later.6 The authors, as an alternative explanation, proposed that the efficacy of zolpidem might be secondary to benzodiazepine muscular weakness and tone relaxation, which could improve rigidity, but this would not explain improvement of eye motor function.6 Zolpidem is a GABA agonist of the benzodiazepine subtype receptor BZ1, found in highest density in the internal pallidum,7 and has been trialled in small numbers of patients with PSP. A double-blind placebo controlled crossover study of 10 patients with PSP showed that patients had improved motor function and voluntary saccadic eye movements with zolpidem compared to placebo or levodopa.8 However, a subsequent case report documented similar improvements but the effect only lasted for 4 weeks and was not repeatable 2 months later.6 The authors, as an alternative explanation, proposed that the efficacy of zolpidem might be secondary to benzodiazepine muscular weakness and tone relaxation, which could improve rigidity, but this would not explain improvement of eye motor function.6 Zolpidem is not routinely recommended for patients with PSP. It is a central nervous system depressant and can impair cognitive and motor performance, particularly in the elderly. This could lead to an increased risk of falls in patients with PSP, because they are already at high risk of falls due to postural instability, gaze palsies and cognitive impairment.

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2. Case report

We describe a 61-year-old man with a 4 year history of PSP who experienced sustained improvement in motor and bulbar symptoms with zolpidem CR over a 6-month period.

This patient had been trialled on levodopa therapy soon after his initial diagnosis with no substantial response and it was subsequently ceased. He remained unmedicated for months prior to commencing zolpidem 3 years ago for the treatment of insomnia. He had a percutaneous gastrostomy tube inserted in July 2006 for supplemental feeding as he was unable to achieve adequate nutrition because of pseudobulbar dysfunction. In August 2006 he changed from the immediate release (IR) preparation to the controlled release (CR) formulation of zolpidem. In October he and his wife noted substantial improvement in bulbar function with reduced saliva pooling, improved swallow and vocalisation, and less bradykinesia.

His wife kept a diary over several months detailing the time and dose of zolpidem CR in relation to observed improvement in symptomatology. Symptoms reported on included drooling, ability to swallow and feed himself, facial expression, production of audible speech, frequency of falls and speed of movement. Frequency of falls was the only domain that was not improved by the medication.

Observations remained consistent, with improvement noted within 1 hour of taking zolpidem CR and lasting for up to 5 hours. Only the CR preparation was effective in improving PSP symptoms and did not help him sleep. The IR preparation treated his insomnia so he established himself on zolpidem CR 12.5 mg mane (morning) and zolpidem IR 20 mg noche (at night). His only other mediations included venlafaxine 75 mg mane, and coloxyl with senna 2 tablets noche.

The patient was admitted to hospital for an observation trial and ceased zolpidem CR 3 days prior to admission. He remained off this medication for a further 3 days in hospital and was assessed daily by an occupational therapist, speech therapist and neurologist. He was then commenced on zolpidem CR 12.5 mg mane and observations and assessments continued. On day 3 he was given zolpidem CR 25 mg. Videos documented the patient prior to treatment (Supplementary video 1) and 3 days after commencing treatment (Supplementary video 2). The therapist continued to observe the patients for a further 3 days. Timed up-and-go and Berg Balance scores were assessed prior to commencement of zolpidem CR and after dose titration. His mini-mental state examination scale scores were also recorded before and after treatment.

3. Results

After 6 days without zolpidem tablets the patient exhibited clinically marked and debilitating features of supranuclear palsy. He had a staring wide-eyed appearance and sat with a slightly stooped posture with his mouth open, tongue protruding and had marked salorrhoea. He was unable to speak and demonstrated slow processing with delayed responses to instructions. There was severe bradykinesia, particularly of upper limb movements, and he had a propulsive and unsteady gait. Eye movements were disrupted with very slow vertical saccades, more marked on the downward gaze, and his pursuit was saccadic. He had dysphagia with severely delayed swallow initiation and pooling of food and fluid, requiring a modified diet and feeding assistance (Supplementary Video 1).

Within 1 hour of taking the first dose of 25 mg zolpidem CR there was a dramatic improvement in motor, pseudobulbar and ocular function that was sustained for 4 hours to 5 hours post-dose (Table 1). There was reduced pooling of saliva with no salorrhoea, and more marked facial expression and display of spontaneous emotion. He could vocalise audibly and appropriately in response to questions and spontaneously, as well as sustain voice-initiated sounds for longer. Fine motor skills and dexterity improved, as demonstrated by Velcro task and cone stacking, and the speed of his rapid alternating movements was much faster. Vertical saccades were also faster and he had notably smoother visual pursuits. There was less delay in swallow initiation and he could resume a normal diet and was able to feed himself (Supplementary video 2). His mini-mental state examination scale score before and after treatment was 25/30.

At follow-up 2 months after his admission to hospital the clinical response to zolpidem CR was the same. Subsequent zolpidem CR withdrawal and rechallenging trials have shown the same medication-related improvement that was demonstrated in our hospital.

4. Discussion

To our knowledge there are no reports of zolpidem CR being used to treat PSP. Although there have been other reports of transient improvements in a few patients with PSP treated with zolpidem IR preparation, results were not reproducible or sustained. The use of zolpidem CR, due to different pharmacokinetic properties, may determine a more sustained improvement compared to the IR formulation.

An important observation is the 2-month delay between the start of treatment with zolpidem CR and a noticeable improvement in the patient. One hypothesis to explain this delay is that prolonged GABAergic agonist stimulation may be required to alter GABAergic output pathways from the internal pallidum and substantia nigra. A threshold level of GABAergic output may be required before symptomatic improvement is noted, or there may be alteration in benzodiazepine subtype receptor BZ1 expression following prolonged and repetitive stimulation by zolpidem CR. This might explain why the benefits seen in our patient were sustained compared to other studies that assessed benefit after a single dose of zolpidem. Further studies trialling zolpidem in patients with PSP over periods of weeks to months would be needed to test this hypothesis. Patients would need to be monitored closely for unfavourable side effects and the drug discontinued should these be unacceptable.

The duration or stage of the disease may be a factor determining a response to zolpidem, similarly to the decline in response to levo-dopa that is observed in Parkinson’s disease (PD). In the latter stages of PSP GABA agonism might be insufficient to overcome the neuronal loss in the cortex and subcortical structures that occurs as PSP progresses.

More research is required into understanding the complex neurochemical pathways involved in the pathogenesis of PSP. The observations based on our patient might provide clues as to where to focus further research. A study trialling zolpidem CR over several days would be necessary and required before symptomatic improvement is noted, or there may be alteration in benzodiazepine subtype receptor BZ1 expression following prolonged and repetitive stimulation by zolpidem CR. This might explain why the benefits seen in our patient were sustained compared to other studies that assessed benefit after a single dose of zolpidem. Further studies trialling zolpidem in patients with PSP over periods of weeks to months would be needed to test this hypothesis. Patients would need to be monitored closely for unfavourable side effects and the drug discontinued should these be unacceptable.

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months in patients with PSP with varying phenotypes and stages of the disease, with PET scanning performed on and off medication, would allow a more meaningful conclusion to be made about the use of zolpidem CR for PSP.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jocn.2009.05.038.

References


