Complete Resolution of Symptoms of Primary Orthostatic Tremor with Perampanel

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Abstract

Background: Primary orthostatic tremor (POT) is an infrequent disorder whose physiopathology is unknown. Current medication is largely ineffective or only offers mild benefits.

Case Report: A 75-year-old female with refractory POT treated with 4 mg/day of perampanel achieved complete symptom resolution. Owing to adverse effects, the patient reduced intake to 2 mg/day, but even at this lower dose the benefit was maintained.

Discussion: We report the complete resolution of POT symptoms using low doses of perampanel, an antiepileptic drug that blocks glutamate-mediated postsynaptic excitation. Further controlled studies are necessary to confirm this finding.

Keywords: Primary orthostatic tremor, perampanel

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Introduction

Primary orthostatic tremor (POT) is an infrequent disorder characterized by tremor and unsteadiness. It only occurs when the patient is upright and immobile, and stops once the patient walks, sits down, or lies down. Patients report a feeling of instability that impacts their quality of life and may affect their activities of daily living; consequently, many such patients experience anxiety, depression, and social phobia.

The physiopathology is still unclear, although neuroimaging and functional studies suggest that the brainstem, cerebellum, thalamus, and primary motor cortex are involved. Medication is largely ineffective, although it may provide some mild relief. Deep brain stimulation has been shown to have some benefit in severe cases.

We report the case of a patient with refractory POT that had developed 15 years previously, whose symptoms were completely resolved with low doses of perampanel, an orally active, selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist.

Case report

A 75-year-old female with a medical history of hypertension, asthma, and hypothyroidism had been diagnosed with POT 15 years earlier. This condition led to a progressive functional decline over the years that significantly affected the patient’s autonomy and quality of life. She had no psychiatric or family history of tremor or other neurological diseases. The neurological examination was normal, revealing no tremor in the upper limbs or signs of parkinsonism.

A surface electromyography (EMG) study of the lumbar axial muscles with the patient in the standing position showed a 14 Hz EMG rhythmic burst pattern (Figure 1).

The patient had previously been unsuccessfully treated with several drugs (daily dose): clonazepam (1.5 mg), gabapentine (1200 mg), pregabalin (300 mg), primidone (750 mg), levodopa (300 mg), levetiracetam (1000 mg), topiramate (200 mg), and zonisamide (200 mg).

Treatment with perampanel was begun with 4 mg/day (after a 4-week introductory dose of 2 mg/day). At the 2-month follow-up...
outpatient visit, the patient described full symptomatic relief, indicating, for instance, that in the kitchen and at the bus stop she could now stand rather than be forced to sit. The patient subjectively rated her improvement as 100%. As an adverse effect she experienced dizziness and reduced her dose to 2 mg/day; despite the low dose, she remains completely asymptomatic. A new EMG study revealed the persistence of 14 Hz rhythmic bursts.

Discussion

We report a case of POT, which, when treated with perampanel (2–4 mg/day), achieved complete resolution of symptoms. To the best of our knowledge, there have been no reports about the use of this drug to effectively treat POT.

The current medication for POT is only partially effective and complete resolution using those drugs is exceptional.1 Currently, the only treatment is symptomatic rather than etiological. The effectiveness of clonazepam and gabapentine—considered to be first-line agents—has been demonstrated in small clinical trials.3,5 Primidone has been shown to have some short-term effect,1,4,6 and valproic acid, propranolol, and bromazepam have been shown to induce a mild response.4 Studies have described patients in which POT preceded Parkinson disease, for whom levodopa or primipexole may work.4,7-9 In non-responders, bilateral thalamic deep brain stimulation of the ventral intermediate nucleus can offer some benefit.10,11

Perampanel is a first-in-class selective, non-competitive AMPA receptor antagonist that functions by blocking glutamate activity in the post-synaptic AMPA receptors, which are the predominant mediator of excitatory neurotransmission in the brain.12 It has been licensed and marketed as an antiepileptic drug and is indicated for patients with partial-onset seizures and primary generalized tonic–clonic seizures. Positive effects have been reported for some patients with epileptic myoclonic jerks, idiopathic generalized epilepsy, and progressive myoclonic epilepsy.13,14

Interestingly, although our patient achieved a complete resolution of symptoms, neurophysiology revealed the persistence of subclinical EMG findings for POT. This would confirm a symptomatic rather than an etiological effect.

Bearing in mind its mechanism of action, the fact that perampanel has proven to be an effective treatment for our patient suggests that glutamate neurotransmitters—also involved in the pathophysiology of essential tremor15—are involved in the physiopathology of POT.16,17 Another possibility is that the neurochemical circuits and structures involved in the physiopathology of POT are segmented, with some circuits modulating tremor frequency (pacemaker function) and other circuits modulating tremor amplitude through increased glutamate-mediated excitatory activity within the pacemaker circuit. Perampanel—which prevents excitation of post-synaptic membranes by inhibiting the glutamate receptors—may therefore modulate flows in reciprocal circuits with abnormal oscillatory neuronal activity and, in this way, significantly regulate tremor amplitude, even though the primary pacemaker may not modify high tremor frequency.18-20

To sum up, we report a case of complete resolution of POT symptoms using low doses of perampanel. Further controlled studies are necessary to confirm this finding. We would recommend a clinical trial of perampanel in patients with refractory POT to current treatments.

References

1. Hassan A, Ahlkog JE, Matsumoto JY, Milber JM, Bower JH, Wilkinson JR. Orthostatic tremor clinical, electrophysiologic, and treatment findings in 184 patients. *Neurology* 2016;86:458–464. doi: 10.1212/WNL.0000000000002328

2. Vidailhet J, Roze E, Maugest L, Gallea C. Lessons I have learned from my patients: everyday life with primary orthostatic tremor. *J Clin Mov Dis* 2017;4:1. doi: 10.1186/s40734-016-0048-5

3. Schöberl F, Feil K, Xiong G, Bartenstein P, Jahn K, Strupp M, et al. Pathological ponto-cerebello-thalamic-cortical activations in primary orthostatic tremor during lying and stance. *Brain* 2017;140(Pt 1):83–97. doi: 10.1093/brain/aww268

4. Labiano A, Benito J, Domínguez C. Tremor ortostático: una entidad enigmática. *Rev Neurol* 2012;54:425–434.

5. Rodrigues JP, Edwards DJ, Walters SE, Byrnes ML, Thickbroom G, Stell R, et al. Gabapentin can improve postural stability and quality of life in primary orthostatic tremor. *Mov Disord* 2005;20:865–870. doi: 10.1002/mds.20392
6. Jones L, Bain PG. Orthostatic tremor. *Pract Neurol* 2011;11:240–243. doi: 10.1136/practneurol-2011-000022
7. Finkel MF. Pramipexole is a possible effective treatment for primary orthostatic tremor (shaky leg syndrome). *Arch Neurol* 2000;57:1519–1520. doi: 10.1001/archneur.57.10.1519
8. Wills AJ, Brusa I, Wang HC, Brown P, Marsden CD. Levodopa may improve orthostatic tremor: case report and trial of treatment. *J Neurol Neurosurg Psychiatry* 1999;66:681–684. doi: 10.1136/jnnp.66.5.681
9. Troccolo JM, Zanotti-Fregonara P, Rosse E, Aparisi E, Legrand A-P, Habert M-O, et al. Dopaminergic deficit is not the rule in orthostatic tremor. *Mov Disord* 2008;23:1733–1738. doi: 10.1002/mds.22224
10. Guridi J, Rodriguez-Oroz MC, Arbizu J, Alegre M, Prieto E, Landecho I, et al. Successful thalamic deep brain stimulation for orthostatic tremor. *Mov Disord* 2008;15;23:1808–1811. doi: 10.1002/mds.22001
11. Lyons MK, Behbahani M, Boucher OK, Caviness JN, Evidente VG. Orthostatic tremor responds to bilateral thalamic deep brain stimulation. *Tremor Other Hyperkinet Mov* 2012;2. doi: 10.7916/D8TQ608K
12. Bogawski M. AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurol Scand Suppl* 2013;197:9–18. doi: 10.1111/ane.12099
13. French JA, Krauss GL, Wechsler RT, Wang X-F, DiVentura B, Brandt C, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy. A randomized trial. *Neurology* 2015;85:950–957. doi: 10.1212/WNL.00000000000001930
14. Shorlemmer K, Bauer S, Belke M, Hermsen A, Klein KM, Reif PS, et al. Sustained seizure remission on perampanel in progressive myoclonic epilepsy. *Epilepsy Behav Case Rep* 2013;1:118–121. doi: 10.1016/j.echcr.2013.07.003
15. Girone A, Marín-Lahoz J. La esencia del temblor esencial: bases neuroquímicas. *Rev Neurol* 2016;62:507–515.
16. Benito-León J, Domingo-Santos A. Orthostatic tremor: an update on a rare entity. *Tremor Other Hyperkinet Mov* 2016;6. doi: 10.7916/D6W66ZBH
17. Lenka A, Pal PK, Bhati DI, Louis ED. Pathogenesis of primary orthostatic tremor: current concepts and controversies. *Tremor Other Hyperkinet Mov* 2017;7. doi: 10.7916/D81N81BT
18. Raethjen J, Muthuraman M. Cause or compensation? Complex changes in cerebello-thalamo-cortical networks in pathological action tremor. *Brain* 2015;138:2808–2810. doi: 10.1093/brain/awu238
19. Cagnan H, Little S, Foltynie T, Limousin P, Zrinzo L, Hariz M, et al. The nature of tremor circuits in parkinsonian and essential tremor. *Brain* 2014;137:3223–3234. doi: 10.1093/brain/awu250
20. Schreglmann SR, Krauss JK, Chang JW, Martin E, Werner B, Bauer R, et al. Functional lesioned neurosurgery for tremor: back to the future? *J Neurol Neurosurg Psychiatry* 2017. doi: 10.1136/jnnp-2017-316301