

Brief Report

Primary Orthostatic Tremor: Experience of Perampanel Use in 20 Patients

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Abstract

Background: Primary orthostatic tremor (POT) is a rare disorder for which current treatments are largely ineffective. Following up on our recent report of complete resolution of POT symptoms in a patient using low doses of perampanel, we describe our experience of perampanel in 20 patients.

Methods: Twenty patients whose neurologists prescribed perampanel were recruited. Initial dose was 2 mg/day, which was increased to 4 mg/day after the first month. Treatment efficacy was self-scored from +3 to -3 at 1 and 3 months.

Results: Eight patients withdrew due to adverse effects. Of the 12 patients who completed the study, 92% indicated that their POT symptoms had improved after 1 month, with 75% indicating moderate to marked improvement (mean score 1.9 ± 0.9). This improvement was not sustained by follow-up at 3 months (mean score 0.9 ± 1.3). A rebound of POT symptoms that lasted 2–6 weeks was observed in most patients who withdrew.

Discussion: Our experience with this series of cases points to the potential of low-dose perampanel as a treatment for POT, although poor tolerance and the possibility of a non-persistent therapeutic benefit need to be considered. Controlled studies are needed to confirm these findings.

Keywords: Orthostatic tremor, primary orthostatic tremor, tremor, perampanel, unsteadiness

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Introduction

Primary orthostatic tremor (POT) is a 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.¹ Patients report a subjective feeling of instability that impacts their quality of life and may affect their activities of daily living, with many such patients experiencing anxiety, depression, and social phobia.²

This disease is very uncommon.³ Its prevalence, furthermore, is unknown, which means it is very difficult to perform therapeutic trials. Medication, although it may provide some mild relief, is largely ineffective.¹

Recently, it has been reported complete resolution of POT symptoms in two patients using low doses of perampanel, an antiepileptic drug that blocks glutamate-mediated postsynaptic excitation.^{4,5} In the current study, we describe our experience of using perampanel in 20 patients with POT. Although ours was not a controlled trial, our findings and conclusions may be of interest due to the low prevalence of this disorder.

Patients and methods

Between January 2018 and January 2019, patients with POT were recruited through contact initiated by a French group of patients with POT. Recruited were 20 patients whose neurologist had acceded to their

request for a perampanel prescription. Electromyography (EMG) data were not available for any patient.

Patients were informed that they could withdraw at any time and were also guaranteed the anonymity and confidentiality of their data. Informed consent was considered implicit in the patient agreeing to provide essential demographic and clinical data, monitor and record treatment efficacy and adverse events, and provide this information to the patient coordinator for email transmission to the trial doctors.

Treatment duration was 3 months, and posology was 2 mg/day for the first month, which was increased to 4 mg/day for the remaining 2 months. Perampanel was taken concurrently with any anti-tremor medication that the patients were taking on while commencing the study.

Treatment efficacy was measured in terms of symptom improvement using a simple self-administered subjective scale, based on part C of Fahn-Tolosa-Marin Tremor Clinical Rating Scale,⁶ scored as follows: 0 = no change; +1 = slight improvement; +2 = moderate improvement; +3 = marked improvement; -1 = slight worsening; -2 = moderate worsening; and -3 = marked worsening. Adverse effects were also recorded.

Patients notified their scores and any adverse event 1 and 3 months after starting treatment with perampanel. Patients who suffered any adverse effect that lasted more than last clinical control (3 months) were followed until symptoms reverted.

Results

The patients recruited for the study ($n = 20$) had a mean age of 68.9 ± 6.3 years, 16 were women, and 17 were being treated with anti-tremor medication. Mean evolution of the disease was 14.4 ± 6.9 years. Of the 20 patients included, 12 completed the study. After 1 month, 11 patients showed some improvement in POT symptoms: three, six, and two patients scored their improvement as marked, moderate, and mild, respectively, and a single patient reported no change.

After 3 months, however, the degree of improvement decreased, with only a single patient indicating marked improvement, four and five patients indicating moderate and mild improvement, respectively, and two patients reporting no change.

The mean improvement score was 1.9 ± 0.9 after 1 month, falling to 0.9 ± 1.3 after 3 months. Non-persistence of the therapeutic effect was observed in 50% of patients.

Of the 20 included patients, eight withdrew in a mean of 10 ± 5 days due to adverse effects: dizziness and instability with increased falls ($n = 8$), weight gain ($n = 2$), and depression ($n = 2$). No further patients withdrew, although following the dose increase to 4 mg/day after the first month, 8 of the remaining 12 patients reverted to 2 mg/day due to mild dizziness and instability.

A rebound in POT symptoms (worse unsteadiness symptoms than patients ever had before) lasting 2–6 weeks was observed in six of the eight patients who withdrew. Of the 12 patients who completed the study, eight opted to continue with perampanel treatment after the study.

The demographic and clinical characteristics of the patients are summarized in Table 1.

Discussion

For our case report series of patients with POT, we observed that perampanel improved POT symptoms over 1 month of treatment in nearly all (92%) of the 12 patients who completed the study, with 75% showing moderate to marked improvement. However, this improvement was not sustained over the 3 months of the study.

Currently, the only treatment administered for POT is symptomatic,¹ mainly clonazepam or gabapentin as first-line agents, or primidone, valproic acid, propranolol, or bromazepam.^{1,7,8} In most cases, however, medication benefits dissipate over time.¹ Non-responders may benefit from bilateral thalamic deep brain stimulation of the ventral intermedial nucleus.⁹

We recently reported complete resolution of POT symptoms in a patient using low doses of perampanel.⁴ After 18 months of treatment, the benefits of perampanel persist for this patient at a dose of 2 mg/day. Neurophysiology revealed the persistence of subclinical EMG findings for POT in this patient, which would confirm a symptomatic rather than an etiological effect of this drug.

Perampanel and its indications, pathophysiology and mechanisms of action have been fully documented elsewhere.^{4,10–15}

Our study pointed to three main drawbacks of perampanel as a treatment for POT. First, tolerance was poor, with 40% of recruited patients withdrawing due to adverse effects (dizziness and instability, weight gain, and depression); furthermore, only 4 of the 12 patients who completed the study were able to tolerate doubling the dose to 4 mg/day after the first month.

In patients with epilepsy, perampanel appears to be associated with a relatively low incidence of serious adverse effects, most especially at low doses.^{16,17} Predictable side effects, such as somnolence and dizziness, tend to be observed more frequently at higher doses. While the fact that psychiatric adverse effects, mainly irritability and aggression, occur at a greater rate with the use of perampanel than with a placebo is a potential concern, the incidence of serious psychiatric effects is nevertheless low. In our study, poor tolerance, as manifested in dizziness and instability, weight gain, and depression, may have been due to perampanel interaction with the concomitant anti-tremor medication (clonazepam, gabapentin, pregabalin, lorazepam, and/or oxycodone) taken by 17 of the included 20 patients.

A second issue with perampanel as a treatment for POT was that the therapeutic benefit failed to persist in around 50% of our patients after 3 months of treatment. This effect has not been described for perampanel used to treat patients with epilepsy, but has been reported for POT pharmacological trials with other anti-epileptic drugs¹; this possibly points to a greater tolerance of anticonvulsant drugs by patients with POT. The reason for the non-persistence of therapeutic benefit is not clear. One possibility is the existence of a placebo effect lasting for some weeks. Another possibility is that the reduced efficacy may result from a dose increase from 2 to 4 mg/day. Efficacy may be greater at low doses, as higher doses would increase the adverse effects and hide anti-tremor efficacy. Further studies are needed to clarify this issue.

A final drawback with perampanel was the lengthy rebound of POT symptoms in most of the patients who discontinued perampanel.

Table 1. Patient Characteristics

No.	Age, sex	Evolution (years)	Concurrent treatment	Perampanel mg/day at 3 months	Improvement score		Rebound	Adverse effects
					1 month	3 months		
1	65, F	17	GBP	2	+2	+1	No	Weight gain, instability
2 ⁺	66, F	5	None	2	+3	+3	N/A	Mild dizziness
3*	78, F	31	CLN	N/A	N/A	N/A	Yes	Dizziness, asthenia
4*	78, M	15	None	N/A	N/A	N/A	Yes	Instability, dizziness
5*	65, F	24	CLN	N/A	N/A	N/A	Yes	Tremor, dizziness
6*	72, F	5	CLN, PRG	N/A	N/A	N/A	Yes	Tremor, instability
7*	75, M	17	CLN	N/A	N/A	N/A	N/A	Instability
8 ⁺	70, F	20	CLN, PRG	2	+2	+2	N/A	None
9 ⁺	71, F	14	CLN	4	+2	+2	N/A	None
10*	75, M	8	TAR, LOR	N/A	N/A	N/A	Yes	Depression
11*	53, F	11	None	N/A	N/A	N/A	N/A	Depression
12 ⁺	75, F	20	CLN	4	+2	+1	N/A	None
13	66, F	15	CLN	2	+1	0	No	Instability
14*	62, F	20	PRG	N/A	N/A	N/A	Yes	Instability
15 ⁺	68, F	7	GBP, CLN	4	+3	+2	N/A	Weight gain
16 ⁺	65, F	5	CLN	2	+3	+1	N/A	None
17	60, F	10	CLN	2	0	0	No	None
18 ⁺	70, M	15	CLN	2	+2	+2	N/A	None
19 ⁺	75, F	10	GBP	4	+1	+1	N/A	None
20	70, F	20	PRG	2	+2	+1	No	Mild dizziness

Abbreviations: CLN, clonazepam; F, female; GBP, gabapentin; LOR, lorazepam; M, male; N/A, not applicable OXC, oxycodone; PRG, pregabalin.
⁺Indicates withdrawal.
^{*}Indicates continuation beyond the study period.

The rebound effect persisted for several weeks after discontinuation, probably due to the long half-life of perampanel.

The main limitation of our study is its non-controlled design and the absence of an objective measure of improvement in POT symptoms. Nonetheless, the rarity and low prevalence of this disease would suggest that our findings are of interest.

Our experience with this series of cases points to the potential of low-dose perampanel as a treatment for POT, although poor tolerance and the possibility of a non-persistent therapeutic benefit need to be considered. Controlled studies are needed to confirm these findings.

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