Zonisamide for Essential Tremor

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ABSTRACT

BACKGROUND: The pharmacologic therapy for ET is inadequate and many patients resort to surgical procedures. Zonisamide is an anti-epileptic with several potential mechanisms of action. **METHODS:** We evaluated zonisamide for ET in an open label pilot trial. The primary efficacy point was the Tremor Study Group rating scale (TSGRS). **RESULTS:** Twenty-two subjects were enrolled (9 male, age was 65.0±12.6 years, and the duration of ET was 25.6±17.1 years). Six dropped due AEs and lack of effect (4) or lack of effect (2). Two were lost to follow-up. Fourteen subjects returned for their complete post-medication evaluation. After three months (88±34 days) the final dose was 200 mg (11), 150 mg (1), 100 mg (1), and 12.5 mg (1). TSGRS improved from 28.9±9.2 to 21.1±6.5, (p=0.02), unpaired t-test. Seven (50%) of subjects had at least a 25% improvement. Subjectively, however, only four reported "marked" or "moderate' improvement, three reported "mild" improvement, and seven reported "no change". AEs included decreased concentration/cognition (2), constipation (1), nocturia (1), abdominal pain/diarrhea (1), and sedation (1). **CONCLUSION:** Zonisamide significantly, albeit modestly, improved ET in this small group of medically refractory subjects. However, the study was complicated by a large drop-out rate due to subjective lack of efficacy and adverse events.

INTRODUCTION

Essential tremor (ET) is one of the most common movement disorders. Primidone, topiramate and several other medications developed for seizures variably improve ET. Nevertheless pharmacologic therapy for ET is inadequate and many patients resort to surgical procedures.[1]

Zonisamide has several potential mechanisms of action. *In vitro* pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca2+ currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization.[2] Although the biochemical pathophysiology of ET is not known, cellular hypersynchronicity is suspected to play a major role. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion that does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide (10-30 ug/mL) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [3H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *In vivo* microdialysis studies demonstrate that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic anhydrase inhibiting activity. Overall, several of these mechanisms are similar to those of topiramate, which has been shown to improve ET.[3]

METHODS

We evaluated zonisamide for ET in an open label pilot trial. The primary efficacy point was the Tremor Study Group rating scale (TSGRS).[4] We also included global impressions and adverse events (AE). Zonisamide was titrated to a maximum of 200 mg/day in two doses over 4 weeks. The subjects could reduce the dose if needed. We allowed subjects with either one or no other medications for ET. Other ET medications remained at a stable dose throughout the study. Subjects were evaluated at the same time of day and instructed to avoid alcohol and use similar amounts of caffeine on the assessment day.

RESULTS

Twenty-two subjects were enrolled (9 male, age was 65.0±12.6 years, and the duration of ET was 25.6±17.1 years). Eighteen (81.8%) had a family history of ET. Six dropped due AEs and lack of effect (4) or lack of effect (2). Two were lost to follow-up. [Table 1]

Fourteen subjects returned for their complete post-medication evaluation. Ten of these were on another agent for ET which was kept constant. [Table 2] The 14 subjects had also tried and stopped a total of 34 additional medications for ET prior to study entry. After three months (88±34 days) the final dose was 200 mg (11), 150 mg (1), 100 mg (1), and 12.5 mg (1). TSGRS improved from 28.9±9.2 to 21.1±6.5, (p=0.02), unpaired t-test. Seven (50%) of subjects had at least a 25% improvement. Subjectively, however, only four reported "marked" or "moderate' improvement, three reported "mild" improvement, and seven reported "no change". AEs included decreased concentration/cognition (2), constipation (1), nocturia (1), abdominal pain/diarrhea (1), and sedation (1).

Table 1. Demographic Data (N=22)

No.	Age	Duration of ET (yrs)	Sex	Family History (Y/N)	Previous Medications for Tremor	Current Medication
Patients Who Completed Study						
1	75	51	M	N	Propranolol Levodopa	None
2	55	6	F	N	Ropinirole Levodopa Pramipexole Propranolol	Propranolol
3	62	2	M	Y	Topiramate Mirtazapine Alprazolam Metoprolol	Metoprolol
4	53	33	F	Y	Propranolol Primidone Gabapentin Pramipexole Ropinirole Topiramate	Gabapentin
5	87	37	M	Y	Primidone Propranolol	Propranolol
6	69	29	F	Y	None	None
7	82	65	M	Y	None	Primidone
8	73	20	M	N	Topiramate Primidone Propranolol Ropinirole Trihexyphenidyl	None
9	62	30	F	Y	Escitalopram	Escitalopram
10	70	20	M	Y	Propranolol Levodopa Amantadine	Primidone
11	50	40	F	N	Propranolol Primidone Levetiracetam Buspirone	None
12	70	40	F	Y	None	Ropinirole
13	38	6	F	Y	Propranolol Botulinum toxin	None
14	76	8	M	Y	Topiramate	Primidone
Patients Who Dropped from Study						
1	69	15	F	Y	Primidone Propranolol Mirtazapine	None
2	69	15	F	Y	Primidone Propranolol Mirtazapine	None
3	67	33	F	Y	Atenolol	Clonazepam
4	76	30	M	Y	Botulinum toxin Nadolol	None
5	57	25	F	Y	Levodopa Ropinirole Gabapentin Propranolol Botulinum toxin	None
6	79	4	F	Y	Gabapentin Propranolol Primidone Clonazepam Botulinum toxin Topiramate Clonazepam	None
7	60	10	F	Y	Propranolol Primidone	None
8	42	2	F	Y	Topiramate	None

RESULTS cont'd

Table 2: Efficacy Data for Completed Subjects

Dose	Total Tremor Observed				Writing		Spiral		Pouring		Total		Adverse Effects
	Head, Face, Tongue, and Voice		Arm										
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
200	0.0	0.0	13	8.5	3.0	3.0	6.0	6.0	4.0	2.0	28	21.5	None
200	0.0	0.0	14	11	2.0	1.0	4.0	4.0	2.0	4.0	24	21.5	None
200	0.0	0.0	9	9	3.0	3.0	3.0	4.0	2.0	1.0	19	18	Nocturia
200	3.0	0.0	10	10	2.0	2.0	5.0	5.0	2.0	1.0	23.5	19.5	Decreased concentration, "Spacy" sensation
200	7.0	2.0	15	13.5	2.0	3.0	6.0	6.0	7.0	6.0	42	30.5	None
12.5	0.0	4.0	11.5	9.5	1.0	1.0	3.0	3.0	3.0	2.0	20	17	Constipation
100	5.0	1.0	11	12	4.0	3.0	4.0	6.0	4.0	4.0	34	25.5	None
200	8.0	2.0	10.5	10.5	2.0	2.0	4.0	4.0	2.0	2.0	34	21	None
200	0.0	0.0	9	10.5	1.0	2.0	3.0	6.0	2.0	2.0	19	22	None
200	7.0	0.0	12	4	2.0	0.0	6.0	2.0	2.0	0.0	31	7	Sedation
200	7.0	2.0	16	12.5	1.0	2.0	7.0	6.0	5.0	3.0	40.5	27.5	Sleepy
200	7.0	5.0	15.5	13.5	3	2	8	8	7	7	43.5	31	Headache
100	1.0	0.0	6.5	5.0	2	3	3	2	3	1	17.5	12.5	None
200	0.0	0.0	10.5	10.5	2	1	4	4	2	2	20	19	None
											28.9	21.1	

DISCUSSION

Zonisamide significantly, albeit modestly, improved ET in this small group of medically refractory subjects who completed the study. However, a large number of subjects dropped the medication prior to a final assessment, usually secondary to a combination of poor subjective efficacy and AEs. The main difference in subjects that dropped was that they had previously stopped more previous medications due to poor efficacy or AE. Only one was on a concurrent medication at study entry. Overall three subjects reported better subjective response to zonisamide compared to any previous pharmacological intervention. Therefore zonisamide may be effective in a subgroup of patients, but the majority of subjects did not subjectively benefit.

Several factors may have mitigated against more robust results. This was a very refractory group at a tertiary referral center. Most were on another ET medication and it is possible that monotherapy would have resulted in a more robust subjective improvement. We also felt that the patient's subjective response was often less positive than our tremor examinations. This is consistent with the report by Zesiewicz *et al*, which found a 40% improvement in accelerometry scores but relatively little subjective benefit from the drug.[5] This may result from a somewhat vague dysthymia effect commonly noted with the medication. Another open label study for ET reported similar improvement of zonisamide to arotinolol.[6] Finally, we have anecdotally noted inconsistent, but sometime robust improvement on zonisamide when used for rest tremor in Parkinson's disease. Others have also reported improvements in PD tremor and other PD motor symptoms.[7,8] Overall, we do feel that controlled trials are justified.

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