OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Letters

Ethosuximide for Essential Tremor: An Open-Label Trial

Alexandre Gironell* **& Juan Marin-Lahoz**

Movement Disorders Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Catalonia, Spain

Abstract

Background: T-type calcium channel activation has been postulated to underlie rhythmicity in the olivo-cerebellar system that is implicated in ET. Ethosuximide reduces T-type calcium currents and can suppress tremor in two animal models of ET. We explored the effects of ethosuximide in subjects with ET in an open-label trial using both clinical scales and accelerometric recordings measures. We initially planned to conduct the trial with 15 patients, but due to lack of efficacy and a high incidence of adverse effects, the trial was stopped after seven patients had participated.

Methods: Seven patients diagnosed with ET were included in the study. The ethosuximide dose was 500 mg daily (BID). The main outcome measures were: 1) tremor clinical rating scale (TCRS) score, 2) accelerometric recordings, and 3) self-reported disability scale score.

Results: Five patients completed the study, and two dropped out due to adverse effects. There were no significant changes in clinical scores in motor task performance (TCRS 1+2), daily living activities (TCRS 3), or in the patients' subjective assessment (TCRS 4) and global appraisal. There were no differences observed for accelerometry data or disability scale scores. Anxiety, nervousness, headache, and dizziness were reported by two patients while on ethosuximide, causing them to stop the trial. No patient preferred to continue ethosuximide treatment.

Discussion: The results of our exploratory study suggest that ethosuximide is not an effective treatment for ET.

Keywords: Essential tremor, ethosuximide, calcium channel

Citation: Gironell A, Marin-Lahoz J. Ethosuximide for essential tremor: an open-label trial. Tremor Other Hyperkinet Mov. 2016; 6. doi: 10.7916/D8FQ9WN0

*To whom correspondence should be addressed. E-mail: agironell@santpau.cat

Editor: Elan D. Louis, Yale University, USA

Received: March 9, 2016 **Accepted:** May 5, 2016 **Published:** July 13, 2016

Funding: None.

Financial Disclosure: None.

Conflict of Interest: The authors report no conflict of interest.

Ethics Statement: This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The authors' institutional ethics committee has approved this study and all patients have provided written informed consent.

Introduction

Essential tremor (ET) is one of the most prevalent neurological disorders in adults and is the most common tremor disorder. The etiology, pathophysiology, and exact anatomy of ET remain unclear. As a consequence, drug treatment for ET remains poor and often unsatisfactory.[1]

There is some controversy to whether ET is a neurodegenerative disease.[2] There is considerable evidence in favor of the "neurodegenerative hypothesis." ET is a progressive disorder of aging associated with cell loss in the majority of pathologic studies, and there is evidence that gamma-aminobutyric acid (GABA) system dysfunction plays a role.[3,4]

The other main theory is the "olivary hypothesis," in which ET is the result of a disturbance in the inferior olivary nucleus, an anatomic structure with inherent oscillatory pacemaking properties.[5,6] T-type calcium channel activation has been postulated to underlie rhythmicity in the olivo-cerebellar system that is implicated in ET.[7,8] Ethosuximide is a clinical anti-absence seizure medication that reduces T-type calcium currents.[9] This drug was shown to suppress tremor in two animals model of ET (GABAa alfa1-null and harmaline models).[7]

We explored the effects of ethosuximide in ET in an open-label trial using both clinical scales and accelerometric recordings. We initially planned to conduct the trial with 15 patients, but due to lack of efficacy and a high incidence of adverse effects, the trial was stopped after seven patients had participated.

Patient/methods

Seven patients (5 males, 10 females; mean age 74.2 years, range 61 to 77 years) with ET were included in the study (Table 1).

The diagnosis of ET was established using the Movement Disorders Society consensus criteria.[10] All of them fulfilled the neurophysiological criteria of ET.[11]

The study protocol was approved by the Hospital Ethics Committee, and informed consent to participate was obtained from all patients. Exclusion criteria were the presence of psychiatric illness, hepatic disease, substance abuse, epilepsy, or dystonia. We also excluded any persons who were professional drivers or operators of heavy machinery, those taking tremogenic drugs, and if there was a suspected interaction between ethosuximide and other medications. Patients were requested to avoid alcohol, caffeine, and smoking for 24 hours before testing.

Three patients were taking propranolol (mean dose: 80 mg daily), two gabapentin (1,200 mg daily), and two primidone (300 mg daily). Antitremoric drug dosages were not changed in the month prior to inclusion or during the trial.

The ethosuximide dose was selected according to the most frequently used regimen in patients with epilepsy. The starting dose was 250 mg daily and increased 250 mg weekly up to a maximum of 500 mg daily (BID).

The main outcome measures were: 1) a tremor clinical rating scale (TCRS),[12] 2) accelerometric recordings,[13] and 3) a self-reported disability scale.[14] A comparison of these measures taken on day 1 (before drug intake) and on day 21 (last dose taken the night before) was performed. All clinical assessments in all patients were performed by the same examiner (A.G.).

The TCRS consisted of the scale proposed by Fahn et al.[12] with minimal modifications. Specifically, clinical examination of postural and kinetic tremor of the hands, legs, head, and trunk (Part 1) according to the following scale: 0 = none; 1 = mild (amplitude <0.5 cm); 2 = moderate (amplitude 0.5–1 cm); 3 = marked (amplitude 1–2 cm); and 4 = severe (amplitude > 2 cm) (maximum score = 40). Face, tongue, and voice scores were not included. Measures of motor task performance (Part 2) including handwriting, drawing spirals (two sizes) and lines, and pouring liquids from one cup to another were scored as follows: 0 = normal, 1 = mildly abnormal, tremulous; 2 = moderately abnormal, considerable tremor; 3 = markedly abnormal; and 4 = severely abnormal, unable to do the task (maximum score = 36). The functional disability rate in daily living activities (Part 3) including speaking, feeding, bringing liquids to the mouth, hygiene, dressing, writing, and working was similarly scored between 0 to 4 (maximum score = 28). The subjective assessment by the patient compared to the last visit (Part 4) was scored as follows: 0 = no changes, +1 = slight, +2 = moderate and +3 = marked improvement; −1 = slight, −2 = moderate, and −3 = marked worsening. All clinical assessments in all patients were obtained by the same examiner (A.G.).

Neurophysiologic recordings were assessed as objective tremor measures with a previously described methodology.[13] Briefly, a triaxial accelerometer transducer (BIOPAC, USA) was attached to the dorsal surface of the index finger of the most affected hand. The patient was comfortably seated upright in a chair. Three 60-s recordings were obtained in a postural position of arms outstretched in front of the chest. The hands were allowed to rest for 40 s between recordings. Tremor was quantified by a power spectra analysis to determine the dominant frequency peak (Hz) and magnitude of the accelerometer signal (absolute power of the dominant frequency peak in μV^2) for each axis (x, y, z). Final data of each time-point was the mean of the three recordings. The study tremor magnitude score was the great value obtained in one of the three axes.

The self-reported disability scale (Bain et al.)[14] consisted of 25 activities of daily living, and each was scored according to the following scale: 1 = able to do the activity without difficulty, 2 = able to do the activity with a little effort, 3 = able to do the activity with a lot of effort, 4 = unable to do the activity (maximum score = 100).

Table 1. Clinical Characteristics of Patients in the Present Series

Patient	Age, Sex	Family History	Evolution (years)	ET Medication	Completed Study	Causes of drop-out
1	74, F	+	10	Propranolol	Yes	
2	66, M	+	8	Primidone	Yes	
3	80, F	+	5	Primidone	No	Nervousness, anxiety, headache
4	79, F	+	15	Propranolol	No	Dizziness, nausea, instability
5	70, F	+	20	Propranolol	Yes	
6	71, M	+	15	Gabapentin	Yes	
7	72. M	+	8	Gabapentin	Yes	

Abbreviations: ET, Essential Tremor; F, Female; M, Male.

Table 2. Scores of the Patients who Completed the Study

Patient	Day 1				Day 22				
	TCRS 1+2	TCRS 3	ACC	DIS	TCRS 1+2	TCRS 3	TCRS 4	ACC	DIS
1	35	15	887	40	35	16	0	901	41
2	43	15	922	47	44	15	0	944	40
5	41	13	788	38	40	13	−1	800	38
6	39	17	966	45	40	17	0	978	45
7	57	15	1,047	61	61	14	0	1,037	64

Abbreviations: ACC, Accelerometer Data (in μV^2); DIS, Bain Disability Scale; TCRS, Tremor Clinical Rating Scale.
[1]Before assessments were taken before drug intake on the test day.

Statistical analysis of medication effects over the main variables was performed using parametric tests with the exception of TCRS part 4, which was assessed with nonparametric Wilcoxon matched-pairs tests. Any $p < 0.05$ was considered significant.

Results

Five patients completed the study. The results are listed in Table 2. Pre-hoc power calculation ($\alpha = 0.05$) for the full sample of 15 patients was 90.3%, and post-hoc power for the reduced sample of 5 patients was 54.3%. There were no significant changes in clinical scores in motor task performance (TCRS parts 1+2), daily living activities (TCRS part 3), or the patients' subjective assessment (TCRS part 4) and global appraisal. Ethosuximide treatment did not influence the accelerometry measurements or disability scale scores.

Anxiety, nervousness, headache, and dizziness were reported by two patients, causing them to stop the trial. No patient preferred to continue on ethosuximide treatment.

Discussion

This is the first study to investigate the efficacy of ethosuximide in ET. In this preliminary study, the comparison revealed no significant improvements in any tremor outcome measures for ethosuximide at the tested dose.

The power of this pilot study was low due to the small number of patients who completed the study. However, we think that results are clinically relevant as none of the patients in this open-label trial experienced any benefit; therefore they discourage the implementation of a controlled study with this drug.

Our results are in discordance with the "olivary hypothesis" of ET and a previous study of ethosuximide in ET animal models.[7] The dose used in the animal study corresponds to the that employed in our study. Thus, the discrepancy between findings in rats and humans might be attributable to the imperfection of the ET animal model. In fact, no existing model exactly recreates all ET features. One of the main problems is the uncertainty of whether the specific transmitter abnormalities/central nervous system lesions seen in the animal tremor model are characteristic of their human counterparts.[15]

The ability of T-type calcium channel antagonists to suppress tremor has been investigated in parkinsonian tremor. One study in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) monkey model showed that ethosuximide at doses of 150 mg/day reduced tremor by 60% after 5 days.[16] However, negative results were reported for a pilot study of human parkinsonian tremor that included patients with Parkinson's disease ($n = 6$) and drug-induced parkinsonian tremor ($n = 4$) at doses of 500 mg/day.[17] Only one patient per group improved, and 80% of the subjects experienced adverse effects including increased tremor.

Taken together, the results of our exploratory study suggest tat ethosuximide is not an effective treatment for ET. Research into developing better ET animal models appears necessary.

References

1. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2011;77:1752–1755. doi: 10.1212/WNL.0b013e318236f0fd

2. Benito-Leon J. Essential tremor: a neurodegenerative disease? *Tremor Other Hyperkinet Mov.* 2014;4. doi: 10.7916/D8763CG0

3. Louis ED, Faust PL, Vonsattel J-PG. Purkinje cell loss is a characteristic of essential tremor: towards a more mature understanding of pathogenesis. *Parkinsonism Relat Disord.* 2012;18:1003–1004. doi: 10.1016/j.parkreldis.2012.06.017

4. Gironell A. The GABA hypothesis in essential tremor: lights and shadows. *Tremor Other Hyperkinet Mov.* 2014;4. doi: 10.7916/D8SF2T9C

5. Deuschl G, Elble R. Essential tremor: neurodegenerative or nondegenerative disease towards a working definition of ET. *Mov Disord.* 2009;14:2033–2041. doi: 10.1002/mds.22755

6. Llinas R, Volkind RA. The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. *Exp Brain Res* 1973;18:69–87. doi: 10.1007/BF00236557

7. Handforth A, Homanics GE, Covey DF, et al. T-type calcium channel antagonists suppress tremor in two mouse models of essential tremor. *Neuropharmacology* 2010;59:380–387. doi: 10.1016/j.neuropharm.2010.05.012

8. Marin-Lahoz J, Gironell A. Linking essential tremor to the cerebellum: neurochemical evidence. *Cerebellum* 2016;15:243–252. doi: 10.1007/s12311-015-0735-z

9. Coulter DA, Huguenard N Jr, Prince DA. Characterization of ethosuximide reduction of low-threshold calcium current in thalamic neurons. *Ann Neurol.* 1989;25:582–593. doi: 10.1002/ana.410250610

10. Deuschl G, Bain P, Brin M, et al. Consensus statement of the Movement Disorder Society on tremor. *Mov Disord.* 1998;13 Suppl 3:2–23. doi: 10.1002/mds.870131303

11. Gironell A, Kulisevsky J, Pascual-Sedano B, Barbanoj M. Routine neurophysiological tremor analysis as a diagnostic tool for essential tremor: a prospective study. *J Clin Neurophysiol.* 2004;21:446–450. doi: 10.1097/00004691-200411000-00009

12. Fahn S, Tolosa E, Marín C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders. Baltimore: Urban & Shwarzenberg; 1988. p. 225–234.

13. Gironell A, Kulisevsky J, Barbanoj M, López-Villegas D, Hernández G, Pascual B. A double-blind placebo-controlled trial of gabapentin and propranolol in patients with essential tremor. *Arch Neurol.* 1999;56:475–480. doi: 10.1001/archneur.56.4.475

14. Bain PG, Findley LJ, Atchinson P, et al. Assessing tremor severity. *J Neurol Neurosurg Psychiatry* 1993;56:868–873. doi: 10.1136/jnnp.56.8.868

15. Wilms H, Sievers J, Deuschl G. Animal models of tremor. *Mov Disord.* 1999;14:557571. doi: 10.1002/1531-8257(199907)14:4<557:AID-MDS1004>3.0.CO;2-G

16. Gomez-Mancilla B, Latulippe JF, Boucheer R, Bédard PJ. Effect of ethosuximide on rest tremor in the MPTP monkey model. *Mov Disord.* 1992; 7:137–141. doi: 10.1002/mds.870070207

17. Pourcher E, Gomez-Mancilla B, Bédard PJ. Ethosuximide and tremor in Parkinson's disease: a pilot study. *Mov Disord.* 1992;7:132–136. doi: 10.1002/mds.870070206