A Randomized Placebo-Controlled Comparative Trial of Gabapentin and Propranolol in Essential Tremor

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Background: New medication is needed to treat essential tremor. Preliminary evidence suggests that gabapentin may be effective in the treatment of this disorder.

Objective: To study the effects of gabapentin in a comparative, double-blind, crossover, placebo-controlled trial of patients who have essential tremor.

Patients and Methods: 16 patients with essential tremor (6 with a new onset and 10 with a 2-week washout period of previous treatment with propranolol hydrochloride) received gabapentin (Neurontin), 400 mg 3 times daily; propranolol hydrochloride, 40 mg 3 times daily; and placebo for 15 days with a 1-week washout period between treatments.

Major Outcome Measures: Major outcome evaluations consisted of a Tremor Clinical Rating Scale, accelerometric recordings, and a self-reported disability scale obtained before drug intake on study days 1 and 15 of each treatment period. In addition, the initial (day 1) and superimposed (day 15) drug effects were studied before and 2, 4, 6, and 8 hours after drug intake.

Results: At day 15, both gabapentin and propranolol demonstrated significant and comparable efficacy in reducing tremor from baseline in all tremor measures. The initial drug effects evaluated through accelerometry revealed no significant changes with the use of a placebo, but gabapentin and propranolol use significantly reduced tremor power.

Conclusion: Gabapentin may be useful for the treatment of essential tremor.

Arch Neurol. 1999;56:475-480

ESSENTIAL TREMOR (ET) is one of the most common movement disorders and is characterized by tremor during the maintenance of posture and active movement. Although benign in its lack of effect on life expectancy, a small percentage of patients suffer serious disability, and a larger number find it a substantial embarrassment.

The drug treatment of ET remains poor and is often unsatisfactory. The efficacy of primidone and β-adrenergic antagonists such as propranolol hydrochloride has been demonstrated, but many patients, particularly elderly persons (ie, >70 years), do not benefit from these drugs because of contraindications, adverse reactions, and failure to achieve adequate tremor control.

In a previous open-label trial using clinical scales as the main outcome measure, gabapentin (1-[aminomethyl]cyclohexaneacetic acid: Neurontin), an anticonvulsant drug, was suggested to be effective in the treatment of ET. In a recent double-blind, placebo-controlled study of gabapentin as an add-on drug to previous antitremor medication and using clinical scales, the improvement in scale scores of the group taking gabapentin did not reach statistical significance (P > .05).

Data from double-blind, placebo-controlled studies using both clinical scales and objective quantitative methods are still lacking. Furthermore, studies comparing gabapentin with standard medication for ET such as propranolol have not been performed. We studied the effects of gabapentin compared with propranolol in patients with ET using a double-blind, crossover, placebo-controlled design. We used both clinical scales and objective accelerometric recording measures, and we studied the long-term (baseline vs end of treatment), intermediate-term (periodic studies during first day of drug administration), and superimposed (periodic studies during last day of drug administration) drug effects.

All 16 patients completed the study. The mean ± SEM of the main variables (TCRS, }
PATIENTS AND METHODS

PATIENTS

Sixteen outpatients attending the Movement Disorders Section of the Department of Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, who had moderate (enough to cause mechanical or social disability) to severe ET (8 men and 8 women; mean age [range], 67.9 [47-79] years; mean tremor duration [range], 12.2 [3-30] years) were included in the study. The diagnosis was established on the basis of chronic (ie, >5 years), persistent (although the amplitude may fluctuate), and bilateral (but may be asymmetrical) postural tremor with or without kinetic tremor involving hands or forearms (although tremor of other body parts may also be present). In addition, the patients had no other neurological abnormalities related to systemic or other neurological disease (with the exception of the presence of tremor, cogwheeling, and the Fron- ment sign) and no other explanation for tremor (eg, the presence of known causes of enhanced physiological tremor, concurrent or recent exposure to drugs known to cause tremor, or the presence of a drug-withdrawal state). The study protocol was approved by the hospital ethics committee and was performed in accordance with international ethical regulations. All patients gave informed consent to participate. Patients were excluded from the trial if any of the following were present: cardiac failure, asthma, peripheral vascular disease, diabetes mellitus, seizures, and active treatment with antacids, histamine-2 antagonists, or tremor-active drugs. The tremor-active drugs included central cholinergic drugs (acetylcholine, muscarinic and nicotinic agonists, anticholinesterases, and antiparkinsonian drugs), central monoaminergic drugs (neur-roleptic agents, phenylethylamines, and indoles), peripheral adrenergic drugs (lithium, amphetamine, corticoste-roids, and thyroid hormone supplements), and others, such as anticonvulsant medications (valproic acid), bronchodilators (theophylline and terbutaline sulfate), or an-tidepressant drugs (amitriptyline hydrochloride). Patients with dystonia were also excluded. Patients were requested to avoid alcohol, caffeine, and smoking for 24 hours before testing.

Besides hand tremor, 5 patients also had tremor of the head. All patients had kinetic tremor of the upper limbs in addition to postural tremor. Six patients had de novo tremor, and the rest had discontinued their previous treatment (9 patients with propranolol [mean dose, 135 mg/d], and 1 patient with diazepam, 15 mg/d) at least 2 weeks before entering the trial.

METHODS

The study was comparative, double blind, crossover, and placebo controlled. Capsules of identical appearance but containing gabapentin, propranolol hydrochloride, or lac-tose (placebo) were given in random order (using a Latin square). To start treatments at a low dose, an introductory capsule containing 400 mg of gabapentin, 40 mg of propranolol hydrochloride, or placebo was taken on day 1. Both active drugs were raised by 400 mg (gabapentin) and 40 mg (propranolol) every second day to a maximum of 400 mg (gaba-pentin), 40 mg (propranolol), or placebo, all of them 3 times daily. Fixed doses of both drugs were used to compare their clinical potency. The gabapentin dosage was selected accord- ing to uncontrolled previous data, but the propranolol dosage was the most-used regimen in clinical tremor trials. Patients received the corresponding full treatment regimen for 13 days, with a 1-week washout period between treatments.

TREMOR CLINICAL RATING SCALE

Main outcome measures consisted of the comparison of results of a Tremor Clinical Rating Scale (TCRS), accelerometric recordings, and a self-reported disability scale (see below) between study days 1 (before drug intake) and 15 (last dose taken the night before). In addition, we used a subscale of the TCRS (parts 1 and 2) and accelerometric recordings to assess the course of initial drug effects, evaluated at day 1 (at baseline and at 2, 4, 6, and 8 hours after the first drug administration [9 AM]), and at day 15 (before last drug intake [9 AM] and at 2, 4, 6, and 8 hours). Adverse events were carefully monitored throughout the trial, with patients questioned about common effects of both drugs. The TCRS consisted of the scale proposed by Fahn et al, with minimal modifications. Specifically, clinical accelerometry, and disability scale) at baseline (day 1, before drug intake) and after 14 days of treatment (day 15, before drug intake) in the 3 interventions (gabapentin, 400 mg 3 times daily; propranolol hydrochloride, 40 mg 3 times daily; and placebo) are presented in the Table. Figure 1 shows the effects of the 3 arms of treatment in individual patients to demonstrate the variability of each treatment on part 3 of the TCRS, which assesses functional disability in daily activities.

CLINICAL EXAMINATION AND MOTOR TASK PERFORMANCE (TCRS, PARTS 1 AND 2)

The analysis showed a nonsignificant period effect ($P = .41$) and a significant treatment effect ($P = .007$). Gabapentin and propranolol treatment reduced the score more than placebo ($-3.03 \pm 1.46 [P<.05]$ and $-4.95 \pm 1.46 [P = .002]$, respectively), and significant differences were not observed between gabapentin and propranolol use ($1.92 \pm 1.46, P = .20;$ post hoc power, 0.72).

ACTIVITIES OF DAILY LIVING (TCRS, PART 3)

The analysis showed a nonsignificant period effect ($P = .23$) and a significant treatment effect ($P = .002$). Gabapentin and propranolol treatment reduced the score more than placebo ($-3.10 \pm 1.10 [P = .01]$ and $-4.50 \pm 1.10 [P = .001]$, respectively), and significant differences were not observed between gabapentin and propranolol use ($1.40 \pm 1.16, P = .23;$ post hoc power, 0.86).
examination was performed of postural and kinetic tremor of the hands, legs, head, and trunk (part 1) according to the following scale: 0 indicates none; 1, mild (amplitude, <0.5 cm); 2, moderate (amplitude, 0.3-1 cm); 3, marked (amplitude, 1-2 cm); and 4, severe (amplitude, >2 cm) (maximum score, 40). Scores for face, tongue, and voice were not included. Postural tremor was assessed with the patient’s hands held prone in front of the nose with the arms abducted while kinetic tremor was assessed in the middle of the transit phase of the finger-to-nose test with a target object held at arm’s length from the patient. Measures of motor task performance (part 2), ie, handwriting, drawing spirals (2 sizes) and lines, and pouring liquids from one cup to another, were scored as follows: 0 indicates normal; 1, mildly abnormal or tremulous; 2, moderately abnormal, with considerable tremor; 3, markedly abnormal; and 4, severely abnormal, ie, unable to do the task (maximum score, 36). Functional disability in daily activities (part 3), ie, speaking, feeding, bringing liquids to mouth, hygiene, dressing, writing, and working, was scored similarly from 0 to 9, with a maximum score of 28. Part 4 (subjective assessment by the patient compared with last visit) was scored as follows: 0 indicates without change; 1, 2, and 3 indicate slight, moderate, and marked improvement, respectively; and −1, −2, and −3 indicate slight, moderate, and marked worsening, respectively. This scale was selected because of its frequent clinical use and our clinical experience with its usefulness, although its reliability and validity have not yet been reported. All clinical assessments in all patients were obtained by the same examiner (A.G.) blinded to study arms.

NEUROPHYSIOLOGICAL MEASUREMENTS

Neurophysiological recordings were assessed as objective tremor measures with a previously described method. Briefly, a single-plane accelerometer (Grass Instruments Division, Astro-Med Inc, West Warwick, RI) transducer oriented in the vertical plane 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 recordings of 60 seconds each were obtained with the patient in a postural position of arms outstretched in front of the chest. The patient’s hands were allowed to rest for 40 seconds between recordings. Tremor was quantified by a power spectral analysis to determine the dominant frequency peak (in hertz) and the magnitude of the accelerometer signal (absolute power of the dominant frequency peak in microvolts squared). The final score of each time point was the mean of the 3 recordings. An electromyographic (EMG) recording of the flexor and extensor forearm muscles was also obtained in each patient.

DISABILITY MEASUREMENT

A self-reported disability scale consisted of 25 items of daily activities. Each item was scored according to the following scale: 1 indicates 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; and 4, unable to do the activity (maximum score, 100).

STATISTICAL ANALYSIS

The medication effects on the main variables (TCRS scores, absolute power of the dominant frequency peak, and total score of self-reported disability scale) were evaluated with an analysis of variance using the least-squares method. The model included the effects and period of treatment. In the analysis of the neurophysiological recordings, the baseline was also included in the model because of the variability of that measure. The differences between treatments (gabapentin vs placebo, propranolol vs placebo, and gabapentin vs propranolol) were analyzed using contrasts. The time course of the initial and superimposed drug effects in clinical assessments (TCRS, parts 1 and 2) and accelerometer was evaluated with a 1-way repeated-measures analysis of variance applied to raw data over time and to changes between treatments. Paired comparisons were also analyzed by a paired Student t test after a Bonferroni adjustment to control inflation type I errors. Any P <.05 was considered significant. Any P value close to .05 associated with a magnitude of effect clinically important was considered significant. In addition, if no significant differences were found between active treatments, post hoc power analysis was performed, with a delta considered the mean significant difference between active treatments vs placebo and a bilateral hypothesis.

PATIENTS’ SUBJECTIVE ASSESSMENT (TCRS, PART 4) AND GLOBAL PATIENT APPRAISAL

A nonsignificant period effect (P = .99) and a significant treatment effect (P = .006) were observed in the analysis of the subjective assessment by the patients compared with their last visit. Gabapentin and propranolol treatments were superior to placebo in the scores (1.37 ± 0.46 [P = .006] for gabapentin and 1.44 ± 0.46 [P = .004] for propranolol). Significant differences were not observed between gabapentin and propranolol use (−0.07 ± 0.46, P = .89; post hoc power, 0.81).

When patients were asked about the treatment course they preferred, although no patient indicated that placebo was the most effective treatment, 8 (50%) thought gabapentin was more effective, 6 (38%) thought propranolol was more effective, and 2 (12%) found both treatments similar. Twelve patients (75%) stated that propranolol was superior to placebo, and 12 patients (75%) also considered gabapentin to be superior to placebo.

NEUROPHYSIOLOGICAL DATA

The mean (range) dominant frequency peak was 5.9 (4.4-7.8) Hz. Tremor frequency was not altered by treatments and did not predict drug response.

A nonsignificant period effect (P = .23) and nearly significant treatment effect (P = .08) were observed in the final value of accelerometer adjusted by baseline. Greater reductions of the absolute power of the dominant frequency peak with respect to placebo were observed with both gabapentin (−2352.0 ± 1153.3; P = .05) and propranolol (−2282.14 ± 1116.58; P = .05). No significant differences were observed between values for gabapentin use
Main Scores Obtained in 16 Patients at Baseline (Day 1, Before Drug Intake) and After 14 Days of Treatment (Day 15, Before Drug Intake)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potential Score Range</th>
<th>Gabapentin</th>
<th>Propranolol Hydrochloride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCRS</td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 1</td>
<td>Day 15</td>
</tr>
<tr>
<td>Parts 1 and 2</td>
<td>0 to 76</td>
<td>24.06 ± 2.88</td>
<td>16.00 ± 2.41†</td>
<td>22.61 ± 2.89</td>
</tr>
<tr>
<td>Part 3</td>
<td>0 to 28</td>
<td>12.88 ± 1.81</td>
<td>6.88 ± 0.94†</td>
<td>10.69 ± 1.21</td>
</tr>
<tr>
<td>Part 4</td>
<td>−3 to 3</td>
<td>1.25 ± 0.32†</td>
<td>1.31 ± 0.29†</td>
<td>−0.125 ± 0.36</td>
</tr>
<tr>
<td>Accelerometry, µV²</td>
<td>0 to 10 000</td>
<td>3902 ± 1557</td>
<td>889 ± 382†</td>
<td>1531 ± 443</td>
</tr>
<tr>
<td>Disability</td>
<td>25 to 100</td>
<td>43.25 ± 3.41</td>
<td>35.0 ± 1.67†</td>
<td>42.50 ± 3.19</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM. Lower values indicate better functions for all items, except for Tremor Clinical Rating Scale (TCRS), part 4. Treatment regimens: gabapentin, 400 mg 3 times daily; propranolol hydrochloride, 40 mg 3 times daily; and placebo. Accelerometry indicates absolute power of the dominant frequency peak; disability, self-reported disability scale; and ellipses, subjective assessment by the patient compared with day 1 visit.
†Significant improvement in relation to placebo. No significant differences were observed between gabapentin and propranolol.

Figure 1. Effects in individual patients together with mean values (broken lines) on functional ability in daily activities (part 3 of the Tremor Clinical Rating Scale [TCRS]) at baseline (day 1) and at the last study day (day 15) of each treatment period.

and those for propranolol use (−70.39 ± 1165.22, P = .95; post hoc power, 0.44).

Electromyographic recordings demonstrated simultaneous bursts of activity in the antagonistic muscles in 9 patients and alternate bursts in 7 patients. In 7 (78%) of the 9 patients with synchronous EMG activity in antagonistic muscles, propranolol was found to be the better treatment both clinically and accelerometrically. When EMG showed alternating activity, gabapentin was the better treatment in 5 (71%) of 7 patients.

SUBJECTIVE DISABILITY SCALE

The analysis of the disability scale showed a nonsignificant period effect (P = .18) and a nonsignificant treatment effect (P = .09). Although gabapentin use reduced the score more than placebo (−0.04 ± 2.75; P = .04), this significant effect was not observed with propranolol use (−0.48 ± 2.75; P = .11). No significant differences were observed, however, between the scores obtained with gabapentin use and those with propranolol use (−1.59 ± 2.75; P = .58; post hoc power, 0.42).

TIME COURSE

When assessing tremor activity with the TCRS, parts 1 and 2 (Figure 2), the time course of initial drug activity presented significant effects of all medications: placebo (P = .002), gabapentin (P < .001), and propranolol (P < .001), and the clinical score improved significantly after all treatments in all recorded times in relation to baseline values. No significant differences were observed in changes between medications.

The time course of the superimposed drug action also displayed a significant effect of all medications: placebo (P = .01), gabapentin (P < .05), and propranolol (P = .02). Although during placebo treatment, significant reductions of the tremor score were observed in all recorded times in relation to predrug values, during gabapentin and propranolol treatments, the reductions in relation to predrug values were only significant after 2 (propranolol) and 4 hours (gabapentin). Changes between medications were significantly different after 4 (P = .02), 6 (P = .02), and 8 (P = .03) hours, with the change after propranolol use being significantly lower than that after gabapentin and placebo use.

When assessing tremor activity by accelerometry (Figure 3), the time course of initial drug action presented a significant effect only with gabapentin (P = .005) and propranolol use (P = .03). The absolute power of the dominant frequency peak obtained 2, 4, and 6 hours after gabapentin use and 4 and 8 hours after propranolol use was significantly lower than that observed in basal conditions. The time course of superimposed drug activity did not show any significant effect for any medication. No significant differences were observed in changes between medications either at day 1 or at day 15.

All the analyses performed in the study were repeated after stratifying for previous propranolol use. No differences between subgroups were obtained in any comparison. It should be noted, however, that the power of this analysis is lowered because of the subdivision of the sample.
ADVERSE EVENTS

Slight daily somnolence occurred in 2 patients taking gabapentin, 1 patient taking propranolol, and 1 patient taking placebo. One patient reported transient paresthesia in the arms while taking gabapentin; 3 patients reported instability with propranolol use (this was disabling in 1 patient, although he decided to continue the study). Mild depressive symptoms (1 patient) and sporadic abdominal cramping (1 patient) were also encountered with propranolol use.

COMMENT

We evaluated the efficacy of gabapentin by using a traditional approach, comparing tremor data (TCRS, accelerometry, and self-reported disability scale) on the first study day with the same data on the last study day (day 15), and by studying the course of the initial (day 1) and superimposed (day 15) drug effects. At the dosage tested, the comparison of days 1 and 15 revealed slightly to moderately significant improvements in all outcome measures for gabapentin and propranolol use, but no significant changes were observed with placebo. Notably, there were no significant differences between treatment with gabapentin, 400 mg 3 times daily, and treatment with propranolol hydrochloride, 40 mg 3 times daily, this latter being the most-used dosage in short-term double-blind studies demonstrating symptomatic efficacy of propranolol in ET. The post hoc power of the comparison between active treatments in the TCRS-described measurements (parts 1 through 4) was good (>0.72), whereas in neurophysiological data and in the disability scale, it fell to 0.42.

Contrasting with the solidity of this study is the variability in our basal accelerometric assessments. This is a well-known limitation of studies using only accelerometric data. Nevertheless, as is shown on the time course of our initial and superimposed study (Figure 2), this basal variability was importantly reduced on the subsequent assessments (after 2, 4, 6, and 8 hours), leading to a pattern of changes reliable enough to ensure the significant active drug effect obtained.

As secondary outcome measures, we studied the initial and superimposed time course effects of both drugs. In this part of the study, only accelerometry was able to assess active treatment effects after the first dosage intake, and clinical estimations were not devoid of a major observer bias. This latter was evidenced in the marked placebo effect appraised at different times after drug intake.

Overall, our study attests to some of the intrinsic difficulties in assessing tremor in clinical trials. Some authors stress the importance of clinical rating scales as the most valid indexes of tremor-induced disability for therapeutic trials. The findings in our study, however, highlight the importance of obtaining different levels of evaluation (clinical, accelerometric, and disability), together with an accurately applied design.

Our study data showed that the overall benefit obtained with a given drug in a given patient was not homogeneous among the different variables examined. Thus, in the same patient, the clinical rating score could improve most with gabapentin use, but accelerometric measures or self-disability scores improved most with propranolol use.

Our results differ from those of the double-blind study by Pahwa et al in which they compared gabapentin use and placebo. Although the patients showed a numerical improvement with gabapentin use, it did not reach statistical significance (P > .05). A possible explanation is that many patients in that study were not discontinued from their previous pharmacological treatment. Patients may not have achieved their therapeutic response before entering the study but then obtained additional benefits when gabapentin was added.

Our study sample included many patients who had previously shown a positive response to propranolol. Although including these patients could be interpreted as a selection bias in that previous responders to propranolol would again respond to propranolol, this latter was not the experimental drug but a control for gabapentin use.

In addition, EMG recordings might be of some use in identifying patients who would or would not respond to gabapentin or propranolol. In our study, patients with synchronous EMG activity in antagonistic muscles benefited more from propranolol, and those with alternating EMG activity obtained more benefit from gabapentin. Al-
though both forms of muscle activity were reported to occur in the same patient, patients with ET with alternating EMG activity may have a lower response to propranolol than patients showing synchronous EMG activity. Although further studies are needed to confirm this finding, this part of our data is in accordance with studies showing that different EMG patterns may condition a different pharmacological response, further suggesting that ET may be a heterogeneous disorder.

Gabapentin is an antiepileptic drug with a structure similar to γ-aminobutyric acid (GABA), which penetrates the blood-brain barrier. Gabapentin is not metabolized by the liver, does not induce hepatic enzymes, and does not interact with other drugs. Furthermore, it is well tolerated, even in elderly patients. Its mechanism of action is not fully understood, but recent data indicate that it can increase human brain GABA levels and reduce intracortical excitability. The antitremor effect of gabapentin might be excerpted by a central nervous system cell modulation mechanism through GABAergic activation.

The origin of ET is unknown. A central mechanism involving the inferior olive is incriminated by most experimental data. The olivary oscillation could be transmitted and possibly amplified through the cerebellum, entrainment and possibly amplified through the cerebellum, and brainstem nuclei. Although the higher cost of this new drug should not be inherent in tremor studies and more conclusively established whether gabapentin might be a first-line drug for ET. A larger, ideally multicentric study enrolling more patients might overcome the methodological difficulties inherent in tremor studies and more conclusively establish whether gabapentin might be a first-line drug for ET. Although the higher cost of this new drug should not be ignored, gabapentin could be a good pharmacological option for patients who have contraindications to β-adrenergoreceptor antagonists and for others who do not respond adequately to standard medical treatment of ET.

Accepted for publication August 10, 1998.

REFERENCES