Efficacy and Tolerance of Pregabalin in Essential Tremor: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Introduction

Essential tremor (ET) is a common neurological disorder characterized by action tremor, predominantly affecting the hands. Several medications, including propranolol, primidone, topiramate and gabapentin, have shown moderate tremorolytic effects in placebo-controlled trials, however, current drug therapies are ineffective in approximately 25-55% of ET patients, and treatment is often limited by adverse effects.

Pregabalin (PGB) is an amino acid derivative of GABA with antiepileptic, anxiolytic, and analgesic properties. PGB binds to the alpha-2-delta subunit of neuronal voltage-gated calcium channels, causing diminished release of excitatory neurotransmitters. Preliminary studies suggest that PGB has tremorolytic effects, and the drug has proven reasonably well-tolerated in elderly patients. Accordingly, we assessed the tolerability and efficacy of PGB in patients with ET in this pilot placebo-controlled, cross-over design trial.

Methods

Participants:
Twenty patients with definite or probable ET, defined according to Tremor Investigational Group criteria, were recruited from the Baylor College of Medicine Parkinson’s Disease Center and Movement Disorders Clinic in Houston, TX. Exclusion criteria included: age <18 or >80 years; any ongoing cause of enhanced physiologic tremor; recent exposure to tremogenic drugs; historical or clinical evidence of psychogenic tremor; prior surgical treatment for tremor; and use of other tremorlytic drugs, apart from the study medication.

Evaluation Procedures:
A randomized, double-masked, placebo-controlled, crossover design study was used with Fahn-Tolosa-Marin Tremor Rating Scale (TRS) normalized total score serving as the primary endpoint. Secondary endpoints were the Clinical Global Impressions of Change (CGI-C), Quality of life in Essential Tremor Questionnaire (QUEST), Hamilton Anxiety Rating Scale (HAM-A), and a health status questionnaire on sleep hygiene (HD-16).

Symptoms were rated at Weeks 1, 3, 6, and 12. Patients were randomized to treatment with PGB or placebo, then switched to the other treatment at 6 weeks, and continued for 6 more weeks. The study protocol was approved by the Baylor College of Medicine Institutional Review Board for Human Research.

Results

Demographics and clinical characteristics of participants at study initiation are listed in Table 1.

Analysis of variance revealed no treatment effect (P > 0.16), period effect (P = 0.67), or treatment-period interaction (P > 0.07). Although TRS measures were worse when patients were taking PGB, this difference did not reach statistical significance (Table 2). There was a statistically significant difference in QUEST scores between PGB and placebo, favoring placebo (P = 0.03).

One patient withdrew from the PGB period of the study due to postural instability and died of a malignant arrhythmia 6 days later. Other adverse effects were mild to moderate in severity (Table 3).

Table 1: Clinical Characteristics of Patients at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Sex, F/M</td>
<td>11/9</td>
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<tr>
<td>Age, mean years ± SD</td>
<td>62.2 ± 12.7</td>
</tr>
<tr>
<td>ET duration, mean years ± SD</td>
<td>25.5 ± 14.9</td>
</tr>
<tr>
<td>Family history of ET, N (%)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Adjusted beta-blocker use, N (%)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Number of failed tremorlytics before enrollment, mean ± SD</td>
<td>2.3 ± 1.8</td>
</tr>
<tr>
<td>Normalized TRS, mean ± SD</td>
<td>20.3 ± 14.9</td>
</tr>
</tbody>
</table>

Table 2: Change in Measures of Efficacy

<table>
<thead>
<tr>
<th></th>
<th>PGB (N=20)</th>
<th>Placebo (N=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-C</td>
<td>3.9 ± 1.3</td>
<td>3.9 ± 0.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Change in QUEST summary index</td>
<td>8.0 ± 2.3</td>
<td>5.7 ± 1.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in HAM-A</td>
<td>1.1 ± 5.2</td>
<td>4.1 ± 5.4</td>
<td>0.26</td>
</tr>
<tr>
<td>Change in HD-16</td>
<td>32.2 ± 146.8</td>
<td>38.6 ± 99.3</td>
<td>0.14</td>
</tr>
</tbody>
</table>

The study was designed as a double-masked, placebo-controlled, cross-over trial with a sample size of 20 patients to detect a 20% difference in the normalized TRS score with 80% power and a 0.05 significance level. No interim analysis or data unblinding was performed.

Discussion

In conclusion, we found PGB to be well tolerated in patients with ET in this pilot placebo-controlled, cross-over design trial.

In this randomized, double-blind, placebo-controlled, cross-over study, PGB failed to significantly reduce ET severity, as assessed by TRS.

In a prior study of PGB for ET, there was a significant reduction in tremor amplitude as measured by accelerometry without a corresponding improvement in TRS subscore scores.

We included the QUEST as a secondary endpoint in this study, as our interest was in demonstrating a reduction in tremor that improved quality of life and motor function. Unexpectedly, we found a statistically significant deterioration in QUEST scores during the PGB period versus placebo. The basis for this change is not clear, as TRS scores were similar for PGB and placebo, and patient-rated CGI-C was essentially unchanged from baseline in both groups.

Given its size, this trial cannot exclude the possibility that PGB has tremorolytic effects, but any effect is likely to be modest, and our results suggest that a larger study is unlikely to yield more favorable results in a similar ET population.

Overall, adverse events of PGB in our ET population were comparable to those previously reported in patients with epilepsy, anxiety and chronic pain conditions.

In conclusion, we found PGB to be well tolerated in patients with moderately severe ET, but without a clinically meaningful tremorolytic effect.

Acknowledgment

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References

6. Fahn S, et al. Hamilton Anxiety Scale (HAM-A) and a Health Status Questionnaire on Sleep Hygiene (HD-16).9