Topiramate in Patients With Juvenile Myoclonic Epilepsy

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Background: Topiramate is a broad-spectrum agent effective against primarily generalized tonic-clonic seizures (PGTCS) as well as partial-onset seizures. Juvenile myoclonic epilepsy is one of the most common idiopathic generalized epilepsies, with most patients experiencing PGTCS.

Objective: To evaluate topiramate as add-on therapy in patients with juvenile myoclonic epilepsy.

Design: Post-hoc analysis of a patient subset from 2 multicenter, double-blind, randomized, placebo-controlled, parallel-group trials.

Setting: Eighteen centers in the United States; 10 centers in Europe; 1 center in Costa Rica (primary trials).

Patients: A total of 22 patients with juvenile myoclonic epilepsy participating in placebo-controlled trials assessing topiramate (target dose, 400 mg/d in adults) in inadequately controlled PGTCS.

Main Outcome Measure: Reduction of PGTCS.

Results: A 50% or more reduction of PGTCS in 8 of 11 topiramate-treated patients (73%) and 2 of 11 placebo-treated patients (18%) (P = .03). Reductions in myoclonic, absence, and total generalized seizures were also observed, although topiramate vs placebo differences did not achieve statistical significance.

Conclusion: As a broad-spectrum agent, topiramate is an effective option for patients with juvenile myoclonic epilepsy.

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METHODS

Two 20-week, double-blind, placebo-controlled trials used identical protocols. Patients with at least 3 PGTCS during an 8-week baseline period were eligible. Patients had to have an electroencephalogram or closed circuit television/electroencephalogram consistent with generalized epilepsy. The similarity of study de-
The most common adverse events in topiramate-treated patients were nausea (n = 5), insomnia (n = 3), upper respiratory tract infection (n = 3), abnormal vision (n = 2), appetite decrease (n = 2), concentration/attention difficulty (n = 2), diarrhea (n = 2), epistaxis (n = 2), and flu-like symptoms (n = 2). Three placebo-treated patients experienced nausea, 2 reported upper respiratory tract infection, and abnormal vision and diarrhea were each reported by 1 patient. Two topiramate patients and 1 placebo patient discontinued treatment owing to adverse events.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 11)</th>
<th>Topiramate (n = 11)</th>
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</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>7 (64)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Baseline seizure types, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGTCS</td>
<td>11 (100)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>5 (45)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Absence*</td>
<td>4 (36)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Median baseline seizure frequency/mo†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGTCS</td>
<td>1.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Myoclonic‡</td>
<td>20.1</td>
<td>28.4</td>
</tr>
<tr>
<td>Absence‡</td>
<td>23.5</td>
<td>29.0</td>
</tr>
<tr>
<td>Myoclonic or absence‡</td>
<td>19.9</td>
<td>36.6</td>
</tr>
<tr>
<td>All generalized seizures</td>
<td>18.2</td>
<td>35.1</td>
</tr>
</tbody>
</table>

Abbreviation: PGTCS, primarily generalized tonic-clonic seizures.
*One placebo-treated and 1 topiramate-treated patient had atypical absence seizures.
†Median frequency for patients with seizures in the baseline.
‡Patient/parent seizure counts without standardized instruction.

Table 2. Seizure Reduction

<table>
<thead>
<tr>
<th></th>
<th>Median Reduction, %</th>
<th>Responders, %*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 11)</td>
<td>Topiramate (n = 11)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 11)</td>
<td>Topiramate (n = 11)</td>
</tr>
<tr>
<td>PGTCS</td>
<td>38</td>
<td>64</td>
</tr>
<tr>
<td>Myoclonic‡</td>
<td>65</td>
<td>78</td>
</tr>
<tr>
<td>Absence‡</td>
<td>-42G</td>
<td>81</td>
</tr>
<tr>
<td>Myoclonic or absence‡</td>
<td>51</td>
<td>69</td>
</tr>
<tr>
<td>All generalized seizures</td>
<td>33</td>
<td>77</td>
</tr>
</tbody>
</table>

Abbreviation: PGTCS, primarily generalized tonic-clonic seizures.
*Greater than or equal to 50% seizure reduction.
†P = .03.
‡Patient/parent seizure counts without standardized instruction.
§Negative value indicates increase in seizures.

Baseline characteristics for the JME patients are summarized in Table 1. During the baseline phase, all patients experienced PGTCS, a criterion for study enrollment in the primary studies. Most also had uncontrolled myoclonic and/or absence seizures during the baseline phase. Valproate was the most common baseline AED (17 of 22 patients, 77%) either as monotherapy (n = 4) or in combination with primidone (n = 1), lamotrigine (n = 7), phenytoin (n = 2), lorazepam (n = 1), clonazepam (n = 1), or carbamazepine (n = 1). The majority of patients (14 of 22, 64%) were being treated with 2 AEDs before topiramate was added.

With the addition of topiramate, seizure frequency was substantially reduced (Table 2). After 20 weeks, the median PGTCS reduction was 64% in topiramate-treated patients and 38% in patients receiving placebo, although the difference did not achieve statistical significance. Significantly more topiramate-treated patients (73% vs 18%; P = .03) responded with a 50% or more reduction in PGTCS. Topiramate treatment was associated with improved control of myoclonic seizures (Table 2), including an increase in the number of weeks without myoclonic seizures (topiramate, 171% increase; placebo, 130% increase); the differences vs placebo were not statistically significant. The number of absence-free weeks in topiramate-treated patients increased by 15%, whereas the number of absence-free weeks decreased by 7% in placebo-treated patients (P = .07). Among topiramate-treated patients, 3 had no PGTCS and 1 had no myoclonic seizures during double-blind treatment; 2 placebo-treated patients had no PGTCS. In 5 placebo-treated patients, seizure frequency increased more than 50% from baseline (PGTCS, n = 1; absence, n = 3; myoclonic, n = 1); seizure frequency increased more than 50% in 2 topiramate-treated patients (absence, n = 1; myoclonic, n = 1).

The most common adverse events in topiramate-treated patients were nausea (n = 5), insomnia (n = 3), upper respiratory tract infection (n = 3), abnormal vision (n = 2), appetite decrease (n = 2), concentration/attention difficulty (n = 2), diarrhea (n = 2), epistaxis (n = 2), and flu-like symptoms (n = 2). Three placebo-treated patients experienced nausea, 2 reported upper respiratory tract infection, and abnormal vision and diarrhea were each reported by 1 patient. Two topiramate patients and 1 placebo patient discontinued treatment owing to adverse events.

COMMENT

Broad-spectrum AEDs are preferred for the management of JME because they tend to be effective against more than PGTCS. Even if they are not effective against all generalized seizures, they are less likely to aggravate myoclonic and/ or absence seizures. Valproate is widely regarded as the agent of choice in JME. Only 1 randomized double-blind study has evaluated valproate in JME, comparing low-dose (1000 mg/d) and high-dose (2000 mg/d) valproate monotherapy in double-blind, crossover fashion. Seizure control did not differ between doses: 37% (6 of 16 patients) and 44% (9
of 16 patients) were seizure free during low-dose and high-dose valproate treatment, respectively; 25% (4 of 16 patients) were seizure free for the entire study. The number of days with absence seizures increased during high-dose treatment in 25% of patients. As the authors noted, the low seizure-free rates in their study may have reflected the inclusion of patients with more refractory epilepsy, the use of fixed rather than individualized doses, and the difficulty in accurately counting myoclonic and absence seizures.

Our report is the first to present placebo-controlled observations in JME. However, the extrapolation of our findings to the JME population overall is limited by the fact that our patient population may represent a selected subset of patients with JME, i.e., those with PGTCS not adequately controlled with other AEDs. Moreover, myoclonic and absence seizure data were collected as secondary information; specific patient instruction/training for recording myoclonic and absence seizure data were not given. Thus, our study may have suffered from the same underreporting and/or inconsistent reporting cited by others.11

Nevertheless, our data show that topiramate reduced PGTCS frequency in patients with JME, the difference from placebo being significant despite the relatively small number of patients in each group. The reduction in the frequency of myoclonic seizures and all generalized seizures as well as the increase in number of absence-free weeks relative to placebo all point to a beneficial therapeutic effect of topiramate. Perhaps we should not be surprised that statistically significant differences between placebo and topiramate were not detected in analyses of myoclonic and/or absence seizures, given the variable seizure frequency at baseline, the difficulty in accurately and consistently counting myoclonic and absence seizures, as well as the small number of patients.

Retrospective case record audits and cohort studies have also found that topiramate can be effective in JME.12-15 In one such study in which good seizure control was defined as less than 1 PGTCS per year and less than 5 myoclonic or absence seizures/clusters per month, 80% (PGTCS), 58% (myoclonic), and 50% (absence) of patients achieved good seizure control with topiramate monotherapy (n = 15) or monotherapy (n = 4) and 76%, 59%, and 78%, respectively, with valproate (monotherapy, n = 36; polytherapy, n = 22).12 However, valproate was typically being used as the first agent whereas topiramate was being used as the third, fourth, or fifth agent in refractory JME. Nonetheless, topiramate compared favorably with valproate, particularly in controlling PGTCS and myoclonic seizures. Studies directly comparing topiramate with valproate are needed to determine the relative efficacy of these 2 broad-spectrum agents in JME.

Seizure worsening during AED therapy in patients with JME is a well-recognized phenomenon, particularly with carbamazepine and phenytoin.3,16 and more recently with oxcarbazepine.17 Paradoxical seizure worsening has also been observed during valproate treatment, including reports that absence/myoclonic seizure frequency increased during valproate treatment in 20%18 and 25%12 of patients with JME. However, reports of seizure worsening during valproate treatment have generally occurred in the context of overdose, encephalopathy, hepatic derangements, or metabolic disorders, which are known to provoke seizures.19 Only a few cases of worsening absence seizures without such confounding factors in valproate-treated patients have been reported.20 However, these events could reflect spontaneous fluctuations in seizure occurrence. In the data we report, seizure frequency increased by more than 50% in 18% of topiramate-treated patients compared with 45% of those receiving placebo, suggesting that seizure worsening was not an effect of topiramate.

Based on more recent studies of topiramate as adjunctive therapy,2 the recommended target dosage for initial evaluation of topiramate's effects is now 200 mg/d rather than the 400 mg/d that patients with JME received. Not surprisingly, 400 mg/d of topiramate was not as well tolerated as in studies with lower topiramate dosages. In refractory partial-onset seizures, maintenance dosages for topiramate as adjunctive therapy have been 300 to 350 mg/d, although some patients require much lower dosages.

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ages.\textsuperscript{21,22} These observations suggest that 400 mg/d of topiramate may have exceeded patients' dosage needs and that additional studies are needed to identify optimal dosages for patients with JME.

Despite their limitations, our data, strengthened by the presence of a control group, strongly suggest that topiramate adjunctive therapy is an effective option for patients with JME.

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REFERENCES