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.

Arch Neurol. 2005;62:1705-1708

JUVENILE MYOCLOMIC EPILEPSY (JME) is one of the most common idiopathic generalized epilepsies. In addition to myoclonic seizures, most patients (approximately 90%) have primarily generalized tonic-clonic seizures (PGTCS).1 The emergence of PGTCS is typically the reason for which patients seek medical attention. Myoclonic and/or absence seizures may go unnoticed, even at the time epilepsy is diagnosed.1,2 By not recognizing the syndrome, clinicians may select antiepileptic drugs (AEDs) that are not only ineffective against myoclonic and/or absence seizures, but also may aggravate seizures.3

Valproate, with its broad spectrum of activity, is widely regarded as first-line therapy in JME. However, effective alternative broad-spectrum agents are needed for patients with JME who do not achieve satisfactory seizure control and for those who are concerned by valproate’s teratogenic, endocrinologic, and weight effects, for example. Topiramate is a newer broad-spectrum agent effective as adjunctive therapy against partial-onset seizures,4-6 PGTCS,7 and seizures associated with Lennox-Gastaut syndrome.8 As monotherapy in newly diagnosed epilepsy, it was as effective as valproate and carbamazepine in a double-blind study in which no seizure type/epilepsy was excluded.9 We report a post hoc analysis of data from patients with JME participating in 2 double-blind, placebo-controlled trials evaluating topiramate as adjunctive therapy in inadequately controlled PGTCS.

METHODS

Two 20-week, double-blind, placebo-controlled trials used identical protocols.7,10 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-
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.

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Placebo (n = 11)</th>
<th>Topiramate (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>27</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Baseline seizure types, No. (%)</td>
<td></td>
</tr>
<tr>
<td>PGTCS</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Absence</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

Median baseline seizure frequency/mo†

| PGTCS     | 1.9                | 3.5                |
| Myoclonic‡| 20.1               | 28.4               |
| Absence‡  | 23.5               | 29.0               |
| Absence‡  | 23.5               | 29.0               |
| All generalized seizures | 19.9               | 38.6               |

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

<table>
<thead>
<tr>
<th>Placebo (n = 11)</th>
<th>Topiramate (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGTCS</td>
<td>18</td>
</tr>
<tr>
<td>Myoclonic‡</td>
<td>60</td>
</tr>
<tr>
<td>Absence‡</td>
<td>25</td>
</tr>
<tr>
<td>Myoclonic or absence‡</td>
<td>50</td>
</tr>
<tr>
<td>All generalized seizures</td>
<td>45</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.

signs and patient populations allowed pooling of data collected in the 2 studies.

After randomization to placebo or topiramate, the starting dose of 30 mg/d topiramate or equivalent number of placebo tablets was maintained for 4 weeks, then increased at 2-week intervals to target dosages of 400 mg/d in adults or 6 mg/kg per day in children. Treatment was continued for an additional 12 weeks.

Patients and parents/guardians maintained seizure diaries, recording the occurrence of all seizures. Systematic instruction was provided for identification and accurate recording of PGTCS. The protocol did not define specific conventions for counting myoclonic or absence seizures, eg, counting individual seizures or episodes of seizure clusters or seizure flurries.

Case record forms for reporting baseline characteristics allowed investigators to report syndromic classification. Among the 160 patients in the 2 studies, investigators recorded a specific epilepsy syndrome in 52 patients, 22 of whom were said to have JME. Baseline and on-treatment data for these 22 patients were extracted and analyzed for median percent reduction from baseline seizure frequency and percent of patients with a clinically significant response (≥50% seizure reduction from baseline seizure frequency). Fisher exact test (2-tailed) was used to compare placebo with topiramate.
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, ie, 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/recording 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. However, 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. 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.5,10 More recently with oxcarbazepine.11 Paradoxic seizure worsening has also been observed during valproate treatment, including reports that absence/myoclonic seizure frequency increased during valproate treatment in 20% and 25% 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.10 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, 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 dosing.
ages.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.

Accepted for Publication: May 24, 2005.
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Author Contributions: Study concept and design: Bourgeois. Acquisition of data: Biton and Bourgeois. Analysis and interpretation of data: Biton. Critical revision of the manuscript for important intellectual content: Biton and Bourgeois. Obtained funding: Biton. Administrative, technical, and material support: Biton. Study supervision: Biton and Bourgeois.

Financial Disclosure: Dr Biton received a research grant from Johnson & Johnson Pharmaceutical Research & Development to conduct the study. He is a consultant to and on the Speakers’ Bureau for Ortho-McNeil Pharmaceutical, Raritan, NJ. Dr Bourgeois has received honoraria/speaker support and grant/research support from and is a consultant to Ortho-McNeil Pharmaceutical.

Funding/Support: This study was sponsored by Johnson & Johnson Pharmaceutical Research & Development LLC, Raritan, NJ.

REFERENCES