Efficacy of Topiramate

J. Bruni

ABSTRACT: In controlled clinical trials, topiramate (TopamaxR) has demonstrated efficacy in refractory patients with complex partial seizures and secondarily generalized tonic-clonic seizures. Approximately 45 percent of 534 patients had a ≥ 50 percent reduction in seizure frequency. Limited open label trials have shown that topiramate has broad spectrum activity and may be effective in patients with primary generalized epilepsies. The efficacy of topiramate compares very favourably with the efficacy of other new antiepileptic drugs recently introduced.

Topiramate (TopamaxR) is a recently approved antiepileptic drug for use as adjunctive therapy in the treatment of refractory patients with partial seizures with or without secondary generalization. The efficacy of topiramate as adjunctive therapy was evaluated in five randomized, double-blind, placebo controlled trials. The analysis of the pooled data from these five clinical trials which included 534 patients demonstrates that topiramate was significantly superior to placebo in reducing the frequency of total seizures, complex partial, simple partial and secondarily generalized seizures, regardless of gender, age, baseline seizure frequency and concomitant antiepileptic drugs.1-8

A retrospective survey of open-label treatment as adjunctive therapy and as monotherapy in patients with partial seizures demonstrates that some patients can be successfully converted to monotherapy.9

Preliminary open-label studies have demonstrated efficacy of topiramate in primary generalized seizures.10

Efficacy in Partial Seizure Disorders

Topiramate has been evaluated in refractory adult patients who were experiencing ≥ 4 seizures per month and receiving up to two standard antiepileptic drugs.

Faught et al.1 conducted a randomized double-blind placebo controlled trial of three doses of topiramate (200, 400, 600 mg) and placebo as adjunctive therapy in a total of 181 patients. Median percent reduction from baseline in average monthly seizure frequency was the primary parameter assessed. Reduction in the monthly seizure rate compared to baseline was 13% for placebo, 30% for the 200 mg dose (p = 0.051), 48% for the 400 mg dose (p = 0.01) and 45% for the 600 mg dose (p = 0.001). The percent of patients who experienced ≥ 50% reduction was 18% for placebo, 27% for the 200 mg dose, 47% for the 400 mg dose (p = 0.013), and 46% for the 600 mg dose (p = 0.027). A significant decrease in secondarily generalized tonic-clonic seizures was also observed.

This study found that 200 mg was the minimally effective dose and the response rate increased with the higher doses. Plasma levels correlated with dose. No significant interaction was observed between topiramate and other standard antiepileptic drugs.

In a second U.S. controlled trial10 190 patients with refractory partial seizures were evaluated in a placebo-controlled dose-ranging trial using 600, 800, and 1000 mg daily doses of topiramate. During the 18-week double-blind treatment period the median percent reduction in monthly seizure frequency was 17% for placebo, 41% for topiramate 600 mg and topiramate 800 mg, and 38% for topiramate 1000 mg. The percent of patients who had a ≥ 50% reduction in seizure frequency was 9% for placebo, 44% for topiramate 600 mg, 40% for topiramate 800 mg, and 38% for topiramate 1000 mg. Twenty percent of patients treated with topiramate had a ≥ 75% reduction in seizure frequency.

In a European study11 60 patients with refractory partial seizures were treated in a double-blind placebo controlled protocol comparing placebo to a 600 mg daily dose of topiramate. Topiramate was found to be superior as indicated by a greater median percent reduction in average seizure rate (46% vs. 12%, p = 0.004), greater number of responders with ≥ 50% reduction in seizures (47% vs. 10%, p = 0.001) and better global assessments by both patients and investigator.

In a target dose study7 56 patients were randomized to receive placebo or topiramate titrated to the target dose of 800 mg or to the maximal tolerated dose. Eleven of 25 (44%) of topiramate treated patients were able to achieve the 800 mg target dose. In the intent-to-treat analysis the median percent reduction in seizure frequency relative to placebo was 54% in the


From the Division of Neurology, Wellesley Central Hospital, University of Toronto, Toronto.

Reprint requests to: Joseph Bruni, The Wellesley Central Hospital, 318JB-160 Wellesley Street East, Toronto, Ontario, Canada M4Y 1J3
Topiramate group (p < 0.001). None of the placebo-treated patients and 43% of the topiramate treated patients experienced a ≥ 50% reduction in seizure frequency (p = 0.0001). Thirty-six percent of topiramate patients had a ≥ 75% reduction in seizure frequency (p < 0.01). Secondary generalized tonic-clonic seizures were also significantly reduced by active treatment (p = 0.044).

In another double-blind add-on placebo controlled study of 47 patients 400 mg/day topiramate was more effective than placebo. The median percent reduction in seizure frequency was 41% for topiramate versus 1% for placebo (p = 0.065). Other efficacy variables favoured topiramate. Thirty-five percent of patients on topiramate versus 8% of patients on placebo had a ≥ 50% reduction in seizure frequency (p = 0.033). There was also a greater reduction in secondarily generalized seizures (p = 0.002) and overall global assessment in favour of topiramate.

In a retrospective study of open-label treatment of 214 patients, 136 patients were still receiving topiramate at the time of analysis (mean 2.5 years). One-third of these patients were successfully converted to monotherapy, and 62% of these had been seizure free for at least three months.

The efficacy of topiramate as monotherapy was also assessed by Sachdeo et al.11 In this trial 48 patients were randomized to treatment with either 100 mg/day or 1000 mg/day after their baseline antiepileptic drugs had been discontinued. The time to exit the study either because of lack of efficacy or adverse effect was greater for the 1000 mg/day group (p = 0.002).

It is apparent from these clinical trials that the overall response rate (≥ 50% responders) is in the range of approximate-ly 45 percent. The optimal response is observed with doses in the range of 400 - 600 mg when topiramate is used as adjunctive therapy and there appears to be a plateauing effect with higher doses. The optimal dose for monotherapy remains to be defined but is probably lower in the absence of hepatic enzyme inducing antiepileptic drugs. A number of patients converted to monotherapy have remained seizure free. These results are encouraging and the role of topiramate in the treatment of newly diagnosed patients needs to be explored.

Efficacy in Primary Generalized Seizure Disorders

The efficacy of topiramate has been largely evaluated in patients with partial seizures, however, efficacy in experimental models of epilepsy and its multiple mechanisms of action raise the possibility of broad spectrum activity and efficacy also against generalized seizures. In an open label extension of a double-blind placebo-controlled trial, 12 of 13 completers of the double-blind trial period elected to continue with open label topiramate therapy.10 Eleven of 12 patients with generalized tonic-clonic seizures, 4 of 5 patients with absence seizures, 1 of 2 patients with myoclonic seizures, and 2 of 2 patients with tonic seizures demonstrated a ≥ 50% reduction in seizure frequency. Seven of 12 patients with tonic-clonic seizures and 3 of 5 patients with absence seizures became seizure free.

In an open label study of topiramate as adjunctive therapy in patients with a variety of refractory partial and generalized seizures, efficacy was evident against both classes of seizures.12

Conclusions

Topiramate is a new antiepileptic drug with multiple mechanisms of action which has demonstrated efficacy as adjunctive therapy in controlled clinical trials in patients with partial seizure disorders. Results of open label studies indicate that the drug may also be effective against generalized seizures, and that conversion to monotherapy is possible in some patients. Comparative studies are needed to define the role of topiramate in newly diagnosed patients. Topiramate offers certain advantages that make it an attractive antiepileptic drug (see Table).

Table: Topiramate - Advantages.

<table>
<thead>
<tr>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel, multiple mechanisms of action 14</td>
</tr>
<tr>
<td>Favourable pharmacokinetics 14</td>
</tr>
<tr>
<td>No effect on plasma levels of other antiepileptic drugs</td>
</tr>
<tr>
<td>No need for monitoring of laboratory parameters</td>
</tr>
<tr>
<td>Safe and well tolerated by majority of patients (1.5% risk of renal calculi)</td>
</tr>
<tr>
<td>Broad spectrum activity.</td>
</tr>
</tbody>
</table>

In a meta-analysis of controlled clinical trials, topiramate compared favourable to the other new antiepileptic drugs gabapentin, vigabatrin, lamotrigine, and tiagabine.13 Controlled clinical trials have generally assessed efficacy of topiramate over the short term but with general clinical use tolerance does not appear to develop.

References