TOPIRAMATE PROPHYLAXIS IN PATIENTS SUFFERING FROM MIGRAINE WITH AURA: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL*

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ABSTRACT

Analyses of results of a trial using topiramate for migraine prophylaxis indicated that patients having migraine with aura experienced a greater reduction in migraine frequency and other migraine characteristics compared with patients without aura. Therefore, results from this subset of patients were evaluated further. Patients with migraine with aura experienced statistically significant reductions in migraine frequency, number of migraine days, severity and duration of attacks, and photophobia with topiramate prophylaxis compared with placebo.

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The use of topiramate as a medication for migraine prevention began with initial case reports followed by case series in cluster headache and single-center pilot studies.1,2

The strength of these studies suggested there was merit to conducting large, multicenter trials using topiramate in patients with migraine, and early results of one such pivotal trial have been recently reported.1

Results of another multicenter trial of topiramate in patients with migraine, with an emphasis on the effects observed on patients having migraine with aura, are presented here.

TOPIRAMATE PHARMACOLOGY

Topiramate pharmacology is still under investigation to determine how it may play a role in migraine prevention (Table). Certainly, topiramate's inhibitory effect in both the calcium and sodium channels affect the release of neurotransmitters. Topiramate also appears to activate gamma-aminobutyric acid type A receptors, inhibiting glutamate excitatory transmission.4-7

Other studies have shown that these ion channels are regulated by phosphorylation by protein kinase A and other kinases resulting in cellular activation. Topiramate may bind at the protein kinase A phosphorylation site to prevent cellular activation and neurotransmission. Alternatively, topiramate may bind at the site only in the dephosphorylated state.8

Several of these potential mechanisms of action may be of particular importance when addressing the aura symptoms often associated with migraine in many patients.

STUDY DESIGN

In this multicenter, double-blind, placebo-controlled, parallel-group study, a total of 211 patients were enrolled with 138 randomized to topiramate and 73 randomized to placebo. The design consisted of a washout period prior to study entry, followed by a 28-day baseline period during which baseline data and headache characteristics were accumulated; an 8-week treatment titration period; and a 12-week treatment maintenance period.

The target dose of topiramate was 200 mg in divided doses daily; however, there was flexibility in dose adjustment during the early phase of the study and patients were not required to reach the 200-mg target.
The mean daily dose of topiramate at the end of the study was approximately 135 mg. Patients were restricted in their use of analgesics or triptans for acute migraine treatment to 8 days per month or less during the study period.

The intent-to-treat population of 211 patients consisted of all patients who had taken at least 1 dose of medication and provided at least 1 outcome measure. However, only 155 patients completed the study. The primary outcome measure was migraine frequency.

**Patient Characteristics**

All patients, aged 18 to 65 years, had an International Headache Society diagnosis of migraine with or without aura and a history of migraine of at least 1 year. Patients could not have more than 8 or less than 3 headaches per month during the 3 months prior to enrollment. All patients had migraine onset before age 50 years and had fewer than 15 headache days per month. Because migraine sufferers may have other headaches, study patients needed to be able to clearly differentiate between migraine and other headaches. Patients with aura symptoms but no associated headache were excluded.

There was an unusually high percentage of patients having migraine with aura in this study. While the pivotal topiramate trials included approximately 10% of patients with aura, which is the percentage that can be expected in the general population, almost one third of patients in this study had migraine with aura. A total of 75 patients experienced migraine with aura at some point during the study. Forty-six patients were randomized to topiramate and 29 to placebo.

**Results**

Overall results of the 211 intent-to-treat patients showed no significant difference in migraine frequency between topiramate and placebo groups. However, statistical significance was achieved when only the 155 patients who completed the study were considered.

A further analysis of the occurrence of a variety of migraine components and events revealed that patients with aura showed a marked reduction in the incidence of aura from baseline. Therefore, a more detailed analysis of this subset of patients was conducted. Because patients were not randomized for an aura investigation, there were some baseline imbalances between active treatment and placebo in terms of migraine attack frequency, migraine days, duration, and severity.

However, in this population, the frequency of migraine attacks decreased from 5.2 attacks per month at baseline to 2.8 attacks per month after topiramate treatment; the placebo group experienced a decrease from 5.2 baseline attacks per month to 4.4 per month. This represented a 42% decrease for topiramate patients (\(P = .018\)) and a 12% decrease for placebo patients.

The number of migraine days also decreased significantly (\(P = .016\)) by 42.7% in the topiramate group compared with 11.2% in the placebo group. Patients receiving topiramate experienced a 30% decrease in attack duration, whereas placebo patients reported a 30% increase; migraine severity decreased 7% among topiramate patients and 0.5% among placebo patients.

Rescue medication use, defined as any medication taken by patients during the study for acute migraine treatment, was 13% less among topiramate patients compared with placebo patients, but the difference was not significant.

### Table. Topiramate Mechanisms of Action

<table>
<thead>
<tr>
<th>Site</th>
<th>Action</th>
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<tbody>
<tr>
<td>Voltage-activated Na+ channels</td>
<td>Limits sustained repetitive firing via state-dependent blockade of Na+ channels</td>
</tr>
<tr>
<td>Ca++ channel subtypes</td>
<td>Reduces slightly the amplitude of high voltage-activated Ca++ currents</td>
</tr>
<tr>
<td>GABA_A receptor subtype(s)</td>
<td>Potentiates GABA-mediated inhibition at GABA_A site not modulated by benzodiazepines or barbiturates</td>
</tr>
<tr>
<td>Glutamate receptor subtypes (kainate and AMPA)</td>
<td>Blocks glutamate-mediated neuroexcitation with no apparent effect on NMDA receptor activity</td>
</tr>
<tr>
<td>Carbonic anhydrase</td>
<td>Inhibits type II and type IV carbonic anhydrase</td>
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</tbody>
</table>

GABA\_A = gamma-aminobutyric acid type A; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; NMDA = N-methyl-D-aspartate.
There was also a 41% reduction in the occurrence of photophobia among topiramate users compared with a 15.4% reduction among placebo patients (P = .02). Although phonophobia symptoms decreased by 40% with topiramate compared with placebo, the difference was not statistically significant.

**Summary**

In this selected group of patients with migraine with aura, adverse events occurred as expected with topiramate. Approximately 43% of patients experienced paresthesias, 24% had fatigue, and 13% reported weight loss compared with placebo. Importantly, only 4 patients dropped out of the study due to adverse effects, suggesting that these side effects are generally tolerable and tend to remit over time.

Tolerability, combined with the significant reduction in migraine frequency, migraine days, duration of migraine attacks, and the incidence of photophobia, suggest that topiramate is a potential treatment for migraine with aura.

**REFERENCES**