Efficacy and Safety of Topiramate in Migraine Prevention: A Dose-Ranging, Placebo-Controlled, Double-Blind, Multicenter Trial*

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ABSTRACT

The antiepileptic agent, topiramate, has been under investigation for prevention of migraine for several years. Results of the first in a series of randomized, controlled, double-blind, multicenter studies show that higher doses of topiramate reduce the number of migraine periods and that this reduction is statistically significant compared with placebo. The mean number of migraine days and the migraine attack frequency were also significantly reduced in patients taking topiramate for 26 weeks.

(Adv Stud Med. 2003;3(6C):S565-S568)

Topiramate is a monosaccharide derivative, originally developed as part of a hypoglycemic drug program, that was found to have antiepileptic properties in animal models. Currently, it is a broad-spectrum, antiepileptic drug approved for the treatment of various seizure disorders in adults and children.

Because antiepileptic drugs have shown efficacy in patients with headache disorder, topiramate has been under investigation during the past several years to determine its potential as a prophylactic treatment for migraine and other headache disorders. Several small pilot trials, as well as one single-center, randomized, controlled trial, indicate that topiramate may be a safe and effective treatment option for migraine patients.1

The first of 3 multicenter, international, placebo-controlled, double-blind trials on the safety and efficacy of topiramate in migraine prophylaxis has been conducted. Preliminary, 20-week treatment results, including 12 weeks of maintenance treatment, were recently reported.2 Trial data after 26 weeks of total treatment time with 18 weeks of maintenance have now been collected and are reported here.

A total of 213 patients aged 12 to 65 years were randomized. Inclusion criteria included an International Headache Society (IHS) diagnosis of migraine with or without aura persisting for at least 6 months, with a frequency of 2 to 12 migraine periods per month during the month prior to trial entry.

Migraine period was defined as time from attack onset to cessation of pain, differing from “migraine day” which is any calendar day during which an attack occurred. For example, an attack beginning at 10 PM...
and lasting until 2 AM was considered 1 migraine period but 2 migraine days. A migraine period lasting more than 24 hours was considered 2 periods.

Patients with headache other than migraine and those with more than 15 headache days per month were excluded. Also excluded were those with headache onset after age 50 years, patients who had failed 2 or more previous preventive medication trials, and those using acute medications, such as triptans, to excess—or more than 8 days per month. Patients were permitted to use acute medications during the study.

Patients were randomized to receive placebo (n = 73) or 1 of 3 target doses of topiramate daily (n = 140). The target doses were 50 mg, 100 mg, and 200 mg daily. There were no significant differences at baseline between randomized groups in patient age, attack frequency, migraine periods, or migraine days. As expected, the entire cohort included more women than men. Most patients were slightly overweight.

**STUDY DESIGN**

Patients were screened, and preventive medication use was tapered during an initial 14-day washout period. This was followed by a 28-day baseline period with patients receiving the baseline dose of topiramate 25 mg daily or placebo. An 8-week titration period followed, with topiramate dose increasing in 25-mg increments weekly until patients reached the target dose. Doses were divided and taken twice daily. Two dosage reductions were permitted during the titration phase if needed.

After titration, the trial continued with an 18-week maintenance period, including a 7-week blinded transition and 11 weeks of open-label treatment. Additional dose reductions were permitted during maintenance treatment as long as no patient had more than 2 dose reductions during the entire length of the study.

The primary endpoint was a reduction in the mean 28-day monthly rate of migraine periods during the double-blind phase, including titration compared with the baseline phase. Secondary endpoints included the responder rate, defined as the percentage of patients with a reduction of greater than 50% in monthly migraine frequency, change in migraine days, and change in migraine attack frequency.
**RESULTS**

Overall, the major primary endpoint of the number of migraine periods showed a dose response and a decrease from baseline for all topiramate groups compared with placebo. This decrease was statistically significant among the groups taking topiramate 100 mg and 200 mg (P < .001). Onset of action also showed a dose response between placebo and the 100-mg and 200-mg topiramate groups, but there was no significant difference (Figure 1).

The responder rate of patients with a reduction of greater than 50% in migraine periods from baseline was 23% in the placebo group, 35% in the topiramate 50 mg group, 54% in the topiramate 100 mg group, and 52% in the topiramate 200 mg group. There was a similar step-wise reduction in number of migraine days with both the 100-mg and 200-mg topiramate doses, reaching a statistically significant difference compared with placebo (Figure 2). Mean attack frequency was also reduced from baseline in a dose-response fashion with the 100-mg and 200-mg topiramate doses, again achieving a statistically significant difference compared with placebo (Figure 3).

Mean body weight also decreased in the study population. Patients taking placebo gained an average of 0.3% of baseline body weight; those taking 50 mg topiramate lost 2.4%, and those taking 100 mg or 200 mg of topiramate lost 3.8% of baseline body weight.

**ADVERSE EVENTS**

Adverse events were more common among patients taking higher doses of topiramate. The most common treatment-emergent side effect was paresthesias; 5% of patients having paresthesias found them treatment-limiting and dropped out of the study. Memory difficulties and language problems caused 2% of patients in the 100-mg group and 2% of those in the 200-mg group to stop treatment.

Other treatment-limiting adverse effects included anxiety, insomnia, and nausea. In some cases, insomnia could be relieved by having patients change from a bedtime dose to a dose taken in the afternoon or early evening.

The overall dropout rate was 38% in the topiramate 200 mg group; there was no difference regarding dropout rate between placebo and the other doses of topiramate.

**SUMMARY**

Topiramate 100 mg or 200 mg was associated with a significant reduction in migraine periods, migraine days, and migraine attack frequency after 26 weeks of treatment. Statistical significance was observed as early as after the first month of therapy. More than one half of patients had a greater than 50% reduction in migraine periods at the higher topiramate doses. On average, patients lost up to 3.8% of their baseline body weight with active treatment.

The most common adverse effects included paresthesias, anxiety, insomnia, nausea, and memory difficulties. There appears to be a dichotomy among patients, with some experiencing no adverse effects at higher topiramate doses and others being quite sensitive.

Secondary analyses of the data are planned. Preliminary analyses suggest that there are patients with 75% and 95% responder rates with greater reductions in attack frequency and even complete cessation of attacks during the study period. Because

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*Figure 3. Reduction in Migraine Frequency with Topiramate vs Placebo*
patients were permitted use of acute medication during this trial, a further analysis of the benefits of topiramate on acute medication use would also be helpful. In addition, an analysis of the 20-week treatment data indicates that patients with migraine with aura had a greater response to treatment compared with those without aura; an analysis of this patient subset using 26-week treatment data is also planned.

REFERENCES
