ABSTRACT

Two randomized, double-blind, placebo-controlled, single-center studies were conducted to evaluate the efficacy of topiramate 200 mg/day in migraine prevention in a total of 70 patients. The studies consisted of a 4-week baseline phase, a 6-week titration phase, and a 12-week maintenance phase. Because of the similarities in trial design, inclusion/exclusion criteria, and outcome variables, the results were pooled and are presented here. Mean 28-day migraine frequencies were significantly lower in the 34 patients receiving topiramate than in the 36 patients on placebo (3.2 vs 3.8; \( P = 0.001 \)). Patients receiving topiramate experienced a significantly higher mean percentage of reduction in migraine rate compared with patients receiving placebo (1.55 vs 0.47, \( P = 0.001 \)). In addition, the percentage of patients who achieved a 50% or greater reduction in migraine frequency was significantly higher among patients receiving topiramate than among patients receiving placebo (35.3% vs 8.3%, \( P = 0.008 \)). Topiramate was generally well tolerated, with the most common adverse events being paresthesias, altered taste, and diarrhea. Discontinuation rates were similar in both groups. These results indicate that topiramate has a role in migraine prophylaxis and that larger multicenter trials are warranted.

Migraine, which affects approximately 18% of women and 6% of men in the United States, is a frequently disabling condition that often has an adverse effect on quality of life. Nearly one-quarter (24%) of patients with migraine experience at least 4 attacks every month, and nearly half (49%) require bed rest or report severe disability associated with their attacks. The average amount of bed rest required among migraine patients specifically attributable to the condition is 4 to 6 days a year.

Although annual direct costs for medical care of migraine are estimated to be $1 billion, indirect costs (eg, time lost from work) are significant as well, particularly because the prevalence of migraine peaks between the ages of 25 and 55.

It stands to reason that effective preventive therapy would reduce the frequency of attacks as well as the associated disability and medical care costs. However, only about 5% of patients with migraine receive preventive treatment, partly because many agents used for prevention are associated with undesirable adverse effects or have not been shown to be effective in controlled trials. An increasing understanding of the pathophysiology of migraine, however, is contributing to the development of newer treatments.

RATIONALE FOR TOPIRAMATE IN MIGRAINE PREVENTION

Results of recent studies utilizing various brain imaging techniques suggest that central nervous system (CNS) hyperexcitability and resulting cortical spreading depression may play a role in the genesis of
migraine attacks with aura. If this is true, medications that depress CNS hyperexcitability and/or inhibit cortical spreading depression may reduce the frequency and severity of migraines.

Topiramate, a broad-spectrum antiepileptic drug, has multiple potential mechanisms of action, including inhibition of voltage-gated Na+ and Ca++ channels and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate-subtype glutamate receptors, and enhancement of gamma-aminobutyric acid (GABA) receptor activity, all of which may counteract CNS hyperexcitability.

Results of several open-label studies suggest that topiramate may be efficacious in the prevention of episodic migraine and cluster headache. Dr. Edwards and colleagues therefore conducted 2 double-blind, placebo-controlled, single-center studies to evaluate the efficacy of topiramate in patients with migraine headaches with or without aura. Because of similarities in trial design, inclusion/exclusion criteria, and outcome variables, data from both studies were pooled for analysis. Results of the pooled data analysis are presented here.

PATIENT POPULATION

A total of 70 patients (68 women, 2 men) between the ages of 19 and 62 years (mean age, 41.1 years) were enrolled in the 2 studies. Key inclusion criteria were a diagnosis of migraine (defined according to International Headache Society guidelines) with or without aura established before age 50; the presence of migraine for at least 1 year, with at least 2 attacks per month; and the ability to comprehend and comply with protocol requirements, provide informed consent, and satisfactorily complete a headache diary. Women who were of childbearing potential were required to have a negative pregnancy test within 72 hours before the start of the studies and to be practicing adequate contraceptive measures.

Excluded from the studies were patients who:

- Used migraine medications for 3 or more 24-hour periods per week;
- Presented with frequent (more than 12 days per month) tension-type headaches;
- Were unable to distinguish between tension-type and migraine headache;

Figure 1. Mean 28-day Migraine Frequency at Baseline and During the Entire Double-Blind Treatment Phase in Patients Randomized to Topiramate (TPM)

Figure 2. Mean Reduction in 28-day Migraine Frequency During the Entire Double-Blind Treatment Phase in Patients Randomized to Topiramate (TPM) or Placebo
nostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for any Axis 1 disorder or for any substance-related disorder within 12 months prior to the screening visit;  
• Had any medical condition that would increase the risk of a significant adverse event or interfere with the assessment of drug efficacy and safety;  
• Had a history of renal calculi;  
• Used carbonic anhydrase inhibitors or any experimental drug or device within 30 days of study onset; or  
• Were pregnant or lactating.

STUDY DESIGN AND EFFICACY ENDPOINTS

The study design consisted of a 4-week baseline phase and a double-blind phase that included a 6- to 8-week titration phase and an 8- to 12-week maintenance phase.

Following screening, eligible patients entered the baseline phase. After 4 weeks, those patients who continued to meet eligibility requirements were randomly assigned to receive either topiramate (initiated at 25 mg/day and then titrated weekly in increments of 25 mg to a target dose of 100 mg bid in 34 patients) or matching placebo (36 patients). Patient visits were scheduled during the titration and maintenance phases to review headache diaries, follow the interim history, and perform safety assessments, which included vital signs, adverse events, and weight. The total study duration ranged from 20 to 22 weeks.

The primary efficacy endpoint was the mean 28-day migraine frequency during the entire double-blind phase in all patients. The secondary efficacy endpoints were the mean reduction in 28-day migraine frequency during the entire double-blind phase in all patients, and the percentage of patients achieving a 50% or greater reduction in 28-day migraine frequency. Weight change from baseline to the end of the study was assessed as well.

Analysis of covariance, with the baseline migraine rate or weight as a covariate, was used to compare between-group differences in mean 28-day migraine frequency, mean reduction in 28-day migraine frequency, and weight change. The Fisher exact test was used to compare the percentage of responders between the topiramate and placebo groups.

Efficacy Results

At the end of the study, treatment with topiramate was found to produce a significant reduction from baseline in 28-day migraine rates (Figure 1; $P = 0.001$) and a significantly greater mean reduction in 28-day migraine frequency (Figure 2; $P = 0.001$) compared with placebo. In addition, the percentage of responders (ie, patients who achieved a 50% or greater reduction in migraine frequency) was significantly higher among patients receiving topiramate than among those receiving placebo (Figure 3; $P = 0.008$).

In comparison with patients receiving placebo, the patients receiving topiramate experienced a statistically significant mean weight loss from baseline ($P = 0.005$) of 5.5 ± 7.1 pounds.

Safety Results

Topiramate was well tolerated in this study. The most common adverse events in patients treated with topiramate were paresthesias (65%), altered taste (32%), diarrhea (21%), and memory impairment (18%). Also seen, each with an incidence of 12%, were insomnia, appetite suppression, emotional liability, and dysarthria. By comparison, paresthesias occurred in
22% of patients receiving placebo, altered taste in 3%, diarrhea in 6%, memory impairment in 6%, insomnia in 8%, appetite suppression in 6%, and emotional lability in 3%.

Study discontinuation rates for the topiramate and placebo groups were similar. Of the 10 patients receiving topiramate who discontinued the study, 6 did so because of adverse events, 1 for lack of efficacy, and 3 for other reasons. By comparison, 8 patients receiving placebo discontinued the study, 4 for lack of efficacy and 4 for other reasons.

CONCLUSION

The results of this study demonstrate that topiramate is effective and well tolerated in the prevention of migraine. In comparison with placebo, treatment with topiramate resulted in statistically significant changes in migraine frequency, as evidenced by lower 28-day migraine rates from baseline, a greater mean reduction in 28-day migraine frequency, and a higher percentage of patients achieving a reduction in 28-day migraine frequency of 50% or more.

More important, these results are consistent with those from previously performed open-label and double-blind studies evaluating the efficacy of topiramate in migraine prophylaxis. In summary, topiramate may offer an important new option for migraine prevention. Larger multicenter trials are warranted.—PTH

REFERENCES