ABSTRACT

Several double-blind, placebo-controlled trials suggest that valproate, gabapentin, and topiramate have utility in migraine prevention. These antiepileptic drugs (AEDs) are generally well tolerated and the response rate (defined as a decrease of 50% or more in migraine frequency) range from about 16% to 40% with placebo subtracted. These AEDs can reduce both the frequency and severity of headaches, thereby improving the function of patients with the most disabling of migraines. Valproate is associated with nausea, tremor, and weight gain. The most frequent adverse event with gabapentin is somnolence, and topiramate therapy is associated with paresthesias and altered taste and—like many other AEDs—significant weight loss, which may actually be beneficial for many patients. Several large double-blind studies with topiramate are under way.

(Most clinicians will consider prophylactic drug therapy for migraine when patients have 2 or more attacks per month.) While the frequency of headaches has been the traditional objective signal for preventive therapy, clinicians realize that several other migraine characteristics or patient needs may also prompt a recommendation for preventive treatment. For example, when patients report attacks that significantly interfere with their daily activities, despite acute treatment, preventive therapy may be appropriate to restore function. In these cases, careful interpretation of the patient’s preferences is required. Preventive pharmacologic care may also be an option when acute therapy is contraindicated, overused, or linked to adverse effects. Finally, certain special situations, such as occurrence of uncommon migraine conditions (e.g., hemiplegic migraine or migraine with prolonged aura) or comorbid conditions (e.g., hypertension or depression), may also shape the clinical decision to offer migraine prophylaxis.

Evidence from recent surveys indicates that preventive therapy for migraine may be underused. Despite the increasing availability of more specific and tolerable acute migraine medications such as the triptans, a significant proportion of patients with migraine headaches remain dissatisfied with their current treatment options. In fact, 65% of patients with diagnosed migraine still report severe impairment or a need for bed rest. About half of migraine patients report at least 1 day each month where productivity at work or school is cut in half. Further, those individuals with the most severe headaches (Migraine Disability Assessment [MIDAS] Grades III and IV) are about 8 times more likely to visit an emergency department and 13 times more likely to see a hospital specialist than those with MIDAS Grade I headaches.

Despite the clear need for improved care, about half of all patients with migraine actually stop seeking care and only 3% to 5% employ preventive agents. While improved diagnosis and more effective use of
Divalproex Sodium

Divalproex sodium, an anticonvulsant with specific actions involving GABA response, has demonstrated clear efficacy in migraine prophylaxis. It is currently the only AED with Food and Drug Administration (FDA) indication for migraine. In one multicenter, randomized, placebo-controlled trial with this agent, the mean 4-week migraine headache frequency decreased from 6.0 at baseline to 3.5 at week 12 with active divalproex therapy (titrated to approximately 70 to 120 mg/L); this compared to a decrease from 6.4 to 5.7 in the placebo group (P < 0.001). Overall, 48% of divalproex-treated patients and 14% of placebo-treated patients showed a 50% or greater reduction in migraine headache frequency from baseline (P < 0.001). Treatment was stopped because of intolerance in 13% of divalproex patients, a rate that was not statistically different from the 5% placebo rate.

A recent long-term open-label follow-up of more than 109 patients in divalproex trials indicated that the attack rate continued to decline over the next year (Figure 1). The authors concluded that the initial benefits of this GABA-active AED were maintained for periods in excess of 1080 days. In terms of safety and tolerability, nausea was reported by 37% of patients taking divalproex after initial therapy but this had declined to a rate of 3% to 6% by 6 months. Similarly, alopecia was reported at an initial rate of 12% but declined in incidence after 6 months. The incidence of tremor and weight gain in patients on divalproex prophylaxis were 34% and 24%, respectively.

Table 1. Preventive Agents for Migraine

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
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<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Valproate, Gabapentin, Topiramate, Trigabine, Betadepressants, Tricyclics, Selective serotonin reuptake inhibitors, Monoamine oxidase inhibitors, Beta-adrenergic blockers, Propranolol, Nadolol, Metoprolol, Atenolol, Calcium channel antagonists, Venlafaxine, Nimesulide, Serotonin antagonists, Methysergide, Methergine, Others, Nonsteroidal anti-inflammatory drugs, Riboflavin, Magnesium, Neurontics</td>
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Gabapentin

A recent randomized double-blind trial of gabapentin indicated efficacy superior to placebo in preventing migraine. After a 4-week titration period during which gabapentin was increased to 2400 mg daily, the 4-week migraine rates were compared over a 12-week monitoring period. Many patients could not tolerate this escalation to the target dose of gabapentin, with 16/98 (16%) discontinuing prematurely because of adverse events compared to 4/45 (9%) placebo-treated patients. The majority (92%) of 87 patients eligible for analysis were white; 83% of patients were female, and...
the mean age was 39.4 years. In the overall intent-to-treat analysis, the responder rate was 36% for gabapentin and 14% for placebo (P = 0.02). Subjects receiving gabapentin had a mean headache rate of 2.7 in the 4-week study periods versus a rate of 3.5 in the placebo group (P = 0.006). When the modified intent-to-treat data (defined in this trial as the patients able to titrate to and maintain 2400 mg daily, or 56/98 patients) were analyzed, the response rate in the active treatment group was about 10% higher (Figure 2), with 26/56 (46.4%) of patients taking the AED having a 50% or greater reduction in their 4-week migraine rate.6

The most frequently reported adverse events of both treatment groups were asthenia, dizziness, and somnolence (Table 2). Adverse events thought by the investigator to be associated with the study drug resulted in patient withdrawal in 13/98 (13%) of the gabapentin-treated patients and 3/45 (6.7%) placebo-treated patients. Somnolence and dizziness accounted for many of the premature withdrawals among those taking the AED.22

TOPIRAMATE

A structurally unique AED, topiramate inhibits voltage-gated sodium and calcium channels and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate-subtype glutamate receptors and enhances GABA receptor activity.25 Several retrospective trials evaluating the efficacy and safety of topiramate in migraine prophylaxis have shown positive results.14,15 In one of these early trials, eg, 37 patients who had failed previous preventive attempts were given topiramate 25 to 100 mg daily and followed for 3 to 9 months; 11 patients (30%) had a reduction in frequency of more than 60% and another 11 (30%) had a 40% to 60% decrease.16

Based on such results, and on the finding that topiramate tends to produce weight loss rather than weight gain, a common reason for discontinuation in preventive therapy,2 several new studies have been initiated. Over the past 2 years, at least 4 double-blind, placebo-controlled, multicenter trials with higher doses of this AED were begun. One of these trials is now approaching full enrollment of 200 patients and 5 additional studies with 480 patients expected to enroll recruiting patients. Preliminary data from 2 of the single centers involved in topiramate double-blind trials are summarized here.

In the first trial, 30 patients randomized to topiramate had a 6-week titration of 200 mg 4 times daily in divided doses.20 No dose reduction was allowed during the course of the 18-week maintenance phase and the actual median daily dose was 173 mg daily. The percentage of responders (patients with a 50% or greater reduction in 28-day migraine headache frequency) during the maintenance phase was 46.7% for topiramate and 6.7% for placebo (P = 0.035) (Figure 3). The mean 28-day frequency of migraine decreased from 4.2 to 3.0 for patients taking topiramate, compared to a reduction from 4.3 to 3.8 for patients on placebo (P = 0.09).

The second double-blind topiramate trial with 40 patients had a similar design except that dose reductions were allowed after the initial titration period, resulting in a median topiramate dose of 125 mg daily.21 Also, many more patients in this trial were receiving adjunctive treatment (about 60% of the active group and 40% of the placebo group, compared to 25% in the other trial). The maintenance phase of this trial was only 8 weeks long.

Overall, the percentage of patients achieving a 50% or greater reduction in migraine frequency in this second trial was 26.3% for topiramate and 9.5% for placebo (P = 0.226). Although this difference in outcome did not attain statistical significance, the median percentage reduction in migraine headache rate was 33% for topiramate versus 8% for placebo (P = 0.0061). Also, the change in the mean 28-day headache rate over the entire double-blind phase was much greater for topiramate (from 5.1 at baseline to 3.3) than for placebo (from 4.4 at baseline to 3.8) (P = 0.0035).

A pooling of data from these topiramate trials contributes to the conclusion that the percentage of patients achieving a 50% or greater reduction in migraine frequency is significantly higher among patients with migraine treated with topiramate than among those receiving placebo (35.3% versus 8.3%, P = 0.008).21 The mean weight loss in the topiramate arm of these 2 trials was 5 to 6 pounds. The pooled data also indicate that topiramate was well tolerated in these studies, with the most common adverse events in patients on active therapy including paresthesias, altered taste, diarrhea, and memory impairment (Table 3). Many adverse events may have been relat-
ed to use of adjunctive agents in the second trial. Overall, the discontinuation rates for topiramate and placebo were similar. Of the 10 patients receiving topiramate who discontinued, 6 did so because of adverse events and 1 because of lack of efficacy. Eight patients receiving placebo discontinued, 4 because of lack of efficacy.5

Several headache centers reported results with topiramate at the recent 10th Congress of the International Headache Society (IHC 2001) in New York. [Editor's note: See poster summaries in this issue of Advanced Studies in Medicine for full descriptions of several AED trials.] One such report provided efficacy results for a case series of 74 patients receiving topiramate for chronic or episodic migraines.6 This was a retrospective analysis of 6 men and 68 women, with a mean age of 43.2 years and mean headache frequency of 20.6 per 28 days. Forty-three of the 50 chronic migraine patients (86%) used acute medications more than 3 days per week, and these patients had already failed an average of 4 preventive therapies. Patients were titrated up to 100 mg twice daily (total 200 mg daily) and the mean daily dose was 208 mg with a mean treatment duration of 133 days.

The mean headache frequency in this trial was reduced from 20.6 days per month to 13.6 days per month (P < 0.001). Almost half of all the migraine patients in this case series achieved a 50% or greater reduction in migraine frequency, slightly more in the episodic group than in the chronic headache group (Figure 4). Headache severity was also reduced from 6.2 to 4.8 (P < 0.001). The mean weight loss was 11.5 pounds for patients on monotherapy. Topiramate was well tolerated with only 3 patients discontinuing because of adverse events, with 96% of all adverse events being mild or moderate in nature.7

A similar chart review of topiramate in the prevention of episodic migraine was also reported at the IHC 2001.8 This retrospective study found that topiramate used as first-line therapy in 70 patients who had not received previous preventive therapy did not decrease migraine frequency from 5.8 per 28 days at baseline to 1.9 per 28 days (P > 0.001). The average severity of headaches dropped from 8.1 to 2.0 (P = 0.003). In the patient's global evaluation, 43 of the 70 patients (61%) reported a marked improvement and were very satisfied; 12 (17%) reported moderate improvement and 15 (21%) reported no improvement.

Conclusion

The results of these and other clinical trials suggest that AEDs are a valuable therapeutic option for migraine headache prevention. As just reviewed, the sizable increases in the percentage of patients who cut their migraine frequency by at least half is a powerful demonstration of the promise of AEDs for too large a group of patients who currently have this ongoing disability. Additional studies are needed to clarify the efficacy and safety profiles of the AEDs.

REFERENCES


