The principle drugs that have been used to prevent migraine attacks include beta-blockers, calcium channel antagonists, and tricyclic antidepressants. In recent years, however, the usefulness of antiepileptic drugs (AEDs) in preventing migraine attacks has been recognized. Of the available AEDs, valproate sodium has been the first agent to show benefits in preventing migraine attacks as well as several other headache types. Favorable experience with valproate sodium in preventing migraine attacks has fostered the continuation of clinical investigations with a number of AEDs for migraine prophylaxis. Among the agents currently under evaluation for migraine and headache disorders are the first-generation AEDs phenytoin and carbamazepine and the newer second-generation agents gabapentin, lamotrigine, and topiramate.1

The mode of action of AEDs in providing pain relief for migraine attacks is not clear. Multiple mechanisms, however, are thought to be involved, and related to voltage-gated ion channels (sodium channels and calcium channels T-type, L-type, N-type, P-type), ligand-gated ion channels, gamma-aminobutyric acid (GABA), glutamate, glycine, combined voltage/ligand-gated channels, and N-methyl-D-aspartate (NMDA) receptors. The primary effect of these mechanisms in epilepsy is reduction of ion flow via inhibition of high-frequency firing, as found in abnormal sodium and calcium channels. Reduced ion flow through these channels results either in a reduction in excitatory synaptic transmission or in an enhancement of inhibitory synaptic transmission, which ultimately leads to an increase in the refractory period for the cell membrane and therefore a slower rate of firing of action potentials.1 How these mechanisms relate to migraine pathophysiology is not known, partly because the exact pathophysiological mechanisms in headache disorders in general have not been fully defined. The mechanisms by which several AEDs are thought to exert therapeutic efficacy in migraine are summarized in turn below.

**Valproic Acid**

Valproic acid is available as valproic acid (capsules), valproate sodium (injection and syrup), or as divalproex sodium (sprinkle capsules, delayed-release tablets), a compound composed of a 1:1 molar ratio of valproic acid and valproate sodium. Valproic acid is thought to increase brain levels of GABA by inhibiting the enzyme responsible for its degradation.1 Increased GABA levels may help to offset imbalances in glutamate levels observed in migraine patients.3 Glutamate is one of the main neurotransmitters involved in the development of cortical spreading depression that is thought to cause migraine aura.4 Valproic acid also slows the recovery rate of voltage-gated sodium channels and therefore limits repetitive firing. It has been suggested that valproic acid may act in migraine by increasing the cortical thresholds for spreading depression propagation (ie, it is not an absolute migraine block), and by blocking the initiation of spreading but not its propagation once triggered.1 Valproic acid has been shown to be effective in preventing migraine with and without aura, chronic daily headache, cluster headaches, and intractable headaches.4-10

**Carbamazepine**

Carbamazepine has been approved for use in treating trigeminal neuralgia.1 Its effects are mediated by slowing the recovery rate of voltage-gated sodium channels and therefore limiting repetitive firing. It also appears to have a minor calcium channel antagonistic effect.1,11
SELECTED POSTERS

GABAPENTIN

Gabapentin is a GABA agonist, but it does not bind to GABA or GABAB receptors. It acts by increasing the release of GABA through an unknown mechanism, possibly by increasing the synthesis of GABA from glutamate. Gabapentin is usually well tolerated and is unlikely to interact with other drugs.

LAMOTRIGINE

Lamotrigine is a glutamate antagonist that blocks voltage-gated sodium channels and therefore reduces sustained repetitive firing. Studies of lamotrigine in migraine prophylaxis are limited. The results of a randomized, double-blind, parallel group study showed that lamotrigine was ineffective in migraine prophylaxis, but the results of 2 recent pilot studies in migraine patients with aura suggest that it warrants further study in this patient population.

TOPIRAMATE

Topiramate is a broad-spectrum AED whose mechanisms of action include inhibition of voltage-dependent sodium and calcium channels and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate glutamate receptors, as well as enhancement of GABA receptor action. Topiramate is now undergoing extensive investigation as a prophylactic agent for migraine and other headaches.

REFERENCES


PROPHYLAXIS

The efficacy and certain safety issues related to the use of AEDs in migraine and other headache disorders were topics of the scientific poster sessions. Highlights of several posters that addressed these topics follow.
EFFICACY OF TOPIRAMATE IN THE PROPHYLACTIC TREATMENT OF INTRACTABLE CHRONIC MIGRAINE: A RETROSPECTIVE CHART ANALYSIS

Based on a poster by M-C Wilson
University of South Florida, Tampa

The charts of 34 patients with treatment-resistant, chronic migraine (31 female, 3 male) were reviewed to assess the efficacy and tolerability of topiramate as prophylactic therapy. All patients met the criteria for chronic migraine established by the International Headache Society (IHS), and were taking at least 1 prophylactic treatment. Migraine headaches at baseline were occurring daily or near daily or from 3 to 5 times per week. Treatment with topiramate was administered at doses ranging from 40 mg to 200 mg daily (mean 98 mg per day) for 4 to 18 weeks (mean 9 weeks). Following treatment, more than half the patients (n = 19) reported improvement or much improvement, and 15 (44%) had no change. Forty-one percent (n = 14) of the patients reported no adverse events with treatment. Of the reported adverse events, fatigue, anorexia/weight loss, acroparesthesias, and concentration difficulties were the most common, in order of decreasing occurrence. The weight loss, which is not uncommon with topiramate use, ranged from 0.45 kg to 11.8 kg (ie, 1 to 26 lbs). Seven patients discontinued because of adverse events, 1 topiramate patient and 2 placebo patients discontinued because of noncompliance or personal reasons. The mean 28-day migraine frequency was significantly lower in the topiramate group compared with the placebo group: 3.31 vs 3.83, P = 0.0015. Patients in the topiramate group experienced 1.83 fewer migraine headaches per 28 days whereas patients in the placebo group experienced 0.55 fewer migraine headaches per 28 days (P = 0.0015). A 50% or greater reduction in migraine frequency was achieved by 26.3% of the patients treated with topiramate compared with 9.5% of the placebo-treated patients. Differences between treatments, however, were not statistically significant. Paresthesia and weight loss were the most common adverse events in both the placebo and topiramate groups followed by taste alteration, anorexia, and memory impairment in the topiramate group. Weight loss was greater in the topiramate group (mean loss 4.9 lbs vs 0.6 lbs). These results in a well-controlled study show that topiramate is an effective and well-tolerated prophylactic treatment for individuals with migraine, with or without aura.

A RANDOMIZED, CONTROLLED STUDY OF TOPIRAMATE AS MIGRAINE (WITH AND WITHOUT AURA) PROPHYLAXIS

Based on a poster by DL Potter, DE Hart, CS Calder, JR Storey
Upstate Neurology Consultants, Albany, NY, USA

This 20-week study evaluated the efficacy and safety of topiramate in preventing migraine attacks in 40 patients who fulfilled the IHS criteria for migraine with or without aura. Patients included in the study had well-defined migraine by the age of 50, with at least 2 attacks per month for more than 1 year. Baseline measurements of migraine attacks were established during the first 4 weeks of the study. Double-blind therapy was then initiated at a starting dose of 25 mg daily, which was increased in 25-mg increments up to 100 mg bid during an 8-week titration period. Treatment was maintained at the titrated dose for 8 weeks for a total of 16 weeks of double-blind therapy. Thirty-five of the 40 patients completed the study. Two topiramate patients discontinued because of adverse events; 1 topiramate patient and 2 placebo patients discontinued because of noncompliance or personal reasons. Differences between treatments, however, were not statistically significant. Paresthesia and weight loss were the most common adverse events in both the placebo and topiramate groups followed by taste alteration, anorexia, and memory impairment in the topiramate group. Weight loss was greater in the topiramate group (mean loss 4.9 lbs vs 0.6 lbs). These results in a well-controlled study show that topiramate is an effective and well-tolerated prophylactic treatment for individuals with migraine, with or without aura.

PROPHYLACTIC TREATMENT OF EPISODIC MIGRAINE: A SMALL CONTROLLED STUDY OF TOPIRAMATE

Based on a poster by KR Edwards, MJ Glantz, JA Norton,
Topiramate at doses up to 100 mg bid (mean 173 mg/day) was compared with placebo as a prophylaxis for episodic migraines. A total of 30 migraine patients (with or without aura) diagnosed according to IHS criteria participated in this 22-week study. Following a 4-week baseline period, patients received double-blind treatment at doses that were titrated over 6 weeks and maintained for an additional 12 weeks. At the start of double-blind therapy, topiramate-treated patients showed a trend toward a lower mean 28-day migraine frequency, the primary efficacy measure, compared with placebo (3.00 ± 2.60 vs 3.78 ± 1.99; \(P = 0.10\)). A similar trend was observed throughout the treatment period (2.63 ± 2.54 vs 3.92 ± 2.63; \(P = 0.10\)).

The percentage of patients achieving a 50% or greater reduction in migraine frequency was significantly higher in the topiramate-treated group compared with placebo (46.7% vs 6.7%, \(P = 0.035\)).

Eleven of the 15 patients in the topiramate group received treatment at the maximum daily dose of 200 mg. Four of the 7 patients who discontinued topiramate did so because of adverse events; the remaining 3 were for other reasons. In the placebo group, 6 patients discontinued: 3 for lack of efficacy and 3 for other reasons. Paresthesia, diarrhea, altered taste, and somnolence were the most common adverse events reported by patients in the topiramate group.

The results of this small but controlled study suggest that topiramate is an effective prophylactic treatment in episodic migraine, although larger randomized, controlled studies are needed for validation.

**Oxcarbazepine for Headache and Migraine Prophylaxis in Patients Who Have Failed AED Therapy**

Based on a poster by JC Krusz, RB Nett

Oxcarbazepine is a "cousin compound" of carbamazepine and has recently been approved for treating partial epileptic seizures. The pharmacological activity of oxcarbazepine is exerted primarily through its 10-monohydroxy metabolite (MHD). In this study, oxcarbazepine was given to 26 patients who had failed other AEDs as prophylaxis including divalproex sodium (n = 14), gabapentin (n = 10), topiramate (n = 4), lamotrigine (n = 4), and carbamazepine (n = 5). Dosing was initiated at 150 mg to 300 mg.
per day for 5 to 7 days, then increased every 7 days
to 1500 mg to 1800 mg per day (on average) in
150- to 300-mg increments. Doses were adminis-
tered as 2 divided doses per day for 4 to 6 weeks.
Other prophylactic medications were retained or
tapered during the trial. All patients, upon entry into
the trial, had an average of 5.5 migraines per month
(more than 2 headaches per week) for more than 5 years,
with or without additional tension-type headaches.
After treatment, 10 patients reported a greater
than 65% reduction in the number of headaches per
month, and 10 patients had up to a 50% reduction in
the number of headaches per month. Six patients had
no definable response and 3 dropped out because of
noncompliance. Two patients discontinued because of
side effects (nausea, vertigo), and 1 patient was lost to
followup.
These preliminary data support further double-blind
trials of oxcarbazepine in migraine and headache pro-
phylaxis because of its efficacy and tolerability in
patients who have failed other AED therapies.

TREATMENT

A RETROSPECTIVE STUDY OF TOPIRAMATE FOR
TRIGEMINAL NEURALGIA

Based on a poster by MJ Haugh, GS Connor
Headache and Neurological Center of Oklahoma, Inc.,
Tulsa, OK, USA

This retrospective chart review was done using data from
7 women and 1 man who had been treated with topi-
ramate for 1 to 20 months for trigeminal neuralgia. Five
of the 8 patients had failed to respond to 1 or more other
agents, including carbamazepine [n = 4], gabapentin
[n = 2], phenytoin [n = 1], and baclofen [n = 1].
The mean dose of topiramate was 175 mg daily
(range 50 mg to 400 mg) and most patients respond-
ed to doses of 200 mg daily or less. The duration of
followup was 3 to 21 months.
Two patients discontinued therapy, 1 because of
adverse events (nausea and dizziness) and the other for
personal reasons. Of the remaining 6 patients, 4
patients reported an "excellent" response to topiramate.
Their doses ranged from 50 mg to 400 mg daily, and
concurrent medications included levetiracetam, atorvas-
tatin, irbasaran, lansoprazole, fluoxetine, clopidogrel,
and carbamazepine. Two patients reported a good
response to topiramate, with a
dose of 100 mg or 150 mg
daily. Concurrent medications
in this group included carba-
mazepine and sertraline. Of
these 8 patients, 4 had
responded to topiramate
monotherapy but 1 (who had
achieved an "excellent"
response) had continued to
take carbamazepine.
Two patients reported poor response to topiramate
at doses of 60 mg and 250 mg daily. Concurrent med-
ications included gabapentin and phenytoin. Adverse
events reported during the trial included disorientation,
paresthesias, and memory loss.
There is substantial evidence supporting the use of
AEDs in treating patients with trigeminal neuralgia—
both empiric and tested. The results of this small study
support the previous findings and argues for the need
for larger, double-blind, placebo-controlled studies
using topiramate.

WEIGHT CHANGE FROM TOPIRAMATE USE FOR
CHRONIC DAILY HEADACHE AND EPISODIC MIGRAINE

Based on a poster by WB Young, MM Hopkins,
M Sanchez Del Rio, AL Shechter
Department of Neurology, Thomas Jefferson University
Hospital, Philadelphia, PA, USA

Anecdotal evidence and data from early studies of
topiramate in migraine indicate that weight loss is
associated with therapy. Weight loss, however, may
be considered a benefit to some patients and incon-
sequential to others.
This study of 37 patients with chronic daily
headache [n = 23] or episodic migraine [n = 14]
evaluated the weight changes in patients taking topi-
ramate from 4 to 15 months. Most of the patients [33
of 37] continued to take other preventive therapies
during topiramate treatment.

Advanced Studies in Medicine
The final topiramate dose ranged from 50 mg to 800 mg daily although the dose did not differ greatly by gender (221 ± 151 mg/day for females; 240 ± 152 mg/day for males). The mean weight change was −7.9 pounds but the range was surprisingly broad: +22 pounds to −45 pounds. Weight loss was not correlated with initial weight, age, gender, or final topiramate dose.

Patients with episodic migraine lost more weight than did patients with chronic daily headache (−10.4 ± 8 pounds compared with −6.3 ± 15 pounds, respectively) but the difference in weight loss was not significant. Interestingly, significantly lower doses of topiramate were taken by patients with episodic migraine than by patients with chronic daily headache (150.7 mg/day vs 268.4 mg/day).

These data reinforce the findings that topiramate use is associated with weight loss, although there were no obvious variables that would predict which patients would lose the most weight.

**TREATING PROLONGED MIGRAINE HEADACHE WITH INTRAVENOUS VALPROATE**

Based on a poster by L Robbins Rush Medical College, Chicago, IL, USA

The intravenous (IV) form of valproic acid offers certain advantages over the oral form including lack of sedation, no significant cardiovascular or respiratory effects, and it is not addictive. These qualities make it an attractive potential preventive therapy for migraine.

In this study, 32 women with moderate to severe headache of at least 48 hours’ duration (ranging from 48 to 105 hours) and a history of refractory migraines received 500 mg IV valproate sodium in an outpatient headache clinic. Valproate sodium was diluted in 5 mL of saline and delivered over 5 minutes. Four of the patients were valproate naive.

Relief was evaluated at 1, 3, and 24 hours postinjection by telephone interview. No relief was indicated by 0% to 25% improvement, mild/moderate relief was indicated by 25% to 80% improvement, and 80% to 100% improvement was considered to be complete.

The results showed that 1 hour postinjection, half the patients showed mild/moderate improvement, and the remainder were evenly split between no and complete relief. By 3 hours, the distribution had not changed significantly. By 24 hours, 37% reported complete relief, 22% reported mild/moderate relief, and 40% reported no relief.

Side effects were minimal, usually transient, and included unusual taste sensation (n = 4), somnolence (n = 2), burning at the injection site (n = 2), nausea (n = 1), increased headache (n = 1), and dizziness (n = 1). These data suggest that IV valproate sodium may be useful for treating moderate/severe headaches.

**VALPROATE SODIUM TO TREAT MIGRAINE ATTACKS**

Based on a poster by E Kavadis, I Dimitrakos, M Bozi, GA Togias, CE Katsiariou Neurology Department, Headache Clinic, Athens General Hospital “G. Gennimatas” Athens, Greece

The effectiveness of valproate sodium in providing relief from migraine pain was evaluated in 54 migraineurs who were recruited from a hospital emergency room. Patients who were diagnosed with migraine according to International Headache Society criteria were randomized to treatment with 800 mg valproate sodium, 400 mg valproate sodium, or placebo, administered intravenously. Patients were evaluated 30 and 60 minutes after treatment based on complete relief, marked improvement, moderate improvement, or minimal/no effect.

The results showed that of patients receiving 800 mg sodium valproate, 39% (n = 7) experienced complete or marked improvement, whereas 22% (n = 4) of those receiving 400 mg sodium valproate and 5.5% (n = 1) of placebo-treated patients indicated this level of improvement. Only the 800-mg treatment group was statistically significantly different from the placebo group.

These data suggest that valproate sodium may be effective in treating individuals with migraine attacks, and the response appears to be dose dependent, although further studies are required.