Key Words: divalproex, valproic acid, divalproex sodium, migraine, headache disorders, chronic daily headache, cluster headache, efficacy, safety

Divalproex in the Treatment of Migraine

By Frederick G. Freitag, DO

ABSTRACT *~ Valproic acid has been used in the treatment of migraine headache for nearly 20 years. During this period of use several additional delivery modes have been developed to either improve tolerability or patient compliance with the divalproex sodium formulation and the extended-release formulation of divalproex sodium. Additionally, an intravenous formulation has become available which permits rapid achievement of therapeutic levels of the drug. There have been a number of reports on the use of valproic acid in migraine and other headache disorders, suggesting it to be an efficacious treatment.*

This paper reviews the results of the published reports of valproic acid in migraine and other headache disorders, including open-label studies, comparator trials, and double-blind, placebo-controlled trials. These studies have been conducted with the various formulations of valproic acid that have been on the market. The papers utilized in this study were obtained though Medline searches on valproic acid and divalproex sodium coupled with the various headache disorders. Additionally, the CD-ROM of past issues of Headache *and* Cephalalgia *was reviewed for similar keywords. Lastly, the indices of the journal* Headache Quarterly *were reviewed for additional articles on valproic acid and divalproex sodium.*

Valproic acid in its various formulations has been demonstrated to be an efficacious and well-tolerated agent for the preventive treatment of migraine, chronic daily headache, and cluster headache. Additionally, it has been demonstrated to be efficacious and well tolerated in treating acute migraine attacks when given as an intravenous solution.
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INTRODUCTION

Antiepileptic medications have been used in the treatment of migraine since the 1950s and 1960s, at first mostly based on empirical evidence. Among the earliest anticonvulsants used were phenytoin and phenobarbital. However, the older antiepileptic drugs (AEDs) were found to have limited efficacy. In the 1970s carbamazepine was studied in migraine treatment,[1] but the results were as disappointing as they had been for the older AEDs. The first report of valproic acid

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being used in the treatment of migraine was published in 1989.[2] At the Diamond Headache Clinic the use of valproic acid began as early as 1984, based on the experience of Dr. Seymour Diamond who had found that some patients were responsive to the other AEDs.

MECHANISM OF ACTION OF DIVALPROEX IN MIGRAINE

Our understanding of the mechanisms by which migraine occurs continues to undergo evolution. Much of what we know about migraine is drawn from laboratory models and has not been established in human migraine pathogenesis. One mechanism that has been implicated in migraine is the increased sensitivity of the nervous system of patients who experience these headaches. Lowering of cortical excitability has also been proposed as one potential mechanism of action of valproic acid in migraine prophylaxis.[3] Clinically, migraine headaches occur as a reaction to overstimulation of a hypervigilant and sensitive nervous system. Strong environmental stimuli such as bright lights or loud noises may trigger or exacerbate migraines. Stress and hormonal fluctuations can also cause changes in the internal milieu that may lead to migraine headaches. This internal change appears to be influenced by excitatory neurotransmitters such as glutamate, as well as by intracellular magnesium deficiency. Increasing evidence suggests that a wave of cortical hyperexcitability, which may be related to changes in sodium and calcium channels, spreading across the cerebral cortex from the occipital pole forward may account for the migraine aura. This excitatory wave is followed by a wave of depolarization, which is associated with a phase of cortical hyperemia that spreads in a manner similar to the depolarization. The spread of the cortical hyperemia does not involve an anatomical vascular distribution but rather follows the cortical surface. This cerebral event may play a role in activating the trigeminal nucleus to release substance P, calcitonin gene-related peptide (CGRP), and neurokinin A from efferent fibers on the dural vessels. In addition, serotonin (5-HT) is released, activating the 5-HT_{1B} receptors. In combination, these processes result in vasodilatation along with a sterile inflammatory response. This, in turn, produces painful stimuli which are fed back into the trigeminal nuclei via afferent fibers, further eliciting a response from the trigeminal nuclei in the trigeminal nucleus caudalis. Communication between the trigeminal nucleus caudalis, the periaqueductal gray matter, the locus ceruleus, superior salivatory nucleus, and adjacent tracks culminates with the development of the migraine headache.

The mechanism by which valproate acts to stop a migraine attack in process or prevents migraine attacks when administered over time is unclear. Valproate exerts multiple effects that may affect many of the events believed to occur in the migraine cascade.[4] A γ–aminobutyric acid

(GABA) receptor-mediated effect likely plays a role.[4-10] Valproate increases GABA levels via activation of glutamic acid decarboxylase. GABA acts to counterbalance the excitatory effects of glutamic acid. Valproate also has an inhibitory effect on GABA aminotransferase, which is a component of the enzymatic degradation process of GABA.[8,9] The modulating effects of valproate on sodium and neuronal calcium channels may also have inhibitory effects on the cerebral activation occurring in the early stages of the migraine process. In animal models of migraine, valproate has been shown to work through $GABA_A$ receptors on neurogenic inflammation by decreasing dural plasma protein extravasation[7] and c-fos immunoreactivity in the trigeminal nucleus caudalis.[10] This modulatory effect may also be important in controlling migraine by acting on the dural vessels blocking the development of the neurogenic, sterile inflammatory response that occurs following 5-HT-mediated vasodilatation. Inhibitory effects of valproate on the sensitization process, believed to occur as migraine headache persists, may be important in preventing short- and long-term effects of migraine on the trigeminal nucleus.

STUDIES OF DIVALPROEX IN HEADACHE THERAPY AND PROPHYLAXIS

Cluster headaches

Following the initial report by Sorenson[2] in 1989 of an open-label trial of valproic acid in migraine, the drug was also reported to be useful in the preventive treatment of cluster headaches in an open-label trial by Hering and Kuritsky.[11] A total of 15 patients were included in this study, 13 of whom had episodic cluster headaches and 2 of whom had chronic cluster headaches. The doses of sodium valproate were patient-individualized, falling between 600 mg/d and 2000 mg/d administered in 2 divided doses. Efficacy and tolerability were used to judge the dose for a given patient. Eleven of the 15 patients treated in this manner had a positive response to sodium valproate. Of the 11 responders, 9 essentially achieved a complete remission of their symptoms. While these results were encouraging, it is difficult to judge the actual benefits of sodium valproate based on this trial alone. Episodic cluster headaches are prone to spontaneous remission by definition. Therefore, it is not possible to determine in the majority of the patients who were responders and who had episodic cluster headache whether it was the drug or the natural history of episodic cluster headache that led to the remission of their headaches.

Divalproex sodium also proved effective in another open-label trial with 21 patients with episodic or chronic cluster headaches.[12] In this study, my colleagues and I used efficacy- and tolerability-based flexible

doses of the direct-release formulation of the drug, given as a single dose at bedtime. The average doses in the chronic and episodic headache groups were 826 mg/d and 850 mg/d, respectively. Treatment proved beneficial among the 15 patients with chronic cluster headaches, 7 of whom achieved complete remission of symptoms. All 5 patients with episodic cluster headaches experienced at least partial response, with 3 of them remitting fully. However, similarly to Hering and Kuritsky,[11] we failed to control for the possibility of spontaneous remission among the patients with episodic cluster headaches.

A recently published double-blind, placebo-controlled trial[13] of sodium valproate in the preventive treatment of cluster headache demonstrated the complicated issue of spontaneous remission of episodic cluster headaches. In this study, 96 patients were enrolled and randomized to active treatment with 1-2 g/d of sodium valproate or placebo. Patients went through a 7-day run-in period during which they kept a diary of their symptoms, followed by 2 weeks of aggressive therapy. As a result, 62% of the patients in the placebo treatment group and 50% of the patients in the active treatment group experienced a 50% or greater reduction in the number of cluster headaches between the run-in period and the second week of treatment.

The severity of the pain of cluster headache, the high frequency of brief attacks, and traditionally low response to placebo in cluster headache trials suggest that, despite the negative outcome of this well-controlled trial, methodological issues are of importance in the design of trials of cluster headache. The open-label trials of valproate and the inconclusive results of the placebo-controlled trial suggest potential efficacy of valproate in cluster headache, at least in chronic, if not in episodic, cluster headache.

Migraine headache

Open-label trials. The first report of potential efficacy of valproic acid in migraine came from the open-label trial by Sorenson.[2] The 22 patients included in this trial had been refractory to other standard therapies and all but 1 patient were experiencing migraines at a frequency between 3 and 16 attacks per month. One patient had chronic migraine. Valproic acid doses were adjusted to maintain serum levels of approximately 700 µmol/L. Follow-up was conducted over a period of up to 12 months. Eleven of the patients were reported to be in remission of their migraines at study completion, with 6 other substantially improved. Four patients dropped out of the study.

Similarly, another group of treatment-refractory migraine patients, who also had abnormal electroencephalograms, was studied in an open-label trial by Viswanathan.[14] Sodium valproate was used as an adjunctive

therapy to other preventive medications. Twelve of the 16 patients were in remission within 2 weeks of initiating valproate therapy. The other 4 patients had an average of a 50% reduction in their migraine frequency. Following the initial dose of 200 mg three times daily, the amount of drug was titrated upwards to 1000 mg/d. This resulted in an additional 2 patients obtaining remission of their migraines.

Another open trial of interest is that of Coria.[15] Patients were treated with sodium valproate 200 mg three times daily for three months. Of the 62 patients in this trial, over two thirds achieved benefit from the sodium valproate therapy, resulting in decrease of migraine frequency. No correlation between the serum drug levels and response to therapy was observed. Of interest was the follow-up the patients underwent. After 3 months sodium valproate was discontinued, and patients were followed for an additional 3 months. Among the initial responders, 67.6% continued to show improvement that lasted for the entire duration of follow-up.

Another open-label trial was a long-term 6-month study of 32 patients with migraine.[16] Treatment was begun with 600 mg/d of sodium valproate in divided doses, and after evaluation of serum levels at the end of the first month, patients were either titrated upwards to serum levels of 70-100 µg/mL if their initial level was 50 µg/mL or less, or maintained on the original dose if their levels were higher than 50 µg/mL. As a result, the authors found a correlation between the serum levels and outcome in this trial (ie, more improvement at higher serum levels), and a pattern of continuing improvement over the entire trial period.

Placebo-controlled trials. The efficacy of sodium valproate versus placebo was evaluated by Hering and Kuritsky[17] in a double-blind, randomized, cross-over study of 29 migraine patients. One group was given 400 mg of sodium valproate twice a day, the other group was given placebo for 8 weeks, and then the groups were crossed over for an additional 8 weeks. They found that 86.2% of the sodium valproate-treated patients had a positive response, experienced as reduction in the frequency, severity, and duration of migraine attacks. Patients in the placebo phase averaged 7.8 attacks per month, compared to 4.4 during the active treatment period (Figure 1). These results were highly statistically significant. In general, the drug was found to have good tolerability in this trial. They also examined plasma levels of valproic acid in patients to look for a correlation between blood levels and response to the medication, and were unable to show a relationship.

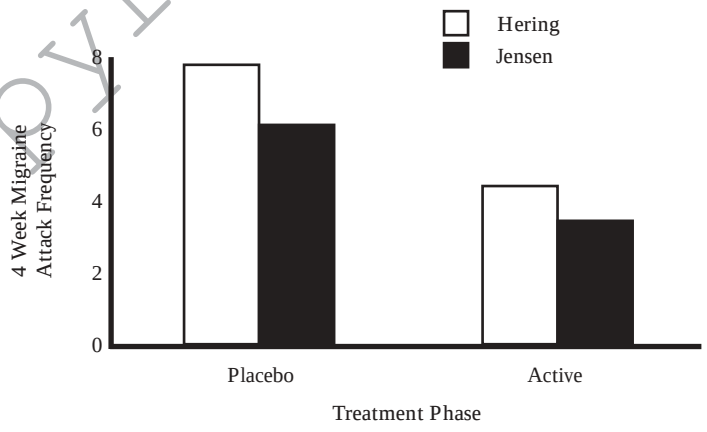
The next placebo-controlled trial was that of Jensen and colleagues (Figure 1).[18] They used a triple-blind, placebo-controlled, crossover method, which was also dose-controlled. A total of 43 patients were enrolled in this trial, with 34 remaining until completion. The study used

a 4-week drug-free lead-in period to determine baseline characteristics. The 43 patients were then randomized to active treatment with delayed-release formulation of sodium valproate or placebo, with 22 patients in the former and 21 in the latter group. Patients using the slow-release formulation of sodium valproate were treated with doses of 1000 mg/d for the first week, at which time serum levels were obtained. Those with serum levels above 50 µg/mL were maintained at 1000 mg/d. Those whose values were below this level were blindly titrated upwards to 1500 mg/d. At the end of the study, the migraine frequency was significantly improved with active treatment compared to placebo treatment periods. At the end of the active treatment period, the migraine days were 3.5 per 4 weeks compared to 6.1 days during placebo treatment; 50% of the patients had at least a 50% reduction in their migraine days. In comparison, during placebo treatment periods 18% of the patients had a 50% or greater reduction in migraine frequency. Side effects were twice as common during the active treatment phase as during the placebo phase, with 33% of the patients having adverse events during active treatment period. However, all negative symptoms were rated as mild to moderate by patients.

Pivotal Trials: Three major pivotal studies provided further proof of valproate's efficacy in migraine therapy. The main findings from these trials are summarized in Table 2 through Table 5. The first of the pivotal trials was reported by Mathew.[19] This multicenter, double-blind, randomized, placebo-controlled trial involved a total of 107 patients. Patients were enrolled from 8 centers in the US and were treated in a single-blind fashion with a placebo during a run-in period of 4 weeks. Those patients still meeting entry criteria were then randomized to active

FIGURE 1

CROSSOVER TRIALS



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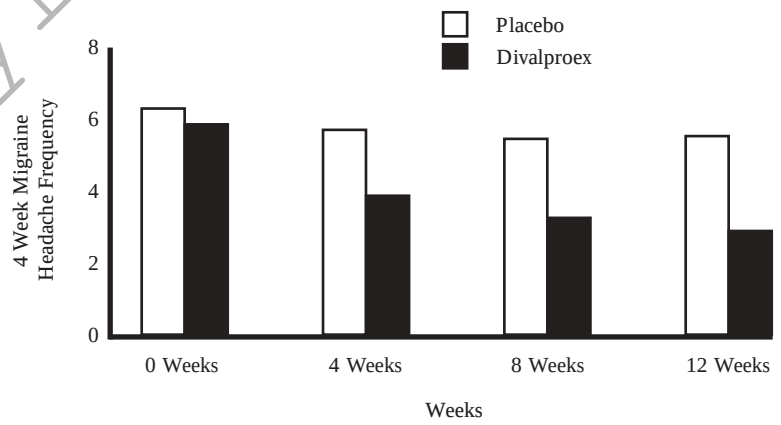
treatment or placebo in a 2 to 1 fashion. The initial dose of divalproex sodium was 250 mg/d. Upward titration of doses occurred over the next 4 weeks, in 250 mg/d increases every second or third day based on body weight, to achieve trough plasma levels between 70 mg/L and 120 mg/L. Patients on placebo had sham values reported and doses titrated in a similar fashion. Further dose adjustments were made on a case-by-case basis by the investigators, according to response and tolerability. The mean dose achieved in the study was 1087 mg/d, with a mean plasma level of 66 mg/L. At the end of the 4-week titration period, patients were maintained on the final achieved dose for an additional 8 weeks before titrating off at the end of the study. Among the placebo-treated patients, migraine headache frequency declined from 6.4 attacks per month at baseline to 5.7 attacks per month at the end of the maintenance phase. The divalproex-treated patients improved from a mean of 6 attacks per month at baseline to 3.5 attacks per month for the final four weeks (Figure 2). Statistically significant differences were seen from the end of the titration phase onwards, with further improvement in this statistical analysis (P=.01 for both time points in the maintenance phase). Forty eight percent of the divalproex sodium-treated patients and 14% of the placebo-treated patients had at least a 50% reduction in the migraine frequency (Figure 5). Nine patients treated with divalproex sodium withdrew from the trial because of adverse events, compared to 2 in the placebo group. The most common adverse event in both placebo and active treatment groups was nausea, which occurred in 46% of the patients on divalproex sodium; 31% of the active treatment patients developed asthenia and 30% somnolence. Tremor occurred in 9 patients on active

FIGURE 2

DIVALPROEX SODIUM VERSUS PLACEBO PIVOTAL TRIAL REPORTED BY MATHEW



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treatment, as did alopecia. In most cases the adverse events were rated as mild to moderate and were statistically more likely to occur in the active treatment group compared to the placebo arm of the study.

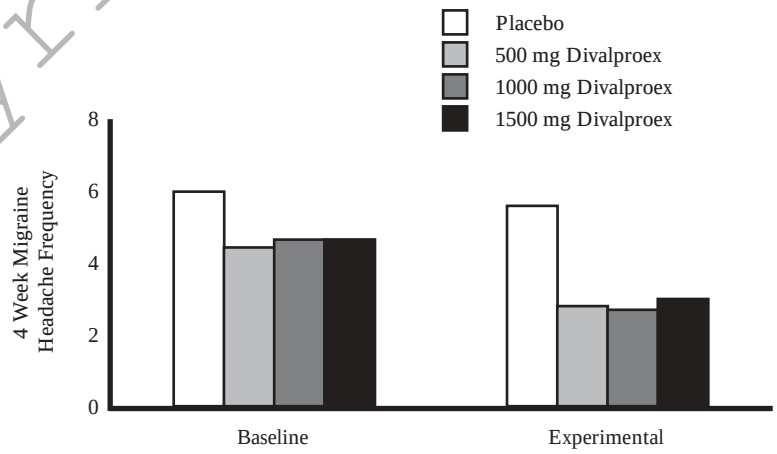
The next major trial of divalproex sodium was reported by Klapper.[20] In a dose-controlled trial, patients went through a 4-week single-blind placebo-controlled baseline phase. Those continuing to meet the initial requirements were randomized to placebo, or divalproex sodium at doses of 500 mg/d, 1000 mg/d, or 1500 mg/d. As in the previous study, the first 4 weeks consisted of a dose-escalation phase to the target dose, followed by an 8-week maintenance phase. Sixteen centers were involved in recruiting a total of 211 patients, of which 176 were randomized. There were 44 patients in the placebo arm; 45 patients received 500 mg/d of divalproex sodium, 43 received 1000 mg/d of divalproex sodium, and 44 received 1500 mg/d of divalproex sodium. Eight patients in the placebo group, 7 in the 500 mg/d group, 10 in 1000 mg/d group, and 14 in the 1500 mg/d group discontinued during the treatment phase. Two of the dropouts on placebo discontinued for adverse events, as did 25 in the active treatment groups. Statistically significant improvement in migraine frequency occurred across all three active treatment groups (Figure 3) compared to placebo (P=.05). Placebo patients experienced an average of 6.1 attacks per 4 weeks at baseline, declining to 5.6 attacks during the treatment phase. The migraine frequency in the 500 mg/d divalproex group went from 4.5 attacks in the beginning to 2.8 attacks during treatment. The 1000 mg/d group went from 4.7 attacks at baseline to 2.7 attacks during treatment, while the 1500 mg/d group went from 4.7 attacks at baseline to 3 attacks in the treatment phase. Forty four percent of the divalproex patients (Figure 5) had at least a 50% reduction in migraine attack frequency, compared to 21% of the placebo-treated patients. Statistically significant reductions occurred in all divalproex sodium-treated groups compared to placebo for other efficacy parameters as well, including disabling migraines, migraines requiring acute treatments, attacks with migraine-associated symptoms, and nonmigraine headaches. The sole exception was the 1000 mg/d divalproex sodium treatment group, whose patients failed to achieve a statistically significant response and continued to experience disability with their migraine attacks. Adverse events were mild to moderate for most patients, but 5% of those on placebo, compared to 16% of those on 500 mg/d of divalproex, 14% of those on 1000 mg/d of divalproex, and 27% of those on 1500 mg/d of divalproex, withdrew from the trial secondary to adverse events.

The third pivotal trial was conducted with the extended-release formulation of divalproex sodium. This involved 24 sites and 237 patients in a placebo-controlled, parallel-group, double-blind study.[21] Since compliance has been raised as a potential issue that may reduce efficacy of migraine

preventive medications,[22] it was felt that once-a-day versus twice or three times daily dosing of divalproex sodium would enhance treatment outcomes. By comparison to the other pivotal trials, the baseline phase in this study did not use a single-blind placebo. Patients continuing to meet the entrance criteria at the end of baseline phases were randomized to receive either active or placebo at a ratio of 1:1. There were 122 patients in the active treatment group, compared to 115 in the placebo group. During the first 2 weeks there was potential for dose adjustment. Patients began with 500 mg/d of the active treatment for the first week, then were titrated up to 1000 mg/d beginning with the second week. Those who had tolerability issues at this dose were allowed to return to the lower dose for the remainder of the trial beginning with the third week. These doses were maintained for the remainder of the 10 weeks of active treatment prior to a 1-week tapering and discontinuation period at the end of the trial. The mean reduction in the 4-week migraine headache rate was 1.2 in the divalproex sodium extended release group, and 0.6 in the placebo group (P=.006) (Figure 4); reductions with divalproex sodium extended release were significantly greater than with placebo in all three 4-week segments of the treatment period. No significant differences were detected between treatment groups in either the overall incidence or in the incidence of any specific treatment-emergent adverse event; 8% of divalproex sodium extended release-treated and 9% of placebo-treated subjects discontinued because of adverse events. The mean dose achieved for the active treatment arm was 876 mg/d of the extended release form of divalproex sodium. Forty one percent of the divalproex-treated patients had at least a 50% reduction in migraine attack frequency, compared to 28% in the

FIGURE 3

CHANGE IN MIGRAINE FREQUENCY



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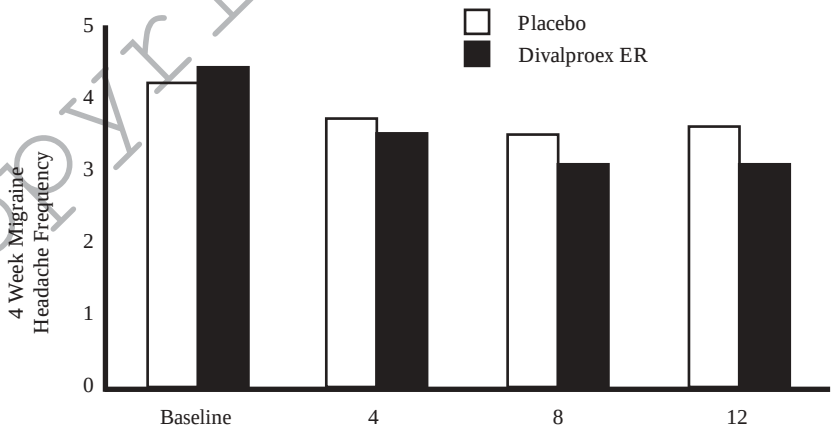
placebo group (Figure 5), which was statistically significant. These results were in the same range of response rates seen in the other pivotal trials. Though not statistically significant, 7% of the active treatment group patients had at least a 75% reduction in their migraine attack frequency.

The pivotal trials, as well as the other placebo-controlled trials, demonstrated that valproic acid, regardless of the formulation, was an effective medication compared to placebo. The results were comparable across the three major trials on outcome parameters (Figure 5). There appeared to be a distinct improvement in tolerability with the extended release preparation compared to the other formulations.

Comparative Trials. There have been 2 comparative trials of divalproex sodium to propranolol, another migraine-specific preventive medication with high levels of efficacy and good tolerability. The first of these was reported by Kaniecki.[23] This was a placebo-controlled clinical trial with a crossover phase. Patients were enrolled in a 4-week diary-keeping phase. Those meeting entry requirements were enrolled in a single-blind placebo phase for 4 weeks. Following that, active therapy was begun with 1 of the 2 agents for 12 weeks, at which time they continued with a washout phase for two weeks, and then crossed over to the other agent for an additional 12 weeks. A total of 37 patients were enrolled in the trial, with 32 patients completing. The divalproex dose was titrated to as high as 2 g/d in 2 patients; the remainder predominately received doses of 1500 mg/d. Twelve patients received lower doses. The propranolol treatment period involved titration to 180 mg/d in 28 of the patients and

FIGURE 4

4 WEEK MIGRAINE HEADACHE FREQUENCY ON DIVALPROEX SODIUM EXTENDED RELEASE



ER=extended release.

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240 mg/d in 1 patient. Three patients received lower doses. Nineteen percent of the patients had a 50% or greater reduction in their headaches during the placebo phase. This compared to reductions in 66% of those treated with divalproex sodium and 63% of those on propranolol. There were minimal differences in doses in responders versus nonresponders nor at later study points or with other assessment parameters. Adverse events were also fairly comparable between the two active agents.

Klapper studied[24] these same 2 agents in an open-label crossover trial. Active treatment lasted for 2 months with each agent, followed by a 2-week wash-out period. Patients were titrated to their highest tolerable dose level for each drug. Patients on divalproex averaged 5.4 attacks per month, compared to 10.2 attacks per month when on propranolol. Only 12 patients completed both treatment arms, with adverse events accounting for withdrawal from the study of 12 patients, 9 of whom withdrew during the divalproex sodium treatment stage.

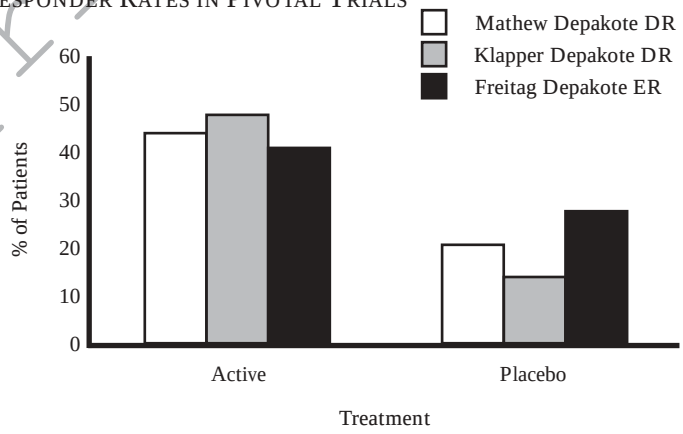
These studies suggest that divalproex sodium is at the least comparable to propranolol as a preventive agent in migraine. Tolerability may have been slightly better with patients taking propranolol, based on the number of dropouts and the need for dose reductions from targeted treatment levels.

Studies in chronic headache disorders

Migraine patients may have headaches other than migraines. These may be tension-type headaches[25] or sinus-related headaches;[26] however, increasing evidence suggests that these headaches may be variant presentations of migraine. Migraine, typically an episodic disorder with pain-free intervals between attacks, may itself evolve to a chronic daily state.

FIGURE 5

50% RESPONDER RATES IN PIVOTAL TRIALS



DR=delayed release; ER=extended release.

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Mathew[27] reported on a group of patients with chronic daily headache who had failed to respond to other therapy. Chronic daily headache has been used synonymously with transformed migraine and chronic migraine. It may also encompass patients with chronic tension-type headaches, as well as some rare variant daily headache syndromes. Of the 32 patients that were treated, roughly two thirds had an improvement in their headache-free days, as well as in calculated index of headaches.

Sianard-Gainko[28] reported on an open-label valproate treatment of patients with migraine, migraine and tension type headaches, or just chronic tension-type headaches. Among the patients, 35 had just migraines, 14 had both types of headaches, and 7 had only chronic tension-type headaches. Nearly one third of the patients overall were overusing analgesics or ergot compounds. Efficacy was based on headache frequency before treatment versus during the 6-month treatment. In patients with combined migraine and tension-type headache and tension-type headaches alone, one third had at least a 50% reduction in their attack frequency. This is compared to the migraine-only group where nearly two thirds of the patients had at least a 50% reduction in their headaches.

Rothrock[29] divided patients with intractable headache into 3 groups: 18 patients with high frequency migraine; 43 patients with an initial history of episodic migraine which progressed to a nearly daily headache pattern with migraine characteristics (referred to at that time as transformed migraine); and 14 other patients who had strictly tension-type headaches. In total, 48% of all patients had at least a 50% reduction in their headache frequency with valproate treatment. On further analysis, those with just frequent migraines had the best response. Sixty one percent of these patients had a 50% or greater improvement in their headaches, compared to marked improvement in 51% of those with transformed migraines and only 21% of those with tension-type headaches.

In a pivotal trial of divalproex sodium by Klapper,[20] assessment of nonmigraine headaches attacks as well as of migraine headaches were conducted. This report found that between 42% and 57% of the nonmigraine headaches had improved by at least 50% compared to baseline. This was not considered significant because 435 of the placebo patients had a similar response.

Long-term effects of divalproex in chronic headache were examined in a small trial by Rothrock.[30] For a period of 3 months, he administered divalproex sodium to a group of patients with transformed headaches in an open-label fashion. If they had a positive response, he discontinued their therapy and followed them for at least an additional 2 months. Twelve of the 20 patients continued to demonstrate a positive benefit after drug discontinuation during the 2-month follow-up interval, and 8 of the 12 continued to show benefits beyond the 2-month window of observation.

Posttraumatic headaches were examined in 100 patients treated by Packard.[31] Of the 100 patients, 58 experienced a conversion of their headaches from chronic to episodic. The reduction in headache severity was minimal. Forty percent of the patients dropped out of the divalproex treatment either because of nonresponse or adverse events.

In another trial,[32] my colleagues and I examined the long-term treatment effects and tolerability of valproate in patients with chronic daily headache. The data were obtained through retrospective chart review with data extraction from headache diaries. We reviewed 642 current patients under treatment that included divalproex for chronic daily headache, 138 of whom were being treated with divalproex alone. Demographic variables of age, sex, initial body weight, final body weight, adverse events, dose of divalproex used, duration of treatment, the ability to categorize their chronic daily headaches into migraine and tension-type headache components, and baseline and end-of-study headache frequency indices were obtained. The mean improvement was 47%, with migraine improving at a rate of about 65% and the tension-type headaches at about 45%. Of 138 patients, 93 had at least a 50% reduction in their headache frequency. These results were statistically significant. Fifteen, or just over 10%, of the patients achieved remission of their headaches and were able to discontinue daily therapy, while 35, or approximately one fourth, of the patients failed to respond to single drug therapy with divalproex. There was no correlation between response and age, sex, duration of treatment, and the dose of divalproex sodium given. Adverse events occurred in approximately 35% of patients, but none were severe. Women were more likely to experience any adverse effects than men. Weight gain, however, was smaller in women than men, averaging 1.9 pounds for women versus 7 pounds for men. Initial body weight and age did not correlate with the weight change.

Divalproex in children and adolescents

Pakalnis and colleagues[33] conducted a retrospective study of divalproex treatment in 23 children between the ages of 7 to 17 years. The headache frequency ranged from as few as 3 attacks per month to as high as 24 episodes per month. Divalproex dosages ranged from 3.1 mg/kg/d to 32.9 mg/kg/d and blood levels were measured at 18-82.3 µg/mL. The patients without any comorbid disease or or those with comorbid epilepsy did better than those with other comorbid psychiatric diseases. This last group failed to respond to divalproex. Overall, 15 of the 23 patients had at least a 50% reduction in their headaches, and 6 became migraine-free on treatment.

A second study[34] examined 15 children aged 9 to 17 years in an open-label study of migraine prevention with sodium valproate. Dosages

ranged from 500-1000 mg/d, with the dosage titrated based on serum levels. Overall headache severity declined from 6.8 on a 10-point scale to 0.7. The average headache frequency declined from 6 attacks per month to 0.8 per month at the conclusion of the 12-week trial. Thirteen of the 15 cases had sustained headache-free remission lasting at least 6 months following discontinuation of therapy.

These studies suggest that valproic acid may be useful in children with migraine and may produce a sustained remission with a relatively short course of therapy.

Intravenous divalproex for acute migraine

The standard of care for migraine currently involves the use of the 5-$HT_{1B,1D}$ agonists such as sumatriptan. Other agents such as dihydroergotamine may be given over the course of several days by intravenous administration to treat refractive acute migraine and aid in the resolution of chronic migraine. Unfortunately, some patients do not respond to these therapies or they may prove to be contraindicated in selected patients. The use of intravenous valproic acid has proven to be an excellent clinical alternative in our experience at the Diamond Headache Clinic and Inpatient Treatment Unit. Several studies have looked at the use of this agent in controlled situations.

The first evidence[35] for this use came from a paper reviewing several cases of status migraine treated with sodium valproate intravenously. Both cases had good resolution of their acute prolonged migraine and excellent tolerability.

Mathew[36] treated 61 patients through 66 migraine attacks. All patients were given an infusion of 300 mg of sodium valproate. Headache relief began on average by 8 minutes following the infusion and complete relief was obtained at 25 minutes. Among the patients 73% had significant improvement with this therapy and there was an additionally significant resolution of the migraine-associated symptoms such as nausea, photophobia, and disability. None of the patients had significant adverse events.

Edwards[37] compared the efficacy and tolerability of dihydroergotamine intramuscularly to intravenous sodium valproate. Treatment with 1 mg of dihydroergotamine along with 10 mg of metoclopramide was compared to an infusion of 500 mg of sodium valproate. Forty patients were treated in an alternating fashion between the 2 treatments. Improvement in pain to levels of mild or no pain from a baseline value of moderate or severe was used as a guide for efficacy. At 1 hour, 50% of the sodium valproate patients and 45% of the dihydroergotamine patients were improved. After 2 hours, 60% of the sodium valproate patients and 50% of the dihydroergotamine patients were improved. By 4 hours the results between the 2 groups were equivalent, with both

reporting 60% improvement. Relief of migraine-associated symptoms was similar in the 2 treatment groups. Adverse events occurred in 15% of the dihydroergotamine patients versus none of the sodium valproate patients.

Chronic daily headache or chronic migraine was treated in 10 patients in an open-label use of sodium valproate.[38] Patients received a load dose of 15 mg/kg, followed by 5 mg/kg every 8 hours for up to several days. The patients received 5 to 17 doses after the loading dose. All of the patients had been determined to be poor candidates for dihydroergotamine therapy, either because of previous failure, risk of adverse events, or medical history. Eight of the 10 patients had a response to treatment and 4 of them became headache-free and maintained improvement after drug discontinuation. In general, tolerability was good with the treatment.

These studies suggest that intravenous sodium valproate is at least as effective as dihydroergotamine in treating migraine headaches, and provide evidence that in those patients with acute or chronic migraines that have failed to respond to other therapies, valproate is an effective and safe alternative.

SAFETY CONCERNS IN THE MIGRAINE PATIENT POPULATION

The long-term safety and efficacy of divalproex sodium was studied by Silberstein[39] in a long-term trial of up to 3 years in patients who had completed the original two pivotal trials.[19,20] Among the patients, 71% remained on divalproex therapy for at least 180 days and 48% for at least 1 year. The majority of adverse events experienced early on resolved with continued treatment, with the exceptions being tremor and weight gain. Tremor appears to be in part related to the dose of the drug used. Weight gain is a problematic side effect that can occur with the vast majority of preventive medications used for migraine prophylaxis. In this study, 7 patients had weight gain in excess of 11 kg, but 2 patients experienced weight loss of 11 kg or greater. Actual body weights were not examined, but reports of weight change were recorded. There appeared to be a correlation with weight gain and initial body weight, with those being heavier at study entry more likely to experience this adverse event. These findings were substantially different from the experiences reported from a long-term open-label trial of divalproex sodium,[32] where actual body weight measurements were recorded and used to assess weight changes.

Other safety issues that have been raised related to valproic acid include pancreatitis, hepatic dysfunction, hyperammonia states with associated encephalopathy, polycystic ovarian syndrome, and birth defects. These are major issues for the otherwise healthy migraine population, especially given that the majority of migraine patients are women of childbearing

age. Based on the experience reported in the literature and that of the practice at the Diamond Headache Clinic, the occurrence of pancreatitis[40] and abnormal liver function tests are rare and probably idiosyncratic events. In those rare cases where we have seen alternations in liver function, it has never been severe and responded to simple discontinuation of the valproic acid. Hyperammonia states with associated encephalopathy have been reported and may also be a result of using a combination of agents in patients with treatment-refractory migraines. The cases that have occurred have responded rapidly to drug discontinuation and the institution of therapy with L-Carnitine 990 mg three times daily until the ammonia levels have returned to normal. An additional factor that may cause encephalitic changes and even coma may result as a drug interaction involving divalproex. The glucuronidation involved in the metabolism of divalproex is also part of the metabolic pathway for the benzodiazepine lorazepam. The combination of these two agents together even though administered in amounts not characteristically associated with toxicity may produce significant alterations of alertness and conciousness[41]. There has been no apparent correlation between drug doses and the development of the previously noted hepatic adverse events.

Weight gain may be associated with a variety of health consequences, one of which is polycystic ovarian syndrome. This is an area that requires further investigation, because the syndrome may also be related to the use of other antiepileptic drugs in addition valproic acid. Based on our experiences at the Diamond Headache Clinic, weight gain has not proven to be a major concern among our patients. We have used a once-daily regimen for the majority of patients who are taking less than 1500 mg per day of divalproex sodium; treatment is administered in the evening, which appears to reduce the tendency for wakeful appetite stimulation.

This nighttime dosing may also have contributed to the low occurrence rates for alopecia in our clinic. The mechanism of hair loss is possibly related to the celation of zinc and selenium in the intestines by valproic acid, leading to a nutritional deficiency causing the hair loss. In addition to the evening dosing, zinc and selenium supplementations are used, which may have further contributed to low occurrence rates of alopecia.

There are serious risks associated with valproic acid use during early stages of pregnancy. Spinal cord deformities may occur, and although the use of supplemental folic acid is recommended, this strategy has never been proven to be a successful preventive measure for this complication. Therefore, it is advisable that in the headache population the patients be counseled to utilize an appropriate form of contraception while taking valproic acid, in order to reduce the risk of complications with pregnancy.

CONCLUSIONS

Valproic acid, regardless of the formulations used, appears to be a safe and effective therapy for migraine headaches. It has efficacy at least comparable to propranolol, which for many years was considered the gold standard of migraine treatment. The efficacy of valproate in chronic migraine and other headache-related disorders is lower compared to that in pure episodic migraine. This is not unexpected and is in line with the experiences with other compounds used in treatment of migraines and chronic migraines. Valproic acid appears to be at least as safe and effective in the childhood migraine population as in the adult population, but an improved sustained remission period may be associated with successful therapy prior to drug discontinuation. Acute migraine therapy with an intravenous formulation of valproate has proven to be an effective alternative, with comparable efficacy and tolerability to dihydroergotamine, the current standard of care in these patients. Safety concerns with valproic acid have proven troublesome for some in the migraine population, in part because of their otherwise normal state of health, but also because of the high percentage of women with migraines who are in their childbearing years. Appropriate safety evaluations at regular intervals using adjunctive laboratory testing may be needed in cases where adverse events are suspected. Appropriate counseling regarding adverse events, steps to minimize their occurrence through appropriate dosing schedules, and counseling may also improved the tolerability of this agent. Women of childbearing age should be counseled to use the same safeguards against pregnancy that they would with other preventive medications for migraine and related disorders that are associated with increased risk of birth defects. ⌘

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