Valproate in the Treatment of Persistent Chronic Daily Headache. An Open Label Study.

Ninan T. Mathew, M.D. and Sabiha Ali, M.D.

From: Houston Headache Clinic, Houston, TX.

Reprint requests to: Ninan T. Mathew, M.D., Houston Headache Clinic, 1213 Hermann Dr. #350, Houston, TX 77004.

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SYNOPSIS

Thirty patients with persistent chronic daily headache, unresponsive to various combinations of pharmacological and non-pharmacological treatment were selected for an open label study using divalproex sodium. All patients had normal liver function tests. After a baseline observation period of 1 month, patients were given divalproex sodium 1000 to 2000 mg per day, for a period of 3 months. Blood valproic acid levels were kept between 75 and 100 mcg/ml. Liver function studies and blood ammonia levels were obtained periodically. Based on weekly headache index, headache-free days, dysfunctional days and patients' general well-being rating and physicians' global assessment, two thirds of the patients improved significantly. The common side effects included weight gain, tremor, hair loss and nausea. Liver functions were unaffected by treatment.

The possible mechanism of action of valproate in headache is discussed. Valproate appears to be a worthwhile addition to the prophylactic treatment of chronic recurrent headache. Key words: valproate, chronic daily headache

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Approximately 30 to 40% of patients seen in a headache clinic have chronic daily headache.1 Patients with chronic daily headache, excluding those with post traumatic headache, can be divided clinically into 3 major categories; namely 1) transformed migraine,2 2) chronic tension-type headache, and 3) new persistent daily headache.3 There is a higher incidence of excessive symptomatic medication usage, sleep abnormalities, depression, and neurotic behavior pattern in these patients.2 Both drug-induced and non-drug related (spontaneous) transformation of episodic migraine into chronic daily headache may occur and the majority of these patients retain some migrainous characteristics of their headache. In general, these patients are difficult to treat. Discontinuing daily use of symptomatic medications, and initiating prophylactic pharmacotherapy combined with behavioral therapy, results in significant improvement in the majority.2 Approximately 30% of patients are difficult to control with the presently available treatment modalities and appear to have a persistent neuro-bio-behavioral disorder.4

Valproate is a new addition to the preventative therapy of chronic recurrent headache. Sorensen,5 in an open study, reported that among 18 treated patients with migraine, 11 became headache-free and 6 had substantially fewer attacks. Only in one patient was the valproate ineffective. The starting dose was 1200 mg daily and the dose was adjusted until the serum valproate was approximately 100 mcg/ml. Raskin (personal communication) has treated over 100 patients and found it to be a very useful drug for migraine prophylaxis. Kuritzky (personal communication) also found statistically significant improvement in a prospective double blind study using valproate.

MATERIAL AND METHODS

A group of 30 patients with persistent chronic daily headache, unresponsive to various combinations of pharmacological and nonpharmacological treatment, was selected for an open label study using divalproex sodium (Depakote). All 30 patients were diagnosed as transformed migraine, since all of them gave a history of episodic migraine in the past which gradually evolved into a daily or near daily headache pattern. According to the International Headache Classification,6 they are categorized as 1.1 and 2.2 (migraine without aura and chronic tension-type headache). In 18 of them, excessive analgesic or ergotamine use was considered to be a factor perpetuating the chronicity of their headaches. This group of 30 patients had previously undergone the accepted standard methods of management, including: a low-tyramine low-caffeine diet; discontinuing daily symptomatic medications; prophylactic pharmacotherapy consisting of different combinations of beta-blockers, tricyclic antidepressants, calcium channel blockers, methysergide, and nonsteroidal anti-inflammatory agents; biofeedback and behavioral therapy. Co-pharmacy of more than I prophylactic agent was tried in all of them. Valproate was started because they were considered resistant to previous treatment.
Prior to the study, all patients had detailed clinical history and physical examination. Laboratory studies including liver function tests and blood ammonia level were done in all patients. Only patients with normal liver functions were selected for the study. All previous prophylactic medications were stopped 1 month in advance. Patients were continued on a low-tyramine, low-caffeine diet. They were instructed to continue to use biofeedback training at home. They were advised to avoid known triggers for their headaches as much as possible. The patients were asked to maintain a headache diary during the baseline observation period of 4 weeks prior to the onset of therapy with valproate, as well as during the study period. During the observation period and during the study period, the patients were allowed to use immediate relief medications such as Midrin, ergotamine, dihydroergotamine, and anti-nausea medications. They were asked to keep a detailed account of the above medications, noting down the number of tablets and injections they took. Patients also were instructed to keep a general well-being rating each week. Previous EEGs were reviewed and a new EEG was obtained in all patients. Divalproex sodium (Depakote) was started in the dose of 250 mg tablet bid and increased to 500mg bid in 2 days, if the initial doses were tolerated. The blood level of valproic acid was obtained in 1 week. If the level was below 75mcg/ml, dosage was increased and the blood level obtained in another week. On an average, a 1000 to 2500 mg of Depakote dose was used and the dosage adjusted according to the blood level and side effects. An attempt was made to keep the blood level between 75 and 100 mcg/ml.

Headache diary, symptomatic medication diary and well-being rating was continued weekly for 12 weeks. All side effects were recorded by the patients and they were advised to call the physician if there were any problems. Fortnightly visits to the clinic were mandatory. Monthly liver function profile, blood ammonia and valproic acid levels were obtained.

The effect of treatment was monitored during the 3 month period based on weekly headache index (number of attacks per week times severity), symptomatic medication used for pain relief, patients’ general well-being rating, physicians’ global assessment, dysfunctional days per week, and number of headache-free days.

RESULTS

The age distribution of the 30 patients entered in the study was 35 to 58 years. There were 28 women and 2 men. Twenty-seven patients completed the study. Three patients dropped out because of inability to tolerate valproate due to severe nausea and vomiting.

Weekly Headache Index. Table 1 is based on the difference between the baseline and the final headache index. Fifty percent or more reduction in headache index was reported in 18 (66.6%) of patients. Thirteen (48.1%) had 75% or more reduction in the headache index over the 3 month period of observation.

Headache-Free Days. Headache-free days during the 3rd month were documented and compared with the month before starting valproate (Figure 1). The average headache-free days during the month before starting the treatment was 5.5 ± 2.1 which increased to 17.7 ± 3.2 during the last month of treatment (P < 0.01).

Dysfunctional Days. Similarly, the average number of dysfunctional days as a result of headache during the month before valproate was started were compared with the dysfunctional days during the 3rd month of treatment (Figure 2). The patients had an average of 22 ± 4.2 dysfunctional days during the month before treatment compared to 8.5 ± 1.8 during the 3rd month of treatment (P < 0.01).

Patients with less than 50% reduction in the headache index were considered treatment failures. Table 2 shows the headache index data of patients who were considered to be treatment failures. Nine (33.3%) did not improve.
History of seizure-like activity or syncope with or without a temporal relationship to headache was reported in 6 out of 30 patients. Abnormal EEGs showing nonspecific paroxysmal activity were seen in 4 patients. There was no correlation between the degree of improvement of headache with valproate and the occurrence of either paroxysmal abnormal EEG activity or history of seizure-like episodes or syncpe.

**Side Effects.** Nine out of 30 patients had side effects listed in Table 3. In 3 patients the nausea and vomiting was so severe that the treatment had to be discontinued. The commonest side effect was weight gain followed by tremor. None of the patients showed any significant hepatic dysfunction as evidenced by elevated enzymes or blood ammonia level during the treatment period.

**DISCUSSION**

In the patient population included in this study, two thirds improved on valproate. Improvement of this magnitude is very encouraging and thus, valproate appears to be a significant addition in our armamentarium of treatment of chronic persistent migraine. Hepatotoxicity was a greatly feared side effect of valproate when it was initially used for seizure disorders in children. When administered to patients over the age of 10 years, hepatotoxicity owing to valproate is extremely rare.

As in this study, the commonest side effects seen are tremor, transient hair loss, nausea and appetite stimulation leading to weight gain. Maximum clinical effect of valproate is often delayed because of the fact that it has multiple pharmacological active metabolites which have much longer half lives. Similarly, the pharmacological effects are seen at least for one week after its withdrawal.

It would be our recommendation not to use valproate in any patient with a history of hepatitis or abnormal liver function. Adequate explanation of the possible toxic effects has to be given before the patient is subjected to treatment with valproate. Monitoring of liver functions and blood ammonia levels are imperative. It is our experience that valproate can be effectively combined with tricyclic anti-depressants in patients with chronic recurrent migraine.

The mechanism of action of valproate in headache is of great interest. Valproate is a GABA-mimetic agent. Valproate acts on GABA receptors including those on the dorsal raphae nuclei, resulting in a decreased firing rate of the serotonergic cells. This effect is in keeping with the known role of serotonergic systems in the pathogenesis of migraine.

The clinical beneficial effect of valproate in chronic recurrent migraine raises another interesting possibility in the basic pathophysiology of migraine. Glutamate has been implicated in the pathogenesis of migraine recently based on certain observations including the elevated levels of glutamate in the platelets of patients with migraine with aura reported by D’Andrea et al. and the elevated levels of GABA in the cerebrospinal fluid of patients with migraine during attacks of headache reported by Welch et. al. Glutamate is also implicated in the mechanism of spreading depression, which is thought to be partly due to increased turnover of glutamate. It is postulated by Welch et. al. that migraine may be a state of neuronal hyperexcitability caused by increased activity of the excitatory amino acid, glutamate. The beneficial effect of valproate may be by counterbalancing the neuronal hyperexcitability caused by the increased activity of glutamate in migraine. Further studies are indicated to clarify these points.

Like many other medications used in the prophylaxis of migraine, tachyphylaxis (progressively decreasing effectiveness as the treatment progresses) may be possible with valproate also. Long term observations are in order, in order to clarify the long term effects of treatment. Further double blind studies are also indicated to establish valproate as a legitimate agent in the treatment of chronic headache.

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**Table 1**

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<th>Measure</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>75% or more reduction in headache index</td>
<td>13</td>
<td>48.11</td>
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<tr>
<td>50-75% reduction in headache index</td>
<td>5</td>
<td>18.5</td>
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<tr>
<td>50% or more reduction in headache index</td>
<td>18</td>
<td>66.6</td>
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**Table 2**

<table>
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<th>Measure</th>
<th>No. of Patients</th>
<th>Percentage</th>
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<tbody>
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<td>30-50% reduction in headache index</td>
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<td>19.5</td>
</tr>
<tr>
<td>10-30% reduction in headache index</td>
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<td>18.5</td>
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<tr>
<td>No improvement</td>
<td>9</td>
<td>33.3</td>
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**Table 3**

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<tr>
<td>Severe Nausea and Vomiting</td>
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</tr>
<tr>
<td>Loss of Hair</td>
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</tr>
<tr>
<td>Weight Gain</td>
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REFERENCES


