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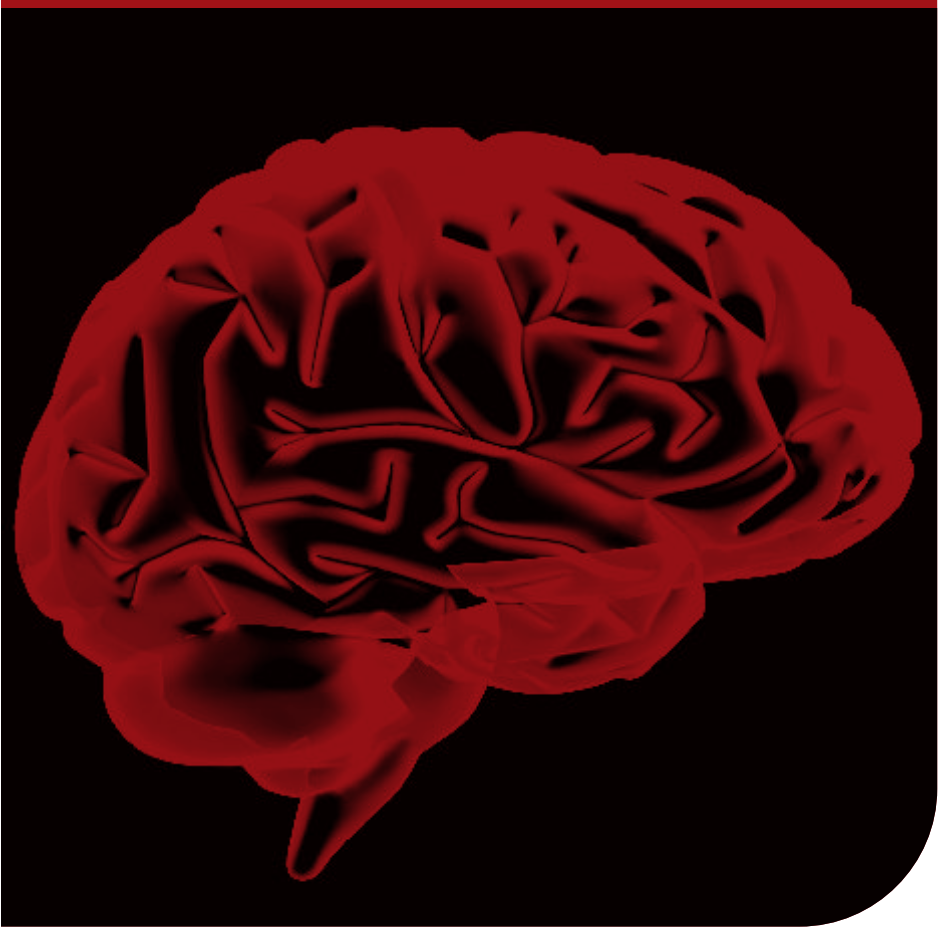

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Topiramate in prevention of cluster headache in the Taiwanese

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Abstract

Topiramate could potentially effective as prophylaxis for cluster headache, but the experience remains limited in Asians. We performed an open-label clinical study to evaluate the efficacy of topiramate in the tolerable dosage to prevent cluster headache. We studied patients who fulfilled the criteria of episodic or chronic cluster headaches (International Classification of Headache Disorders second edition) prospectively. Headache severity was assessed using a verbal rating scale (excruciating, severe, moderate, mild, and no headache). Treatment was started with a topiramate dose of 50 mg twice daily and was increased by 50-100 mg a day every 3 to 7 days as tolerated to a maximal daily dosage of 400 mg. Of the 12 patients with episodic cluster headache, nine patients had remission of headache at a mean daily dosage of 273 mg (range 100-400 mg), and the patient with chronic cluster headache had remission at a daily dosage of 400 mg. The adverse effects included: paresthesia (84%), slow speech (54%), and dizziness (46%), but were tolerated by most patients. Two patients discontinued topiramate due to adverse events and one due to lack of efficacy. This open-label study suggests that topiramate is effective in the treatment of cluster headache in Taiwanese patients.

Key words: *Anticonvulsant, cluster headache, chronic cluster headache, topiramate*

Introduction

Cluster headache is one of the most severe forms of head pain and is distinct from other forms of headache in terms of clinical features and management.[1] Cluster headache is characterized by periodicity, typically one or two cluster periods a year, with each one lasting two to three months.[2,3] The sufferers usually experience moderate to severe disability, which may lead to decreased productivity and job loss. Recently, a few clinical studies have shown the effectiveness of topiramate in the prophylaxis of cluster headache,[4-8] however, the experience in Asians is still limited. We performed an open-label trial to evaluate the efficacy of topiramate at the tolerable dose in the prevention of cluster headache.

Materials and Methods

Thirteen patients who fulfilled the criteria of episodic (n=12) or chronic (n=1) cluster headache of the International Classification of Headache Disorders second edition (ICHD-II)[2] were studied prospectively. In all the patients demographic data, medical history, and headache profile were recorded. Non-contrast magnetic resonance imaging (MRI) of brain was normal in all the patients. The patient with chronic cluster headache and three patients with episodic cluster headache were being treated with traditional preventive treatment such as non-steroid anti-inflammatory drug and verapamil, but with no effect. Topiramate treatment started at a dosage of 50 mg twice daily. The daily dose was increased by 50-100 mg every three to seven days as tolerated, with a maximum dose of 400 mg/day. Headache severity was assessed using a five-point verbal rating scale (excruciating, severe, moderate, mild, and no headache).[9] All participants were trained on how to rate their pain and record headache diaries. Remission was defined as having no headache for at

least three days. After a remission period of over two weeks, the daily dose was reduced by 50 mg every three to seven days in patients with episodic cluster headache. The Hospital Ethics Committee has approved the study according to the Helsinki rules and informed consent was obtained from each subject.

Results

Thirteen patients (two women and eleven men) fulfilling the ICHD-II criteria for episodic cluster headache (Cases 1-12) or chronic cluster headache (Case 13) were enrolled in this study. Mean age at onset of cluster headache was 34.7 years (range 25-52) and the mean age at initiation of topiramate treatment was 39 years (range 30-58). The mean duration of cluster headache period prior to topiramate treatment was 17.6 days (range 8-30 days) for the patients with episodic cluster headache and eight years for the patient with chronic cluster headache.

The clinical features and the response to treated with topiramate are summarized in Table 1. Of the 12 patients with episodic cluster headaches, nine patients experienced headache remission with topiramate therapy at a mean daily dosage of 273 mg (standard deviation (SD) ± 127, range 100-400). At the start of the study, of the nine patients with episodic headaches, eight patients rated their headaches as excruciating degree and the other one as severe. Topiramate significantly shortened the cluster period in these nine patients, and reduced the initial intensity of headache from excruciating to severe in a mean period of 4.3 days (SD 1.7, range 2-6), to moderate in 5.8 days (SD 2.6, range 2-10), and to mild in 7.4 days (SD 2.6, range 4-13). The mean period for remission was 10.7 days (SD 3.9, range 6-18), representing a reduction in the duration of 15% to 85% (median 51%) [Table 1]. Adverse effects were often mild to moderate but tolerable and included: paresthesia (84%), slow speech (54%), and dizziness (46%). Two patients discontinued the topiramate treatment due to adverse effects (Case 10 and 11), and one due to lack of efficacy (Case 12). After a remission period of more than two weeks, topiramate was gradually tapered. Case 9 had recurrence of headaches 16 days after completely discontinuing topiramate. The recurrent headaches remitted within three to four days after re-administration of topiramate in the previous dosage. The other eight patients had no relapse of cluster headache during a 3-month follow-up after withdrawal of topiramate therapy.

Case 13 was a 33-year-old woman, who suffered from attacks of stabbing pain in the periorbital region with ipsilateral lacrimation, nasal stuffiness, and conjunctiva injection for eight years, fulfilling the criteria for chronic cluster headache. She used to experience up to seven attacks a day, each lasting 60-120 minutes. Triptans and hyperbaric oxygen therapy were ineffective. High doses of steroid, verapamil (240 mg/day), lithium (900 mg/day) and other aggressive treatments including gabapentin (2400 mg/day), valproate (3000 mg/day), and imipramine (75 mg/day) had all failed to reduce the frequency of headaches. After topiramate treatment in a dosage of 400mg/day, there was rapid reduction in her headaches and had complete remission of headaches. Six months later, she discontinued the topiamate treatment, but had recurrence of headaches a week after the total withdrawal. However, the recurrent headaches remitted again within three to four days after re-administration of topiramate. Two years after topiramate therapy, she suffered from flank pain and renal stone of the right kidney was diagnosed.

Table 1: Features and response of cluster headache in patients treated with topiramate

Age/ Sex	Duration of previous usual cluster period, d	Time to starting TPM, d	Headache intensity, frequency/d before TPM treatment	Final TPM dose, mg/d	Outcome (d after treatment)	Onset of adverse effects (d)
34/M	56	15	E, 1	300	R (11)	P (3), SP (7)
*31/M	--	35	E, 1	400	R (10)	P (3), SP (5)
30/M	53	10	E, 1	400	R (18)	P (4), SP (7)
32/M	21	8	E, 1	300	R (6)	P (2), SP (6)
31/M	54	30	E, 1	100	R (16)	D (1)
58/M	48	22	E, 1	150	R (9)	P (7), D (1)
49/M	53	15	E, 1	400	R (9)	P (2), D (1), SP (6)
31/M	61	9	E, 1	400	R (10)	P (1), SP (7)
54/F	95	7	S, 1	200	R (7)	P (3)
45/M	23	12	E, 1	100	WD (3)	P (1), D (1)
49/M	45	23	E, 1	100	WD (14)	P (1), D (1)
30/M	55	25	E, 4	300	WD (8)	P (3), D (2), SP (6)
**33/F	8 yrs	8 yrs	E, 4-6	400	R (30)	Renal stone (2 yrs)

* Denotes the case with the first attack; **Denotes the case with chronic cluster headache; M - Male; F - Female; d - Day; yr - Year; TPM - Topiramate; E - Excruciating; S - Severe; WD - Withdraw; R - Remission; P - Paresthesia; D - Dizziness; SP - Slow speech

Discussion

The present study suggests that topiramate is effective in the prevention of episodic and chronic cluster headache. Wheeler and Carrazana were the first to report remission of cluster headaches in nine of the ten patients within one to three weeks at a low dose of topiramate (50 to 125 mg/day).[4] In a recent open-label trial, of the 26 patients, 15 (58%) patients had headache remission within 1 to 28 days after topiramate treatment at doses ranging from 25 to 200 mg/day.[6] Another study reported no significant change in headache frequency with topiramate at 50 to 250 mg/day, with the daily number of attacks reduced by > 50% in just seven (21%) patients.[7] The effect of topiramate at low dosage in the prevention of cluster headache seems varied. Patients suffering from cluster headaches consistently report it as the most severe pain they have ever experienced. Immediate and optimal therapy is therefore urgently needed to alleviate headache intensity and prevent a cluster attack. Therefore, we decided to start with 50 mg twice daily of topiramate and rapidly titrate upwards depending on the tolerability. In the present study, we observed that 10 (77%) of 13 patients responded well to topiramate therapy and the cluster durations were reduced to approximately half of the previous usual cluster durations.

Chronic cluster headache accounts for 10-21% of all cluster headaches,[3,10,11] but is rare in the Taiwanese and Asians,[12] with Case 13 in the present series being the first case of chronic cluster headache ever reported in Taiwan.[13] Interestingly, she did not have a good response to topiramate treatment until the dose was reached 400 mg/day. In addition, when topiramate was withdrawn, her headache recurred within a few days. A similar observation has been reported in three patients with chronic cluster headache who had no response to topiramate 200 mg/day.[8] Though limited, these observations suggest that higher doses of topiramate may be beneficial to some patients with chronic cluster headache, who have no response at a low dose.

Oral bioavailability of topiramate is greater than 80%, and increases in the serum concentration are linearly dose-related at doses of 200-800 mg.[14] The incidence of adverse events may increase with an increasing dosage. Most adverse effects are related to the central nervous system. However, in studies relative to topiramate in partial epilepsy, most adverse effects of topiramate were not clearly dose-related, and there was no correlation between the topiramate dosage and the frequency of side effects leading to discontinuation across higher doses (200-1000 mg/day).[15,16] In addition, the adverse-effect profile of topiramate in Taiwanese was different from that in whites.[15-17]

Topiramate is metabolized in the liver by the P450 microsome enzymes, such as CYP3A4.[18] The activity of the metabolic enzymes is mainly dependent on genetic, physiologic, and environmental effects. For instance, inter-ethnic and inter-individual difference in the distribution and frequency of metabolic enzyme variant alleles is often responsible for the development of a significant number of adverse drug reactions.[19-23] These genetic and environmental factors may explain why frequency of adverse effects is not related to the dose of topiramate, and the incidence is different between different populations. The incidence of adverse events was high, but tolerable in our patients. It seems our patients could endure higher dose of topiramate. Although slow titration is likely to alleviate occurrence of the adverse events, individual response may vary widely. Our study suggests that the tolerably rapid titration may be possible in certain patients with excruciating cluster headache for the additional benefits. Paresthesia was the first appearance of adverse effects, and occurred frequently in our patients, which is consistent with previous reports of topiramate therapy for cluster headache and migraine,[6,24] but higher than that observed in patients with epilepsy who were treated with topiramate.[15-17] While the underlying mechanism remains unclear, it is possible that the activities of carbonic anhydrase are inhibited by rapid titration to high doses of topiramate[25] or this enzyme in the patients with cluster attack becomes more efficient to react with topiramate.

In conclusion, our study supports that topiramate is effective in the prevention of cluster headache. Since cluster headache is a very severe form of headache, our results suggest that a prompt dosage of topiramate upwards according to tolerability may be possible to offer immediate and additional benefits for both chronic and episodic cluster headache.

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