Topiramate for Prophylaxis of Basilar Migraine in Children and Adolescents

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Abstract

Objective: The aim of this study is to assess the efficacy and safety of topiramate for prophylaxis of basilar type of migraine in children and adolescents.

Methods: A prospective outpatient dose comparison study of patients with BM as defined by the International Classification of Headache disorder (second edition) where patients with >4 migraines/month were randomized to receive either 25mg or 75mg/day topiramate.

Results: Fifteen children (5 boys, 10 girls) completed the study (8 in the 25-mg group and 7 in the 75-mg group). During the prospective baseline, the mean headache frequency of the combined group “all migraines” per month was 4.5/month (25mg) and 4.8/month (75mg). Average duration of migraine was 5.5 hours (25mg) and 5.0 hours (75mg) and average mean pain (5-point faces scale) was 3.3 for both (25mg 75mg).

The reduction in median monthly migraine rate relative to baseline was 2.9 (64.4%) and 3.6 (75.0%) for the 25-mg and 75-mg topiramate-treated groups, respectively (p<0.001).

The reduction in median monthly BM rate relative to baseline was 2.5 (74.24%) and 2.3 (82.8%) for the 25-mg and 75 mg topiramate-treated groups, respectively. The overall reduction in BM attacks reduced from 2.84/month to 0.59/month (79.2%; p<0.001).

Overall, 86% of patients responded with a greater than 50% reduction in migraine frequency (100%, 25mg and 71%, 75mg). Mean reduction in migraine duration was 18 minutes (25mg) and 89 minutes (75mg). There was no significant difference in migraine severity between the 2 groups. There were no serious adverse events in both groups.

Conclusions: Preventive therapy with topiramate resulted in reducing the overall migraine frequency and the frequency of attacks of BM at both 25mg and 75mg doses relative to the historical baseline and prospective baseline periods. The 2 treatment groups resulted in comparable outcomes.

Key Words: Topiramate – Migraine – Prophylaxis – Children.

Introduction

IN the last 20 years the International Headache Society (IHS) has fostered the development of high quality research in headache including migraine. The 2004 (2nd) edition of the International Classification of Headache Disorders [1] provides a framework for headache research, including clinical trials which has become rather more child relevant. Migraine is in essence a familial episodic disorder whose key marker is headache with certain associated features. These features, according to HIS, include any two of the following; unilateral headache, moderate to severe, worsened with exercise and throbbing in association with one of the following: photophobia or phonophobia and nausea or vomiting.

Approximately 30 million people in the United States suffer from migraines, with 18% of women and 6% of men experiencing at least 1 migraine headache annually [3]. Because of its significant impact on quality of life and interpatient variability in treatment response, migraine management remains challenging for many health care professionals. Migraine has a significant societal burden resulting in costly medical bills and lost productivity, averaging about 64 to 150 million work days lost each year [4]. Consequently, migraine headache has been classified by the World Health Organization as one of the 19 most disabling diseases worldwide [1]. Acute or abortive migraine management encompasses specific and nonspecific migraine therapeutics, including nonopioid and opioid analgesics, triptans, and ergotamines. Prophylactic migraine management data span the pharmacological spectrum from antiepileptic and antihypertensive agents to botulinum toxin type A [5]. Special considerations for migraine management also must be applied in various populations, including children, pregnant women, and the elderly [6].
The clinical course of migraine is especially difficult to predict in children. Migraine will come for weeks, months or a few years then remit for months or years, sometimes returning unpredictably later on. Long term follow-up is difficult and studies have demonstrated this variability [2].

Basilar-type migraine (BM) is a common clinical entity estimated to represent 3-19% of migraine in children and adolescents. The onset of BM tends to be in young children, with mean age being 7 years, although the clinical entity probably appears as early as 12-18 months as episodic pallor, clumsiness, benign paroxysmal vertigo and cyclical vomiting. Attacks are characterized by episodes of intense dizziness, vertigo, visual disturbances, ataxia, and diplopia. These early, transient features may last for several minutes, or up to 1 hour, and are then followed by the headache phase [7].

Material and Methods

A prospective outpatient controlled study to assess the efficacy and safety of topiramate, a novel antiepileptic agent that has been established as effective for the prevention of migraine in adults and children, in the prophylaxis of basilar migraine in children and adolescents by comparing two doses, 25mg and 75mg/day. Fifteen patients aged less than 16 were collected among attendants of the pediatric and neurology outpatient clinics in the Fayoum University Hospital and other private clinics from October 2008 through June 2010.

Selection of the patients was done according to the following criteria:
- The age is less than 16 years.
- The headache fulfills the criteria of migraine with or without aura with two or more of the following symptoms:
  - Vertigo.
  - Dysarthria.
  - Diplopia or double vision.
  - Tinnitus.
  - Decreased hearing.
  - Simultaneous bilateral parasthesia.
  - Decreased level of consciousness.
- Four attacks of migraines headache per month.
- Exclusion of other associated causes of headache as chronic sinusitis, disturbed sleep disorders (due to central causes as other neurological diseases or obstructive causes as adenoid, deviated nasopharynx, nasal, oral or laryngeal space occupying lesions) or general medical diseases.

According to a prospective baseline headache characteristic period of 4 weeks, patients where divided into two groups; group (A) included 8 patients and received topiramate at 25mg/day, and group (B) included 7 patients who received topiramate at 75mg/day.

These baseline headache characteristics were the following: average monthly migraines days, average severity of migraines, average duration of migraines in hours and proportion of headaches requiring abortive medicines. Collection of these data was achieved through the patient him or her self when possible or through the parents.

After a period of regular intake of topiramate for 11-14 weeks (average 12 weeks) in both groups, the efficacy outcomes were compared between the two groups. These efficacy outcomes included the following:
- Reduction in frequency, severity, and duration of basilar symptoms.
- Reduction in migraine pain severity and duration.
- Reduction in migraine episode and headache episode frequency.
- Reduction in total headache days.
- Proportion of responders (i.e., the proportion of subjects who experience a ≥50% reduction in migraine days and migraine episodes).
- Reduction in the use of acute/abortive medications.
- Adverse events.

A grading scale as a measurement of the headache disability was used as follows; grade I (non to mild), grade II (mild), grade III (moderate) and grade VI (severe). The proportion of each grade at the baseline was reported.

Statistical analysis was conducted with SAS v. 9.1 (SAS Institute, Cary, NC, USA) using intent-to-treat principles. A 2-sided level of significance, where \( \alpha = 0.10 \), was set.

Results

Fifteen patients enrolled in this study were divided into 25mg group (A) and 75mg group (B). The baseline patient demographics is presented in Table (1).

Before entry into the prospective baseline period, history of the headache was recorded and this is presented in Table (2).
The mean age of onset of migraine was 8 years (25-mg group) and 10 years (75-mg group) and the average number of “all” migraine attacks per month (both migraine with aura, including BM, and migraine without aura) was 8 in the 25-mg group and 5 in the 75-mg group. The average duration of attacks was 4 hours and 12 of 15 patients described the pain as severe or excruciating. Nine of 15 rated the disability caused by their migraine as producing moderate-to-severe disability. There was no significant difference between the two groups at screening.

The patients then entered a 4-week prospective baseline period to capture the headache frequency and severity for later comparison with the treatment phase (Table 3). The patients were permitted to use acute (abortive) medicines to treat attacks but were permitted no other preventive therapies. The average monthly migraine days were 4.5 (25mg) and 4.8 (75mg) and the average duration and severity were similar between the 2 groups. About half of the 25mg group used abortive medicines and 75% of the 75mg group took acute treatments during the prospective baseline.

<table>
<thead>
<tr>
<th>Prospective baseline headache characteristics</th>
<th>25mg, n=8</th>
<th>75mg, n=7</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average monthly headache days</td>
<td>4.52</td>
<td>6.76</td>
<td>Wilcoxon rank-sum test, p=.49</td>
</tr>
<tr>
<td>Average monthly migraine days</td>
<td>4.52</td>
<td>4.83</td>
<td>Wilcoxon rank-sum test, p=1.0</td>
</tr>
<tr>
<td>Average severity of headache</td>
<td>3.37 (0.53)</td>
<td>3.26 (0.79)</td>
<td>t-test, p=.77</td>
</tr>
<tr>
<td>Average duration of migraine, in hours</td>
<td>5.48 (3.51)</td>
<td>5.02 (1.80)</td>
<td>p=.76</td>
</tr>
<tr>
<td>Average severity of migraine</td>
<td>3.37 (0.53)</td>
<td>3.4 (0.67)</td>
<td>p=.91</td>
</tr>
<tr>
<td>Proportion of headaches requiring abortive medicines (%)</td>
<td>28/58 (48.3%)</td>
<td>42/56 (75%)</td>
<td>Fisher’s exact test, p=.004</td>
</tr>
</tbody>
</table>
Table (4) demonstrates the primary outcome for “all migraines” showing a reduction of headache frequency “overall” (groups combined) and in both the 25- and the 75-mg group. A reduction of 3.97 migraine days/month was observed from the prospective baseline to treatment maintenance phase \((p<.001)\) without significant difference between the 2 groups \((p=0.86)\). The reduction in mean monthly migraine rate relative to baseline was 2.9 (64.4\%) and 3.6 (75.0\%) for the 25-mg and 75-mg topiramate-treated groups, respectively. For the target headache subtype, BM, the overall combined reduction of monthly attacks was 2.49 \((p<.0042)\) with a reduction of 2.96/month in the 25-mg group and 1.93/month in the 75-mg group (Table 5). The reduction in mean monthly BM rate to baseline was 2.5 (74.24\%) and 2.3 (82.8\%) for the 25-mg and 75-mg topiramate-treated groups, respectively. Again, no significant difference was noted between the 2 groups, both showing reduction in headache frequency.

For BM, average monthly migraine days reduced from 3.41 (25mg) and 2.8 (75mg) during the prospective baseline to 0.88 (25mg) and 0.48 (75mg) during the treatment maintenance phase. Overall, the BMs reduced from 2.84/month to 0.59/month during the treatment phase. All of the patients (8/8) in the 25mg group and 5 of 7 patients in the 75-mg group were categorized as “responders”, as defined by a >50% reduction in migraine days/month. Overall, 86\% of patients responded with a greater than 50% reduction in migraine frequency.

There were no serious adverse events reported. Numbness and tingling in the face and hands were the most common adverse events, but no patient withdrew from the study because of these symptoms. One patient in the 75-mg group reported “learning difficulty” but demonstrated no objective deterioration in school performance.

<table>
<thead>
<tr>
<th>Table (4): Primary outcome: All migraines combined.</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>----------------</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Maintenance</td>
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</table>

Table (5): Primary outcomes: Basilar-type migraines.

<table>
<thead>
<tr>
<th>Difference in Average Monthly Basilar Migraine Days During the Following Periods</th>
<th>Combined treatment group</th>
<th>Each treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (p)-value</td>
<td>25mg/day, n=8 (p)-value</td>
</tr>
<tr>
<td>Prospective baseline vs maintenance, mean (SD) (min, max)</td>
<td>-2.49 (2.55) (p&lt;.0042)</td>
<td>-2.96 (2.46)</td>
</tr>
<tr>
<td></td>
<td>(+2.40, -7.51)</td>
<td>(0, -7.51)</td>
</tr>
</tbody>
</table>

Discussion

The treatment of migraine headache in children and adolescents requires an individually tailored regimen of acute therapies (i.e., ibuprofen, acetaminophen, “triptan” agent), biobehavioral strategies (ie, sleep hygiene, regular exercise, biofeedback, stress management), and preventive agents. Daily preventive agents should be limited to those patients whose headaches occur with sufficient frequency or severity so as to warrant a daily treatment program. Most study designs require a minimum of three headaches per month to justify a daily agent. A clear sense of functional disability must be established before committing to a course of daily medication [8].

A diverse group of medications, including antihistamines, antidepressants, antihypertensives, and antiepileptics, are used to prevent attacks of migraine in children. Encouraging data are, however, emerging regarding the use of antiepileptic agents including disodium valproate, levetiracetam, and topiramate for the prevention of pediatric migraine. Migraine preventive medications, when given, should decrease the number, intensity, and duration of headaches, improve how patients respond to acute treatment, and improve the quality of life [9].

Topiramate is a novel antiepileptic agent that has been established as effective for the prevention of migraine in adult [10].

This study, specifically targeting patients with a migraine variant, observed that preventive therapy with topiramate was effective in reducing overall migraine frequency and also in reducing the frequency of attacks of BM at both 25-mg and 75mg doses relative to the prospective baseline period. Regardless of treatment dose (25mg Vs. 75mg), patients had significantly fewer monthly migraine
days and experienced significant improvement in migraine-associated disability and quality of life. Overall, 86% of patients responded with a greater than 50% reduction in migraine frequency (100%, 25mg and 71%, 75mg). However, the duration and severity of individual migraine attacks were not significantly different (mean reduction in duration was 18 minutes [25mg] Vs. 89min. [75mg] and there were no other statistical differences noted between the 2 treatments groups.

Given the disabling nature of BM, the design of this study incorporated a 1-month prospective baseline period following which the patients were divided into a high-dose (75mg) or low-dose (25mg) comparison groups. This design chosen follows epilepsy models (high dose Vs. low dose). No placebo used in this study because of the vulnerable nature of the enrolled patients who suffering from disabling symptoms so the decision was made not to expose these patients to duration “off treatment”.

Winner et al. [11], conducted a multicenter, parallel-group, double-blind trial comparing topiramate with placebo in 162 children, aged 6 to 15 years. Patients were randomized in a 2:1 fashion, topiramate to placebo. A total of 54.6% of patients taking topiramate and 46.9% of patients taking a placebo experienced a >50% reduction of mean migraine days per month. No difference was found between groups. However, 32.4% of patients in the topiramate group experienced >75% reduction in migraine days, whereas only 14.3% of patients taking a placebo had the same effect (p=.02).

Campistol et al. [12], in a 24-patient case series also found topiramate to be beneficial for migraine prophylaxis in children (aged 6-14 years) for whom other prophylaxis medications had failed. Topiramate was titrated up to 200mg daily or 6mg/kg/day. The mean monthly migraine episodes decreased from 3.6 at baseline to 2.9 at 2 month (p<.0001) and 2.7 at 4 months (p=.001), in addition, 90% of children experienced a shorter migraine than previously.

Other trials [13-15] evaluated topiramate in older adolescents and adults and found beneficial results as well. Topiramate may be considered in pediatric patients who require migraine prophylaxis.

The results of this study suggest that when choosing to begin a patient on topiramate for migraine prophylaxis, a low starting dose is used and a slow titration method (incremental dose increases every 2-3 weeks) is employed using clinical symptomatology as the endpoint rather than a dose/kg target.

Conclusion:
This study found topiramate to be effective for decreasing migraine frequency, duration, and severity in children, as well as reducing the school days missed and improving quality of life in the child.

References
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