Saudi Pharmaceutical Journal (2010) **18**, 239–243

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Efficacy of combined topiramate/thioctic acid therapy in migraine prophylaxis

Ahmed M. Ali [a,*], Thanaa G. Awad [b], Nagwa M. Al-Adl [a]

[a] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, October 6 University, October 6 City, Central Axis, Part 1/1 October 6 Governate, Egypt*
[b] *Health Insurance Organization, Cairo, Egypt*

Received 10 April 2010; accepted 10 July 2010
Available online 30 July 2010

KEYWORDS

Topiramate;
Thioctic acid;
Migraine

Abstract Migraine cannot be cured and the aim, shared with the patient, is to minimise the impact of the illness on the patient's life and lifestyle. The aim of prophylaxis is to reduce the number of migraine attacks. Prophylaxis should be considered when appropriately used acute management gives inadequate control of symptoms. The efficacy and safety of topiramate 50 mg/d and thioctic acid (α-lipoic acid) 300 mg/d either as monotherapy or in combination were investigated as migraine prophylactic agents. Forty secondary school migraineur girls were enrolled in the study. The study was conducted in two phases, a prospective baseline phase and 1-month treatment phase. Combined topiramate/thioctic acid therapy was more effective than either topiramate or thioctic acid monotherapy as a migraine-preventive treatment. Combined topiramate/thioctic acid therapy decreased the mean monthly migraine frequency from 5.86 ± 1.2 to 2.6 ± 0.98 ($p \leqslant 0.05$), topiramate (50 mg/d) from 5.71 ± 1.4 to 4.75 ± 1.5 and thioctic acid (300 mg/d) from 5.68 ± 1.6 to 5.22 ± 1.8. Reduction in mean monthly migraine days was also significantly greater in the group receiving combined topiramate/thioctic acid (from 12.32 ± 1.85 to 5.74 ± 1.1) compared to those receiving either topiramate 50 mg/d (from 12.7 ± 1.34 to 11.85 ± 1.35) or thioctic acid 300 mg/d (from 12.5 ± 1.72 to 11.65 ± 1.44). The responder rate (% of patients showing ⩾50% reduction in monthly migraine frequency) was 85% in patients receiving combined topiramate/thioctic acid therapy compared to 30% and 20% in patients receiving either topiramate or thioctic acid, respectively. The incidence of adverse events was higher in patients receiving topiramate (50 mg/d) monotherapy. The most common adverse events were nausea, fatigue, paraesthesia and taste perversion.

* Corresponding author.
E-mail address: AhmedZoghary@yahoo.com (A.M. Ali).

doi:10.1016/j.jsps.2010.07.006

Production and hosting by Elsevier

We conclude that combined topiramate/thioctic acid therapy is more effective and better tolerated than topiramate monotherapy. The combination has lower monthly medication costs compared to the traditionally used topiramate 100 mg monotherapy.

1. Introduction

Migraine is a recurrent headache disorder with intense pain that may be unilateral and accompanied by nausea or vomiting as well as photosensitivity and phonosensitivity. The incidence of migraine headache is claimed to be 25% in women and 8% in men. Migraine also affects about 5–10% of children and adolescents (Carolyn et al., 2009). Approximately 53% of patients with severe migraine report that their attacks require bed rest or are a source of severe impairment (Lipton et al., 2001). The cost of missed workdays and impaired performance because of migraine is estimated at $18 billions (Silberstein et al., 2002) in the USA.

The exact cause of migraine headache is still unknown. Current research suggests that inflammation in the blood vessels of the brain causes them to swell and press on nearby nerves, causing pain (Salomone et al., 2009). This inflammation may arise in or be stimulated by signals from the trigeminal nerve, the main sensory nerve of the face (Debruyne and Herroelen, 2009). The role of oxidative stress in the pathogenesis of migraine was supported by the findings of various studies. A significant increase in plasma levels of thiobarbituric acid reacting substances (TBARS) has been reported in migraineurs (Tozzi-Ciancarelli et al., 1997; Tuncel et al., 2008). Changes in platelet superoxide dismutase (SOD) activity have been reported in patients having migraine with aura (Shimomura et al., 1994). One study has reported a significant increase in urinary nitric oxide metabolites and lipid peroxidation by-products in migraineurs (Cinancarelli et al., 2003). Significant reductions in erythrocytic glutathione peroxidase (GSH-Px) and SOD activities have been reported in migraineurs with and without aura (Bolayir et al., 2004).

The United States Headache Consortium recommends preventive treatment when the following occurs: (a) migraine significantly interferes with daily routine, despite acute treatment; (b) acute medications fail, are contraindicated or lead to troublesome adverse events; (c) acute medications are overused; (d) there are circumstances, such as hemiplegic migraine or risk of permanent neurologic injury; (e) the patient experiences frequent headache attacks (>2 per week); or (f) the patient prefers preventive treatment (Silberstein, 2000). Effective preventive migraine treatments include antiepileptic drugs (Vikelis and Rapoport, 2010), antidepressants (Nagata, 2009; Koch and Jürgens, 2009), β-adrenoceptor blockers (Evers et al., 2006, 2009), calcium channel blockers (Negoro, 2009), botulinum toxin (Taylor, 2008; Mathew and Jaffri, 2009) and surgery (Guyuron et al., 2009). The antiepileptic drug "topiramate" is approved for the prophylaxis of migraine headache in adults. Topiramate, at doses of 100 and 200 mg/d (but not 50 mg/d), had been reported to be effective as a migraine-preventive therapy (Silberstein et al., 2004). Thioctic (α-lipoic) acid is both water- and fat-soluble antioxidant that is directly (*by removing reactive species*) and indirectly (*by chelating transition metal ions*) involved in the protection of biological components from the damage of oxidative stress (Haenen and Bast, 1991; Coon et al., 2003; Packer et al., 1996; Cronan et al., 2005). The use of thioctic acid in migraine prevention has been reported by some investigators (Sun-Edelstein and Mauskop, 2009). This study evaluated the efficacy and safety of topiramate 50 mg/d, thioctic acid 300 mg/d or a combination of both in migraine prophylaxis. The Egyptian MOH registration number for Topamax® is 21628. The MOH registration number for Thiotacid is 20943. Topamax® is indicated for migraine prophylaxis and as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic–clonic seizures. Thiotacid is indicated for the treatment of diabetic polyneuropathy, neuritis, poly-neuritis, optic neuritis and encephalopathies.

2. Methods

2.1. Study design

The study subjects were entered into a prospective 1-month baseline phase and headache records were reviewed. Baseline phase completers who met the study criteria were randomized to either topiramate 50 mg/d, thioctic acid 300 mg/d or a combination of both. Topiramate dose was titrated by 25 mg/week to the assigned dose. During the maintenance period, topiramate 50 mg was given in two divided doses (morning and evening), while thioctic acid 300 mg was given on a once daily basis in the morning. All treatments were continued for 1 month.

During the treatment period, school clinic visits were planned weekly. Headache, medication and adverse reaction records were collected and analyzed and new records were dispensed. To ensure better compliance, the study medications were refilled freely every week (7 doses per regimen). Subjects were allowed to take acute migraine mediations (including aspirin, paracetamol, NSAIDs, triptans and ergot derivatives) recording the name and amount of the medication used.

2.1.1. Patients

Forty secondary school girls with $\geqslant$3-month International Headache Society (IHS) migraine history were enrolled in this randomized open-label efficacy study. Patients were randomized to either topiramate 50 mg/d, thioctic acid 300 mg/d or a combination of both. All drug regimens were continued for 1 month.

2.1.2. Setting

Out-patient treatment at secondary school Health Insurance Clinics, Cairo, Egypt.

2.1.3. Inclusion criteria

Secondary school girl migraineurs aged 16–20 years experienced 5–11 migraines and 10–14 migraine days during the prospective 1-month baseline phase. All patients should fulfil the IHS diagnostic criteria for migraine headache (International Headache Society Clinical Trials Subcommittee, 2000).