Topiramate Monotherapy in Epilepsy and Migraine Prevention

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ABSTRACT

Objectives: The purposes of this review were to assess the efficacy of topiramate as monotherapy for epilepsy and migraine prevention, describe how it should be used, and give clinical advice on how to manage the practical aspects of dosing, titration, and possible adverse events in these 2 indications.

Methods: We searched the PubMed and BIOSIS databases using the key words *topiramate, epilepsy*, and *migraine* from the year 1987 onward, and subsequently focused the search on larger controlled trial studies of topiramate as monotherapy.

Results: Studies have evaluated the use of topiramate as monotherapy in the treatment of partial-onset and generalized seizures and in the prevention of migraine. In a randomized study, 75% of epilepsy patients treated with 400 mg/d topiramate remained seizure free at 1 year. Patients in the same study treated with a lower dose of topiramate (50 mg/d) also experienced notable seizure reductions, with 59% of patients free of seizures at 1 year. A comparison trial of topiramate (100 or 200 mg/d), valproate, and carbamazepine found that topiramate was associated with a similar time to first posttreatment seizure as the other 2 agents (P = NS). Trials of topiramate monotherapy in migraine prevention found that 100 mg/d was associated with a ≥50% reduction in monthly migraine frequency in 49% to 54% of patients. The migraine prevention trials typically used a starting dose of 25 mg/d, with weekly increases of 25 mg and an initial monotherapy target dose of 100 mg/d. The most common adverse events associated with topiramate are paresthesia, weight loss, and other centrally mediated symptoms, many of which may be ameliorated by proper titration and dosing and by good communication between physician and patient.

Conclusions: Data from controlled trials suggest that 100 mg/d topiramate as monotherapy is effective in the treatment of partial-onset and generalized seizures and in the prevention of migraine. (*Clin Ther.* 2005;27:154–165) Copyright © 2005 Excerpta Medica, Inc.

Key words: topiramate, antiepileptic, epilepsy, migraine, monotherapy, titration, adverse events, paresthesia, tolerability, prophylaxis, prevention, dosage.

INTRODUCTION

Topiramate is a compound with neurostabilizing properties originally synthesized as an intermediate product for a series of sulfamate derivatives of fructose intended for use as antidiabetic agents.[1] Topiramate did not exhibit beneficial effects on glucose metabolism when administered acutely to normoglycemic rodents fed a high-fat, high-sucrose diet, and consequently was not pursued as a potential antidiabetic agent.[2] Topiramate shares some structural similarities (eg, a sulfanilamide side group) with antiepileptic drugs and was subsequently tested for, and exhibited anticonvulsant activity in, several animal epilepsy models.[3] In one animal model (maximum electroshock seizures test), the potency of topiramate was similar to that of phenytoin, carbamazepine, and phenobarbital and was about 10 to 20 times greater than that of valproate.[4] Clinical studies have led to its current indication in the United States as adjunctive

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therapy in adults and children aged ≥2 years with primary generalized tonic–clonic seizures, partial-onset seizures with or without secondary generalization, and seizures associated with Lennox-Gastaut syndrome.[5] Topiramate is indicated as either adjunctive therapy or monotherapy for various types of epileptic seizures in many other countries as well, although topiramate is not yet indicated as monotherapy for the prevention of epileptic seizures in the United States or Canada.

Topiramate possesses a variety of pharmacodynamic properties, some of which suggest potential efficacy in conditions other than epilepsy. Pilot studies and smaller controlled trials have assessed its efficacy in several psychiatric conditions, including alcohol dependence,[6] binge-eating disorder,[7] bulimia nervosa,[8] and posttraumatic stress disorder,[9] although larger trials are needed to confirm its efficacy in these disorders. Larger controlled trials have assessed the efficacy of topiramate for weight loss in obese patients[10] and in migraine prevention.[11–13] As a result of these trials, topiramate is now approved for migraine prevention in >20 countries throughout the world, including the United States.

The purposes of this review were to assess the efficacy of topiramate as monotherapy for epilepsy and migraine prevention, describe how it should be used, and give clinical advice on how to manage the practical aspects of dosing, titration, and possible adverse events in these 2 indications.

METHODS

Clinical trial data were obtained by performing a search of the PubMed and BIOSIS databases using the key words *topiramate, epilepsy*, and *migraine* for the year 1987 onward. We focused the search on larger controlled studies of topiramate as monotherapy in epilepsy or migraine prevention.

TOPIRAMATE MECHANISMS OF ACTION

Topiramate has several pharmacodynamic properties that may contribute to its efficacy in epilepsy and migraine, including inhibition of excitatory glutamate-mediated neurotransmission at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainate receptor subtypes, enhancement of inhibitory γ-aminobutyric acid receptor A–mediated chloride flux, state-dependent inhibition of voltage-gated sodium channels, inhibition of high-voltage–gated calcium channels, inhibition of selected subtypes of carbonic anhydrase,[1] and enhancement of some types of voltage- and calcium-gated potassium channel currents.[14] The net effect of these potential mechanisms of action might be a decrease in neuronal excitability, which could explain the efficacy of topiramate (and other antiepileptic drugs) in the prevention of epileptic seizures and migraine attacks, 2 conditions that may exhibit disordered neuronal excitability as a common pathophysiology.[15]

COMORBIDITY OF EPILEPSY AND MIGRAINE

Comorbidity refers to a greater than coincidental association of 2 conditions in the same individual. Migraine and epilepsy are comorbid,[16,17] which may be partially explained by altered neuronal excitability. Recently, an open study assessed the clinical characteristics of 589 consecutive patients admitted to outpatient clinics for headache, epilepsy, or both in Germany.[18] Sixty-one patients were diagnosed with comorbid migraine and epilepsy, 280 patients had epilepsy alone, and 248 patients had migraine alone. The investigators found that migraine with aura and other features (eg, phonophobia and photophobia) were more common in patients with comorbid migraine and epilepsy than in patients with migraine alone. Forty-one percent (n = 25) of the patients with comorbid migraine and epilepsy experienced migraine with aura, compared with 25.8% (n = 64) of those patients with only migraine ($P = 0.019$). In addition, 80.3% (n = 49) of patients with migraine and epilepsy experienced phonophobia compared with 56.5% (n = 140) of migraine patients ($P = 0.001$), and 78.7% (n = 48) of comorbid patients experienced photophobia compared with 54.4% (n = 135) of migraine patients ($P = 0.001$). The authors speculated that the pathophysiologic link between migraine and epilepsy (at least for some patients) could be disordered neuronal activity, manifested by cortical spreading depression.

Cortical spreading depression is characterized by a wave of neuronal activity that originates in the occipital cortex and spreads in an anterior direction at a rate of about 3 mm/min, and is followed by a sustained depression of neuronal activity.[19] Spreading depression correlates with the auras that sometimes precede a migraine attack[20] and may be caused by imbalances of neurotransmitters and ions that contribute to neuronal excitability.[21,22] Although it is unlikely that a single phenomenon serves as the only link between migraine and epilepsy, the neuronal hyperexcitability that may contribute to each condi-