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Topiramate or valproate in patients with juvenile myoclonic epilepsy: A randomized open-label comparison

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Abstract

Few randomized, controlled trials evaluating antiepileptic drug (AED) efficacy and tolerability have focused solely on patients with juvenile myoclonic epilepsy (JME). We conducted a pilot, randomized controlled trial comparing topiramate ($N = 19$) and valproate ($N = 9$) in adolescents/adults with JME to evaluate clinical response when these broad-spectrum agents are titrated to optimal effect. Rating scales were used to systematically assess tolerability. Among patients completing 26 weeks of treatment, 8 of 12 (67%) in the topiramate group and 4 of 7 (57%) in the valproate group were seizure-free during the 12-week maintenance period. Median daily dose was 250 mg topiramate or 750 mg valproate. Two (11%) topiramate-treated patients and one (11%) valproate-treated patient discontinued due to adverse events. Systemic toxicity scores, but not neurotoxicity scores, differed substantially between the two groups; greater systemic toxicity was associated with valproate. Our preliminary findings that topiramate may be an effective, well-tolerated alternative to valproate warrant validation in a double-blind trial.

Keywords: Topiramate; Juvenile myoclonic epilepsy; Primary generalized epilepsy; Valproate

1. Introduction

Juvenile myoclonic epilepsy (JME) is one of the most common epilepsy syndromes. Yet data from well-controlled trials of antiepileptic drugs (AEDs) as monotherapy in JME are very limited, a deficiency noted in various efforts to develop evidence-based guidelines for epilepsy [1,2]. Based on open-label studies and nearly 30 years of clinical experience, valproate is widely regarded as the drug of choice in JME.

Evidence has accumulated that topiramate may also be effective in JME. Its multiple mechanisms of action [3–5] and activity in animal models of genetically determined generalized epilepsy [6] support clinical observations. Results from double-blind, randomized controlled trials have documented the efficacy of topiramate monotherapy in primary generalized tonic-clonic seizures (PGTCS) [7,8], with effects comparable to those of valproate [8]. In double-blind, placebo-controlled trials of topiramate as adjunctive therapy in treatment-resistant PGTCS [9], topiramate was effective in a subset of patients with JME [10]. However, the number of patients was too small to assess its effects on myoclonus, although it appeared that myoclonus was not aggravated.

We conducted an exploratory trial with blind randomization of adolescents/adults with JME to 26 weeks of open-label treatment with valproate or topiramate titrated to optimal response. Because these two agents have different

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side effect profiles, the relative side effect burden was quantified with toxicity rating scales patterned after those in the Veterans' Administration (VA) Cooperative Study [11].

2. Methods

Patients eligible for this 26-week randomized, parallel-group, open-label study were adolescents/adults (12–65 years old, ⩾25 kg) with a confirmed diagnosis of JME. Diagnostic criteria included myoclonic jerks, seizure onset at 8–26 years of age, and coexistent generalized tonic-clonic seizures with generalized epileptiform abnormalities on EEG consistent with JME. Patients had to have active epilepsy in the form of myoclonus or ⩾1 PGTCS in the 3 months before study entry. Topiramate or valproate could be initiated as monotherapy or as an adjunct to another AED (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy. Females of childbearing potential had to be premenarchal, physically incapable of bearing children, or practicing an acceptable method of contraception.

Exclusion criteria included previous discontinuation of topiramate or valproate due to an adverse event; abnormal cranial CT or MRI scan; dementia or mental retardation; progressive myoclonic epilepsy; clinically unstable medical conditions; history of nephrolithiasis; SGOT and/or SGPT levels greater than two times the upper limit of the normal range; co-therapy with a carbonic anhydrase inhibitor or barbiturate AED; and use of an experimental medication or device within 30 days of study entry.

A 14-week titration phase was followed by a 12-week maintenance phase. After blinded randomization in 2:1 ratio to topiramate or valproate, the assigned agent was titrated according to clinical response. Blinded randomization was achieved by providing study sites with individual envelopes containing medication assignments generated by computer. The patient, investigator, and pharmacist remained blinded to medication assignment until screening was completed and the envelope was opened.

The topiramate target dosage was 3–4 mg/kg/day (maximum, 9 mg/kg/day) for patients 12–16 years of age and 200 mg/day (maximum, 600 mg/day) for patients >16 years of age. Valproate target dosages were 10 mg/kg/day in patients 12–16 years of age and 750 mg/day in those >16 years (overall maximum, 60 mg/kg/day). Medications were titrated at 1- to 2-week intervals according to clinical response and were administered in divided doses. Topiramate was provided as 25- or 100-mg TOPAMAX tablets; valproate was provided as 125-, 250-, or 500-mg Depakote tablets.

Seizure counts were captured with seizure diaries maintained by patients and were reviewed at each study visit. Seizure data were used to calculate reduction from baseline monthly seizure frequency. Patient and investigator global evaluations of improvement (i.e., marked, moderate, minimal, none, or worse) in overall outcome, alertness, activities of daily living, seizure severity, interaction with patient's environment, and response to verbal requests were obtained at the final study visit.

Questionnaires assessing drug-related systemic toxicity and neurotoxicity (Table 1) were adapted from those used in the VA Cooperative Study [11] to reflect adverse effects commonly associated with valproate and topiramate treatment, as well as nonspecific central nervous system effects with AEDs in general. The questionnaires were completed at each post-baseline visit (4, 8, 14, and 26 weeks). For both scales, signs/symptoms were scored relative to the patient's prestudy condition, with higher scores corresponding to greater frequency/severity of treatment-emergent toxicity. The highest possible severity score for individual parameters was 50. Total scores ⩾10 were considered clinically significant. With respect to side effect scores: 10 indicated occasional vomiting, moderate weight gain/loss (7–12 pounds), mild tremor, occasional sleepiness during the day, or moderate impairment of cognitive function; 20–25, frequent vomiting, large weight gain/loss (18–18 pounds), moderate tremor, or difficulty staying awake; and 50, severe tremor, severe gait disturbance requiring assistance, stuporous, or severe cognitive impairment that interferes with all daily activities. Median scores for both scales were calculated at 4, 8, 14, and 26 weeks for each treatment group. The proportion of patients for whom toxicity scores were zero at each time interval was determined.

Table 1
Systemic toxicity and neurotoxicity assessment[a]

Systemic toxicity
Nausea, vomiting
Reduced platelet or white blood cell count
Hypersensitivity reactions
Impotence (libido or potency)
Hyponatremia
Liver disease/abnormal liver function tests
Weight gain/loss
Hair loss, texture changes, hirsutism
Neurotoxicity
Diplopia
Nystagmus
Dysarthria
Ataxia
Tremor
Sedation
Affect and mood
Attention/concentration
Language
Dizziness
Headache

[a] The questionnaires assessing drug-related systemic toxicity and neurotoxicity were patterned after those in the Veterans' Administration Cooperative Study [11].

3. Results

Baseline characteristics for patients randomized to topiramate and valproate are summarized in Table 2. Contrary to the protocol, two patients were receiving valproate at dosages that investigators considered suboptimal at study entry. One patient was randomized to topiramate; the other was randomized to valproate. Despite randomization, the topiramate group had a higher proportion of females as well as patients with PGTCS, and fewer patients receiving AED therapy at study entry. At study entry, 5 of 19 (26%) in the group assigned to topiramate and 2 of 9

Table 2
Baseline characteristics of randomized patients ($N = 28$)

	Topiramate ($N = 19$)	Valproate ($N = 9$)
Age	15 (9–42)[a]	16 (12–34)
Gender, female	13 (68%)	4 (44%)
Weight (kg)	66 (32–116)	72 (55–109)
Baseline seizure type		
Myoclonic	14 (74%)	9 (100%)
PGTCS	12 (63%)	4 (44%)
Absence	2 (11%)	2 (22%)
Baseline AED		
None	12 (63%)	4 (44%)
Carbamazepine	3 (16%)	0
Oxcarbazepine	1 (5%)	0
Phenytoin	1 (5%)	2 (22%)
Lamotrigine	1 (5%)	1 (11%)
Valproate	1 (5%)	1 (11%)
Ethosuximide	0	1 (11%)

[a] Data are given as median (range) or N (%).