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Role of topiramate in adults with intractable epilepsy, mental retardation, and developmental disabilities

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The efficacy and safety of topiramate in patients with intractable mixed seizures, mental retardation (MR), and developmental disabilities (DD) were investigated. Twenty patients (eight females and 12 males) aged 21–57 years old with intractable epilepsy with mixed seizures, MR [profound (five), severe (three), moderate (two), mild (eight) and borderline (two)], and DD were treated with adjunctive topiramate 25 mg per day for 1 week followed by titration to clinical response (range 50–350 mg per day). Other antiepileptic drugs (AEDs) were decreased simultaneously. Topiramate therapy was discontinued in four patients for adverse events consisting of disorientation, unsteadiness, and pneumonia (one patient); anaphylactic shock from a tuna fish allergy (one); patient choice (one); and loss to follow-up (one). Seizures improved by $\geqslant$50% in 11 of 16 patients (69%). Two patients (13%) were seizure free, including one patient who prior to topiramate therapy was seizure free but experiencing an intolerable adverse effect during therapy with another AED. Seizure duration and/or severity decreased in seven patients (44%). An increase in alertness was observed in 11 patients (59%). Topiramate was associated with improvement in seizure severity and alertness in this series and may be useful as adjunctive therapy in patients with mixed seizures, MR, and DD.

Key words: topiramate; epilepsy; mental retardation; developmental disabilities; seizures.

INTRODUCTION

Epilepsy is a co-existing neurological disorder in 40–50% of individuals with mental retardation (MR) and developmental disabilities (DD). Many of these patients have seizures that are not controlled satisfactorily with their current antiepileptic drug (AED) therapy. For example, in a chart review of 100 patients with MR, DD, and intractable seizures, we found that 40% of patients were still experiencing seizures despite treatment with two to three AEDs[1]. Thus, a substantial number of patients with MR and DD could benefit from improved seizure control.

Topiramate has been shown to be effective as adjunctive therapy in a wide range of seizure types, including partial-onset seizures[2–7], seizures associated with Lennox–Gastaut syndrome[8], and primary generalized tonic–clonic seizures[9]. Most commonly reported side effects in the double-blind adjunctive therapy trials in adults with refractory partial onset seizures were related to the central nervous system and included somnolence, dizziness, abnormal thinking, fatigue, ataxia, confusion, paresthesia and impaired concentration[10]. Most adverse events with topiramate tended to appear early in the course of treatment and to resolve with continuing therapy. Cognitive and CNS adverse effects may occur less frequently with a lower initial dose of topiramate and slower titration[11].

It is uncertain whether patients with underlying static CNS dysfunction may be more, or less susceptible to potential CNS-related side effects of AEDs, or whether cognitive function will improve as a result of improved seizure control, or a reduction of total AED requirements. This evaluation was undertaken to determine the usefulness of topiramate in individuals with intractable mixed seizures, MR, and DD.

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METHOD

Patients

Study patients were selected based on a chart review of 368 epilepsy patients who were ⩾21 years of age, had MR and DD, and were being treated at the neurology clinic of the Westchester Institute for Human Development. Severity of mental retardation was determined through a combination of IQ scores and psychological evaluation and was graded as profound, severe, moderate, mild, or borderline. Eligible patients had the following entry criteria: mixed seizures (i.e. mixed generalized seizures or mixed partial and generalized seizures) that were uncontrolled by treatment with standard or newer AEDs; or intolerable adverse effects with current AED therapy. Seizure episodes were classified according to guidelines for seizure classification of the International League Against Epilepsy[12]. Patients with a history of renal stones were excluded. The study protocol was approved by the institutional review board, and written informed consent was obtained from patients or their guardians prior to study entry.

Procedure

Topiramate therapy initially was given in addition to baseline AEDs at a dosage of 25 mg per day for 1 week. The topiramate dosage was then increased to a level that was dependent on seizure frequency and tolerability. Concomitant baseline AEDs were gradually withdrawn when appropriate. Based on data forms completed by patients and/or care givers, the following were monitored during topiramate therapy: seizure occurrence (time, type, and duration of seizures); adherence to AED therapy; adverse events; precipitants of seizures; and the number of emergency room visits and the treatment provided in the emergency room. At the final study visit, investigator's and patients' global evaluations of overall improvement were recorded. The investigator rated improvement as worse, none, minimal, moderate, or marked; and patients assessed their improvement as poor, fair, good, or excellent. Based on physician's evaluations during clinic visits and information from care givers, adverse events were determined. During study visits, patients and/or care givers were asked specifically about patient alertness. Clinical laboratory tests (i.e. AED plasma levels, CBC, and serum electrolytes) were performed during the first 2–4 weeks of topiramate therapy and then every 3 months thereafter.

RESULTS

Twenty patients (eight females and 12 males) entered the study and were treated with topiramate. Demographic characteristics of these patients are presented in Table 1. The age of the patients ranged from 21–57 years old. The level of mental retardation was: profound in five patients, severe in three, moderate in two, mild in eight, and borderline in two. The seizures experienced by these patients were uncontrolled on various combinations of phenytoin, carbamazepine, phenobarbital, primidone, lamotrigine, or divalproate sodium.

Table 1: Patient characteristics.

Variable	
N	20
Age	21–57 years
Gender	
Female	8
Male	12
Baseline seizure frequency	
Median	4.5/month
Range	0–20/month
Seizure type, N (%)	
Generalized tonic–clonic	19 (95%)
Partial complex	16 (80%)
Atonic	8 (40%)
Tonic	7 (35%)
Clonic	6 (30%)
Myoclonic	3 (15%)
Drop attacks	2 (10%)
Absence	1 (5%)
Mental retardation, N (%)	
Profound	5 (25%)
Severe	3 (15%)
Moderate	2 (10%)
Mild	8 (40%)
Borderline	2 (10%)
Baseline AEDs	
1 AED	5%
2 AEDs	55%
3 AEDs	40%

Four patients discontinued topiramate treatment during the study for reasons presented in Table 2. Among the 16 patients completing the trial, the mean dosage of topiramate was 189 mg per day (range 50–350 mg per day) and the mean duration of therapy was 42 weeks (range 20–54 weeks). Seizure frequency was reduced by ⩾50% in 11 of 16 patients (69%) and two patients were seizure free (13%) (Fig. 1). There was no change in seizure frequency in three patients, including one patient who was seizure-free at baseline (but experiencing intolerable adverse effects while on other AED therapy) and remained seizure-free during topiramate therapy, and seizures increased in two patients. Seizure duration and/or severity was reduced in seven patients (44%). Global evaluations of improvement were obtained in 18 patients. Based on investigator global evaluations, improvement was