Original Article

Efficacy and Safety of Topiramate in Refractory Epilepsy of Childhood: Long-Term Follow-Up Study

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ABSTRACT

This study aimed to evaluate the long-term efficacy and safety of topiramate in treating children with drug-resistant epilepsy. A multicentric, retrospective, open-label, add-on study was undertaken of 277 children (mean age 8.4 years; range 12 months to 16 years) affected by drug-resistant epilepsy. The efficacy was rated according to the seizure types and epilepsy syndrome. After a mean period of 27.5 months of treatment (range 24–61 months), 11 patients (4%) were seizure free and 56 (20%) had more than 50% reduction in seizure frequency. The efficacy of topiramate treatment was noted in localization-related epilepsy and in generalized epilepsy. In addition, in a group of 114 patients, we compared the initial efficacy (evaluated after a mean of 9 months of follow-up) and the retention at a mean of 30 months of topiramate with regard to loss of efficacy (defined as the return to the baseline seizure frequency). Fifty-five (48%) of 114 patients were initial responders. The retention at a mean of 30 months was 23 of 114 patients (20%), 4 of whom (3.5%) were still seizure free. A loss of efficacy occurred in 32 of the 55 initial responders (58%). It was prominent in patients with generalized epilepsy, such as symptomatic infantile spasms and Lennox-Gastaut syndrome, as well as in those with Dravet syndrome. By contrast, a well-sustained topiramate efficacy was noted among patients with localization-related epilepsy. Globally, adverse events were observed in 161 patients (58%) and were mainly represented by weight loss, hyperthermia, sedation, and nervousness, which, in most cases, disappeared after slowing titration or reducing the dosage of the drug. In conclusion, the present long-term study confirms that topiramate represents a useful drug effective in a wide range of seizures and epilepsy syndromes. Moreover, preliminary data seem to suggest that the efficacy of topiramate, when evaluated in the long-term perspective, is more sustained in localization-related epilepsy than in generalized epilepsy. (*J Child Neurol* 2005;20:893–897).

Topiramate is an antiepileptic drug with a broad range of antiseizure activity.[1] Indeed, it has been shown to be effective in partial-onset seizures[1–6] and generalized seizures.[7] The efficacy of topiramate in epilepsy syndromes has been proved in West syndrome,[8,9] myoclonic-astatic epilepsy,[10] and Dravet syndrome,[11] as well as in refractory status epilepticus.[12,13] Topiramate can also be helpful as add-on therapy in Lennox-Gastaut syndrome.[14–16] However, there are only a few studies on the long-term efficacy longer than 24 months of topiramate, in children in particular.

In the present open-label, retrospective, multicenter study, we evaluated the safety and the long-term efficacy longer than 24 months of topiramate in a series of children with drug-resistant epilepsy.

METHODS

The patients were recruited from eight Italian centers and selected according to the following criteria: (1) aged from 12 months to 16 years; (2) seizures refractory to at least two first-line antiepileptic drugs; (3) at least four seizures a month during the 3 months before topiramate was admin-

Received March 20, 2004. Received revised November 19, 2004. Accepted for publication December 28, 2004.

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istered; and (4) at least 24 months of follow-up. Family and personal histories were registered, and neurologic examinations were performed on all patients. In all patients, electroencephalograms (EEGs) and video-EEGs were recorded during wakefulness, spontaneous sleep, and arousal, with hyperventilation and photic stimulation. Seizures were classified in accordance with the International League Against Epilepsy classification of epileptic seizures[17] and epileptic syndromes.[18] All patients underwent brain magnetic resonance imaging. Biochemical analyses, chromosomal investigations, and screening for metabolic disorders were carried out in all patients. IQ was evaluated by the Brunet-Lézine test and by the Wechsler Intelligence Scale for Children-Revised (WISC-R), according to the age of the patient.

Patients

Two hundred seventy-seven patients (151 boys and 126 girls) of 471 patients fulfilled the clinical criteria and therefore entered the study. The mean age was 8.4 ± 5.6 years (range 12 months to 16 years). Mental retardation was present in 254 patients (92%) and was considered severe in 82, moderate in 113, and mild in 59. Ages at the onset of epilepsy ranged from 2 months to 13.5 years (mean 6.7 ± 3.6 years). The mean seizure frequency was 35 seizure/month (range 3–151), and the mean age at the first seizure was 6.8 years (range 0.6–14 years). The mean duration of the epilepsy history was 8.2 years (range 1–15 years). Epilepsy was symptomatic in 139 patients, cryptogenic in 99, and undetermined in 39 patients. Ninety patients were affected by generalized epilepsy, 110 patients by localization-related epilepsy, and 77 by an unclassifiable type of epilepsy (Table 1). In 44 patients, partial seizures evolved to secondary generalization. Overall, 103 patients had more than one type of seizure. Topiramate was added to the previous treatment in an open fashion on a "named patient basis." Seizure frequency, type, and duration were recorded by parents and caregivers over a period of 3 months before starting treatment with topiramate. The mean number of antiepileptic drugs tried before introducing topiramate treatment was 8 (range 2–13), whereas the number of antiepileptic drugs administered when the drug was instituted varied between 1 and 5 (median 2).

Treatment and Monitoring

Topiramate was administered at a daily dose of 0.5 to 1 mg/kg, followed by a week's increasing titration at increments of 1 to 3 mg/kg/day. The mean total daily dose was 6.2 mg/kg (range 1–12.5 mg/kg). However, in three infants with secondary infantile spasms, topiramate was administered up to a maximum of 16 mg/kg/day. High topiramate doses (600 mg/day) were also administered in two obese prepubertal girls. The presence of adverse events was obtained from parents at each control. When they occurred, the titration phase was prolonged on the basis of clinical conditions. During the treatment, in all patients, general clinical and neurologic examinations and EEG recording were performed every 4 to 6 months. Complete peripheral blood counts, urinary analysis, and determinations of blood creatinine level and alanine and aspartate aminotransferase levels were also performed.

Response

In comparison with the baseline seizure frequency and severity, the response to topiramate treatment was classified as follows: complete cessation (100% seizure control), very good (decrease in seizure frequency by 50–99%), minimal (less than 50% of seizure reduction with minimal change in seizure severity), unmodified (less than 20% of seizure reduction), or worsening (increase in seizure frequency). Patients with more than 50% reduction in seizure frequency were defined as responders.

Topiramate Retention at 30 Months

In a group of 114 patients (all followed up in only one center), the initial topiramate efficacy, defined as the number of responsive patients after a mean of 9 months of follow-up (range 7–10 months), was compared with the retention at 30 months of topiramate with respect to loss of efficacy. Retention at 30 months of topiramate, a composite of efficacy and adverse events in clinical practice, was defined as the percentage of patients still taking topiramate after a mean period of 30 months of follow-up (range 24–59 months). Loss of efficacy was defined as the return to the baseline seizure frequency.

Statistical Analysis

Statistical evaluation was performed by Fisher exact test, by analysis of variance (ANOVA), and by the two-tailed Wilcoxon rank sum test for nonparametric data.

RESULTS

Clinical follow-up ranged from 24 to 61 months (mean 27.5 months). The mean topiramate daily dose was 6.2 mg/kg (range 1–12.5 mg/kg/day).

Efficacy

Seventy-five (27%) children remained on topiramate therapy at the latest follow-up. In the remaining 202 patients, the drug had been tapered off because of inefficacy or the appearance of adverse events. In detail, 10 children (4%) became seizure free, 55 (20%) had

Table 1. Characteristics of Epilepsy Syndromes at Onset of Treatment and Efficacy of Topiramate

Epilepsy Syndromes	*No. of Patients*	*Responders/Seizure Free*
Localization-related epilepsy	110	34/6
Cryptogenic	45	18/4
Symptomatic	65	15/2
Generalized	90	22/4
Infantile spasms	24	9/1
Dravet syndrome	10	2/0
Myoclonic-astatic epilepsy	7	3/1
Myoclonic absence seizures	2	1/0
Cryptogenic generalized	7	2/1
Ohtahara syndrome	3	ND
Lennox-Gastaut syndrome	15	2/0
Myoclonic epilepsy	8	2/1
Symptomatic generalized	10	1/0
Others	4	ND
Unclassifiable	77	9/0

ND = no data available.

Table 2. Efficacy of Topiramate According to the Type of Seizure

Type of Seizure	*No. of Patients*	*No. With > 50% Seizure Reduction*
Complex partial	143	48
Simple partial	23	7
Atonic	18	2
Tonic	26	2
Generalized tonic-clonic	55	10
Myoclonic	59	6
Absence	61	5
Infantile spasms	24	8

a seizure reduction of more than 50%, and 97 (35%) had a 20 to 50% decline (in 10 of these patients, topiramate was continued because of the improvement in their cognitive abilities). In a further 88 patients (32%), seizure frequency remained unchanged, whereas 27 (10%) experienced an increase in the frequency of seizures. Therefore, 65 patients (23%) were still responders after a mean period of 27.5 months of follow-up as they presented with more than 50% reduction in their seizure frequency. Seizure reduction was demonstrated over a wide range of epilepsy syndrome (see Table 1) and seizure types (Table 2). Topiramate appeared to be more effective in localization-related (52% of responders) than in generalized epilepsy (34% of responders). In five patients, four affected by localization-related epilepsy and one by generalized epilepsy, topiramate monotherapy was successfully instituted because all of them were still seizure free at the last follow-up visit. In a further 22 children, one or more concomitant drugs were tapered off or reduced in dosage without affecting seizure frequency.

Topiramate Retention at 30 Months

The group of 114 patients was not different from the remaining patients in terms of age, sex, epilepsy history, seizure frequency, and the number of antiepileptic drugs administered (Wilcoxon rank sum test). Fifty-five patients (48%) were initial responders. The retention at 30 months was 23 of 114 patients (20%), of whom 4 (3.5%) were still seizure free. Fourteen of these patients (12%) were affected by localization-related epilepsy, eight (7%) by generalized epilepsy, and one (0.9%) by an unclassifiable type of epilepsy. A loss of efficacy occurred in 32 of the 55 initial responders (52%). In a further three initial responder patients, topiramate was discontinued, in spite of its efficacy, because of the occurrence of hyperthermia (one) and severe weight loss (two). According to epilepsy syndromes, loss of efficacy was less prominent in patients with localization-related epilepsy (50%) than in those with generalized epilepsy (62%). In the latter group, low rates of loss of efficacy were observed among patients with cryptogenic infantile spasms (25%). By contrast, high rates of loss of efficacy were observed in patients with symptomatic infantile spasms and Lennox-Gastaut syndrome, as well as in those affected by Dravet syndrome (Table 3).

Safety

Adverse events occurred in 161 patients (58% of the total commencing). In 31 patients, more than one side effect occurred. The most frequently reported treatment-related side effects were weight loss, anorexia, loss of appetite (84 patients), hyperthermia (48), drowsiness (41), behavior disturbances or aggressiveness (14), attention or concentration difficulty (11), spatiotemporal disorientation (2), and acute psychosis (6). Topiramate was ceased in a total of 22 patients (8%), including the 6 patients with acute psychosis, 11 patients with severe weight loss or anorexia, 3 patients with behavior disturbances or aggressiveness, and 2 patients with severe hyperthermia. All patients with acute psychosis were adolescent girls. All but one had previous behavior disturbances. Hyperthermia was observed only during summer months. It was severe (> 38.5°C) in the two cited patients, in whom topiramate was discontinued, and mild (around 37.5°C) in the remaining group. In the latter patients, hyperthermia disappeared after decreasing the dose of topiramate. No patient underwent pilocarpine iontophoresis sweat test production. However, other possible causes of fever were adequately excluded. When globally evaluated, side effects could be considered mild in severity, and they were resolved by slowing the rate of drug titration or reducing the topiramate dosage.

Table 3. Topiramate Efficacy According to Epilepsy Syndromes After a Mean Follow-Up Period of 9 and 30 Months, Respectively

Epilepsy Syndromes	*No. of Patients*	*After a Mean of 9 mo (R/SF)*	*After a Mean of 30 mo (R/SF)*	*Loss of Efficacy (%)*
Localization-related epilepsy	51	28/6	14/2	50
Cryptogenic	21	15/3	8/2	67
Symptomatic	30	13/3	6/0	54
Generalized	44	21/4	8/2	62
Infantile spasms				
Cryptogenic	5	4/1	3/1	25
Symptomatic	7	2/0	0/0	100
Dravet syndrome	7	5/1	1/0	80
Myoclonic-astatic epilepsy	2	2/1	1/1	50
Cryptogenic generalized	3	1/0	1/0	0
Lennox-Gastaut syndrome	7	3/0	0/0	100
Myoclonic epilepsy	5	3/0	1/0	67
Symptomatic generalized	8	1/1	1/0	0
Unclassifiable	19	6/0	1/0	83

R = responders; SF = seizure free.

In a group of 114 cases (all followed up in only one center), the patients' weights before topiramate therapy, expressed as standard deviation scores, and the type of drug combination (topiramate-carbamazepine against topiramate–valproic acid) of the 34 patients (30%) presenting with weight loss were compared with those of the remaining series of 80 patients (70%) who did not lose weight. Neither the weight standard deviation scores of patients before topiramate treatment ($P = .9$ by ANOVA) nor the drug combination ($P > .05$ by Fisher exact test) appeared to influence weight loss in our population (data not shown). There were no significant laboratory anomalies in terms of liver function, renal function, or hematologic tests. Symptoms compatible with renal stones, glaucoma, or hand desquamation and metabolic acidosis were not reported.

DISCUSSION

Controlled and long-term studies have demonstrated the efficacy of topiramate in a wide range of seizures and epilepsies.[1–3,6,7] Topiramate efficacy was also demonstrated in open-label and retrospective investigations, in which the proportion of responders (patients with > 50% of seizure reduction) was variable and mainly depended on the length of the follow-up period. Indeed, higher responsiveness rates (around 60% of patients) were observed in those studies with a short to medium follow-up period,[19–21] whereas lower responsiveness rates (around 30% of patients) were registered in those few long-term studies that included children.[22,23]

Of course, retrospective studies lack the rigor of the blinded studies,[24] but they might provide useful insight into the efficacy of a new antiepileptic drug. In fact, a new antiepileptic drug is not necessarily used in controlled trials in the same manner as it will be used in clinical practice. In addition, long-term, open-label studies in which antiepileptic drug dosages are adjusted to optimize patient response can also provide useful information about long-term response to a newer antiepileptic drug. The population we reported on here constituted pediatric patients with intractable epilepsy referred to tertiary centers for epilepsy cure. All patients in the present series were undergoing multiple drug therapy, and almost all were mentally retarded. It must be emphasized that our study population was heterogeneous in terms of seizure type, epilepsy syndrome, and etiology. It comprised children with intractable epilepsy who had received a mean of eight antiepileptic drugs and in whom topiramate was added to a median of two antiepileptic drugs. Clinical follow-up lasted a mean of 27.5 months. The data we found are compatible with those reported in studies with long-term follow-up.[22,23] Indeed, after a mean period of 27.5 months, 4% of patients were still seizure free and a further 20% still experienced a reduction of more than 50% in seizure frequency. In five patients, the other antiepileptic drugs were withdrawn, leaving them on topiramate monotherapy. In general terms, topiramate appeared to be effective in a wide range of seizure and epilepsy types.

In a group of 114 patients (all followed up in only one center), we compared the efficacy observed after a mean of 9 months of follow-up with the retention at 30 months of topiramate with regard to loss of efficacy. Globally, 23 of 144 patients (20%) were still responsive to topiramate after a mean of 30 months of follow-up. Loss of efficacy occurred in 32 of the 55 initial responders (58%). Interestingly, when loss of efficacy was evaluated according to epilepsy syndromes, high rates of loss of efficacy were mainly observed in patients affected by generalized epilepsy (62% of the initial responders), such as symptomatic infantile spasms, Lennox-Gastaut syndrome, and Dravet syndrome. By contrast, a well-sustained topiramate efficacy was noted in patients with localization-related epilepsy (see Table 3). Because comedication was not (or only little) changed before seizure relapsing, we suppose that the loss of efficacy in topiramate was related to the development of tolerance. Of course, it should be underlined that all children involved in the present study were affected by severe refractory epilepsy, in whom a mean of eight drugs administered before topiramate treatment had been ineffective. Moreover, further clinical studies are needed to validate our observations.

In the present study, we observed that 58% of patients experienced at least one adverse event. Therefore, the percentage was higher than that expected from the literature. According to Reith et al, this is probably related to the longer follow-up period than for previous studies.[25] In adults, the side effects of topiramate treatment are mainly represented by behavioral and cognitive difficulties.[26] By contrast, weight loss and sedation are the most common complaints in children.[3,14] In the open-label studies, the incidence of patients with weight loss was extremely variable, ranging from 6% to 14%[21,22] to around 40%.[20,23] The rates of anorexia or weight loss we observed were more similar to those reported by Moreland et al[20] and Uldall and Buchholt[23] because 30% of patients presented with these adverse events. As weight loss has been reported to be more frequent among patients with previous eating difficulties,[21] we compared in a group of 114 patients (all followed up in only one center) the weight of the patients (standard deviation scores) who had this side effect with the weight of those patients who did not and found no significant difference. Moreover, knowing the effects of valproic acid on appetite,[27] we also evaluated, in the same group of patients, the influence of the drug combination (topiramate-carbamazepine versus topiramate–valproic acid) on weight loss. No statistical differences were observed in drug combinations between patients with weight loss and the remaining population. To date, therefore, the significance of the controversial data regarding the incidence of weight loss in different studies,[11] considering the similar topiramate daily dosage used, remains unclear. On the other hand, fewer children presented with sedation and slow thinking in this series (14%). However, as in the other study,[11] it was difficult to evaluate the real incidence of such side effects because most of the patients were already mentally retarded. A severe adverse effect we observed in our population occurred in six adolescent girls who presented with acute psychosis-like symptoms. In one of them, aggression was associated with deep depression and suicidal thoughts. In all of them, the symptoms subsided after topiramate was withdrawn. A similar incidence of acute psychosis has already been reported in other extensive studies.[28,29] It is of interest that symptoms appear at low dosages and rapidly subside after topiramate discontinuation.[11,21,22] In addition, psychosis seems to occur in adolescent or adult patients and is uncommon in younger children. No ophthalmologic side effects, reported in previous studies,[30,31] have been observed in the present series of patients. However, no systematic instrumental investigations were performed. Moreover, hematochemical investigations detected no side effects deriving from the association of topiramate with valproic acid, as described elsewhere.[32,33] With respect to hypohydrosis and related hyperthermia, recent reports showed that up to 65% of patients submitted to topiramate therapy had reduced sweat quan-

tity under pilocarpine iontophoresis sweat test. However, only a minority of them were aware of heat intolerance.[34–36] It is very difficult to establish exactly the frequency of such an adverse event because it is directly related to the environmental temperature. In the present series, 23% of patients had hyperthermia, which was observed exclusively during summer months. In only two patients, hyperthermia was so severe that it prompted us to withdraw the drug. In the remaining group of patients, hyperthermia was mild (up to 37.5°C) and disappeared after decreasing the dosage of topiramate. In accordance with data previously reported in the literature, we noted that side effects can be resolved by slowing the rate of drug titration or reducing topiramate dosages.

In conclusion, topiramate treatment was demonstrated to be widely tolerated in children with drug-resistant seizures. When relating this to previously reported data, topiramate appears to be a potent antiepileptic drug effective against a broad spectrum of epilepsy syndromes. Moreover, preliminary data indicate that topiramate efficacy is more sustained in patients with localization-related epilepsy than in those affected by generalized epilepsy.

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