Original Article

Clinical Experience With Open-Label Topiramate Use in Infants Younger Than 2 Years of Age

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ABSTRACT

To assess the efficacy, safety, and tolerability of topiramate in infants younger than 24 months of age, we conducted an open-label, multicenter chart review study of infants who received topiramate. Twenty-eight patients were evaluated. All had refractory epilepsy. The mean age of seizure onset was 3.8 months (range 0–10 months). Refractory infantile spasms were the most common epilepsy syndrome. Among infants without infantile spasms, complex partial seizures were the prominent seizure type in eight, followed by simple partial seizures in six. Topiramate was prescribed as add-on therapy in 25 cases and as monotherapy in 3 cases. Seven of the eight infantile spasms cases improved on topiramate therapy, attaining topiramate monotherapy in three infants. Half of the infants with other seizure types responded to topiramate. The average treatment duration among topiramate responders was 11 months. Topiramate was prescribed after a mean of 3.3 antiepilepsy drugs had been used in these infants. In no case was topiramate the first prescribed antiepilepsy drug. Adverse effects occurred only in five patients, leading to topiramate discontinuation in two patients. Topiramate was efficacious and well tolerated in infants younger than 24 months of age with refractory epilepsy. Prospective data are needed to corroborate this observation. (*J Child Neurol* 2003;18:258–262).

Topiramate is a potent new antiepilepsy drug with a broad range of antiepileptic activity. Premarketing and early postmarketing controlled studies showed topiramate to be effective as adjunctive therapy against partial-onset and generalized tonic-clonic seizures in adults,[1–3] against partial seizures in children,[4] and in reducing drop attacks associated with the Lennox-Gastaut syndrome.[5] Data on clinical experience with topiramate use in infants and young children are scarce. With the exception of its use in infantile spasms,[6,7] reports on open-label topiramate therapy in children principally address older children and young adults.[8–10] Hence, there is little information on the safety, tolerability, and efficacy of topiramate in infants and young children. We review our clinical experience with open-label topiramate in patients younger than 2 years of age with refractory epilepsy.

METHOD

This review is based on clinical data obtained from five pediatric epilepsy clinics in Israel at tertiary referral centers in the Tel Aviv area and in Jerusalem. A multicenter chart review was performed on patients from birth to 24 months of age who received topiramate for epilepsy. General data recorded included demographic information on patients, significant medical and perinatal history, developmental status at the onset of topiramate therapy, epilepsy history and classification, previous antiepilepsy drug treatment, and neuroimaging and electroencephalographic (EEG) results. Regarding topiramate use, we documented the age at which topiramate was started, the time lapsed between the diagnosis of epilepsy and the introduction of topiramate, antiepilepsy drugs prescribed before and concomitantly, and the overall topiramate efficacy. The fashion in which topiramate was introduced (either as adjunctive therapy or as monotherapy) and whether the patient was eventually

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Table 1. Clinical Characteristics of 28 Infants and Young Children Treated With Topiramate

Patient No.	*Main Seizure Type*	*Etiology*	*Age at TPM Add-on (mo)*	*Number of Previous AEDs*	*Concomitant AEDs*	*Topiramate Duration (mo)*	*Efficacy*
1	Myoclonic	Unknown	19	5	LTG, CLNZ	5	–
2	Simple partial	Inversion chromosome 13	3	5	PB	3	+++
3	Complex partial	Unknown	7	5	PHT, PB, LTG, VGB	10	–
4	Tonic	Unknown	16	3	LTG, OXCBZ, K diet	7	++
5	Infantile spasms	Duplication X chromosome	7	5	ACTH, PHT, CLNZ	14	+++
6	Infantile spasms	Periventricular leukomalacia	12	1	VGB	6	++++
7	Simple partial	SMEI	7	3	CLNZ, VPA, PB	3	–
8	Infantile spasms	Periventricular leukomalacia	1	1	CLNZ	13	++++
9	Infantile spasms	Unknown	7	2	CLNZ, B_6	12	+++
10	Complex partial	Unknown	8	2	PB, CLNZ, CBZ, K diet	18	++
11	Complex partial	Unknown	19	3	VPA	11	++++
12	Myoclonic	Unknown	20	3	VPA	19	++++
13	Myoclonic	Unknown	1	3	PB, VGB, K diet	26	++
14	Simple partial	Unknown	4	1	PB	25	+++
15	Infantile spasms	Unknown	9	2	VGB	4	–
16	Simple partial	Unknown	7	4	VGB, B_6	3	–
17	Absence	Subdural hematoma	12	7	CLNZ, VPA, LTG	6	–
18	Complex partial	Tuberous sclerosis	8	4	None	4	+++
19	Infantile spasms	Tuberous sclerosis	12	1	VGB	18	++++
20	Complex partial	Temporal lobe lesion	5	1	PB	0.5±	–
21	Infantile spasms	MCA stroke	18	1	VGB	18	+++
22	Complex partial	Intrauterine ischemia	14	3	VPA, CLNZ	22	+++
23	Complex partial	White-matter disease	8	5	CLNZ, PHT	11	++
24	Complex partial	Microcephaly	9	9	VPA, B_6	2	–
25	Infantile spasms	Porencephalic cyst	6	5	VPA, B_6	24	+++
26	Simple partial	SMEI	12	3	None	3	++++
27	Simple partial	Meningitis/stroke	5	3	Midazolam, PB	1	++++
28	Myoclonic	HME	1	5	Midazolam, PB	2	–

Acute seizures ± seizure aggravation.
ACTH = corticotropin; AED = antiepilepsy drug; B_6 = pyridoxine; CBZ = carbamazepine; CLBZ = clobazam; CLNZ = clonazepam; HME = hemimeganencephaly; K diet = ketogenic diet; LTG = lamotrigine; OXCBZ = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; SMEI = severe myoclonic epilepsy of infancy; TPM = topiramate; VGB = vigabatrin; VPA = valproic acid.
Efficacy: ++++ = > 75% seizure reduction; +++ = 50–75%; ++ = 25–50%; – = 0–25%.

switched to topiramate monotherapy were also recorded. Clinical response to topiramate was based on the caregiver's reports for ambulatory patients and on staff reports for hospitalized infants. Response was classified as follows: very efficacious (more than 75% seizure reduction up to total seizure control), efficacious (between 50% and 75% seizure reduction), moderately efficacious (25–50%), and not efficacious (0–25%). Finally, adverse effects were noted, especially with regard to their effect on topiramate dosing or discontinuation.

RESULTS

Twenty-eight patients (15 girls, 13 boys) had received topiramate or were currently receiving topiramate at the time of the study. Age at onset of epilepsy ranged from the first month of life to 10 months of age (mean age 3.8 months). An epilepsy syndrome was established in 14 cases: 8 had infantile spasms and 2 had severe myoclonic epilepsy of infancy. In all, 15 infants experienced a significant improvement with topiramate and 9 patients showed no response, and in 1 case, seizure aggravation occurred on introducing topiramate. The main clinical data on all patients are depicted in Table 1.

Eight patients had infantile spasms as the main seizure type. Complex partial seizure was the prominent seizure type in seven cases, followed by simple partial seizures in six and myoclonic seizures in five. Secondary generalization occurred in six cases.

Seven of the patients with infantile spasms had symptomatic spasms and one had cryptogenic seizures. Topiramate was beneficial in six symptomatic cases and in the cryptogenic case. Spasm reduction was greater than 50% in all responders. Topiramate was added to at least one antiepilepsy drug in all cases. Corticotropin (ACTH) was administered to three patients: two infants who showed no response to ACTH improved on addition of topiramate; in the third case, ACTH was introduced after no response was seen with vigabatrin, pyridoxine, and topiramate. The clinical data on the eight infants with infantile spasms are presented in Table 2.

The etiology of chronic epilepsy was established in 14 cases: periventricular leukomalacia in 2 patients, chromosomal abnormalities in 2 cases, tuberous sclerosis in 2 patients, and intrauterine central nervous system insults in 2 cases. Microcephaly, previous stroke, white-matter disease, temporal lobe lesion, hemimegalencephaly, and trauma occurred in 1 patient each.

Nineteen patients had moderate to severe developmental delay. Two had mild impairment, and five were developmentally normal. One patient could not be assessed because he died at age 2 months and another patient because only a few weeks had elapsed since topiramate was pre-

Table 2. Clinical Response to Topiramate Among Infants With Infantile Spasms

Age at Infantile Spasms Onset (mo)	*Infantile Spasms Type*	*AEDs Prior to Topiramate*	*Duration of Infantile Spasms Prior to Topiramate Use (mo)*	*Topiramate Added to*	*Topiramate Monotherapy Attained?*	*Topiramate Efficacy*
4	Symptomatic	PB, B_6, VBG, CLNZ, ACTH	3	ACTH, CLNZ	No	+++
10	Symptomatic	CLNZ, VGB	2	VGB	Yes	++++
1	Symptomatic	VGB, CLNZ	1	CLNZ	No	++++
6	Cryptogenic	CLNZ, B_6	1	CLNZ	Yes	+++
5	Symptomatic	CLNZ, VGB	4	VGB	No	–
5	Symptomatic	VGB	7	VBG	No	++++
6	Symptomatic	VGB	12	VGB	Yes	+++
5	Symptomatic	VGB, B_6, ACTH, VPA	2	VPA	No	+++

ACTH = corticotropin; AED = antiepilepsy drug; B_6 = pyridoxine; CLNZ = clonazepam; PB = phenobarbital; VGB = vigabatrin; VPA = valproic acid.
Efficacy: ++++ = > 75% seizure reduction; +++ = 50–75%; ++ = 25–50%; – = 0–25%.

scribed for an acute central nervous system insult following a previously normal development.

Topiramate was prescribed as adjunctive therapy in 26 cases. It was the first add-on antiepilepsy drug in 6 patients. An average of 3.3 antiepilepsy drugs was prescribed before topiramate was added to the treatment. However, the mean number of antiepilepsy drugs previously received by topiramate responders was 2.7, compared with 4.5 antiepilepsy drugs for nonresponders. Topiramate was added on to a single antiepilepsy drug in 10 cases. Five of the seven patients with mainly complex partial seizures improved with the addition of topiramate, although only one had a > 75% reduction in seizure frequency. Among the six children with simple partial seizures as the predominant seizure type, one received topiramate via rapid titration up to 25 mg/kg/day for acute seizures owing to meningitis and stroke, another child had an over 50% reduction in seizure frequency on addition of topiramate to phenobarbital, and a third patient with severe myoclonic epilepsy of infancy became seizure free after topiramate was started as monotherapy following the discontinuation of his previous antiepilepsy drugs for video-EEG monitoring. With the exception of cases of infantile spasms, those patients with predominant myoclonic seizures responded poorly to topiramate: it had no effect in four patients and caused a < 50% seizure reduction in another infant.

Topiramate treatment period ranged from 2 weeks (in this patient, topiramate was discontinued owing to seizure aggravation) to 25 months. Topiramate efficacy was as follows: very efficacious in seven patients, efficacious in eight, and moderately efficacious in four. No response occurred in nine patients. The average daily dose of topiramate ranged between 6 and 12 mg/kg/day, with the exception of cases 27 and 28 (see below). Topiramate was introduced as monotherapy in three cases: one infant with infantile spasms (> 75% spasm reduction), one baby with tuberous sclerosis (50–75% seizure reduction), and the patient with severe myoclonic epilepsy of infancy described above (> 75% seizure reduction). Four children achieved topiramate monotherapy. Three patients went on to a ketogenic diet while receiving topiramate. No metabolic acidosis occurred in these patients, although the combination of topiramate and this diet was not very efficacious in these cases. Adverse effects, alone or combined, occurred in five children: anorexia and weight loss in two (topiramate discontinued in one case), seizure aggravation in two (discontinued), irritability in one, and drowsiness in one case.

Seizure aggravation occurred in two infants following the addition of topiramate: a patient with a right temporal lesion (of unknown etiology by the time of data collection) and predominantly complex partial seizures received topiramate as add-on therapy to phenobarbital. Following a rapid titration to 10 mg/kg/day, clusters of partial tonic seizures ensued, prompting topiramate discontinuation after 2 weeks of treatment. The second child suffered from myoclonic seizures and developmental delay of unclear etiology. Adding topiramate to lamotrigine and clonazepam resulted in an apparent worsening of the myoclonic jerks, which subsequently improved on topiramate discontinuation.

Two infants received topiramate in rapid titration (over 72 hours): case 27 was a 5-month-old girl with numerous bihemispheric seizures as a complication of pneumococcal meningitis and stroke. Her acute seizures were controlled with midazolam drip, intravenous phenytoin, and intravenous phenobarbital. At this stage, topiramate was introduced rapidly, reaching a daily dose of 22 mg/kg/day within 48 hours, thus allowing the discontinuation of all three parenteral medications. Case 28 involved a neonate with hemimegalencephaly and uncontrolled seizures who died at age 2 months. Topiramate was introduced after five other medications had failed to reduce his seizures. Topiramate in rapid titration to a high dose (25 mg/kg/day) had very little effect on seizure frequency.

DISCUSSION

Topiramate is currently approved in Israel for the treatment of patients older than 2 years of age with partial seizures and secondarily generalized seizures, as well as seizures associated with the Lennox-Gastaut syndrome. The recommended daily dose is 5 to 9 mg/kg.[8,10,11] Similar to findings in adult studies, topiramate was found to be effective in reducing partial seizures with and without secondary generalization in children aged 2 to 16 years (mean age 9

years).[4,12] It also appears to be highly effective against primary generalized tonic-clonic seizures in patients with juvenile myoclonic epilepsy.[13]

Data on topiramate use in infants and young children are scarce. Most available information relates to its role in infantile spasms. In a pilot study by Glauser et al, 5 of 11 children with long-standing, nonresponsive infantile spasms became spasm free during the initial 1 to 13 weeks of treatment.[14] Topiramate was added to their current antiepilepsy drug regimen using rapidly increasing doses up to 24 mg/kg/day. Of the 9 patients who improved with the addition of topiramate, 7 were able to achieve topiramate monotherapy. After an average follow-up of 18 months, 8 children were still receiving topiramate at a mean dose of 29 mg/kg/day. Four of these patients were spasm free, and 3 were receiving topiramate as monotherapy.[6] Herranz reported on his clinical experience with open-label topiramate use in 224 patients, children and adults.[7] Thirteen infants had West's syndrome; 4 were cryptogenic and 9 were symptomatic. Nine infants received topiramate as the first-line antiepilepsy drug at maximum doses of 16 mg/kg/day. Two patients became spasm free, and 7 had a more than 50% seizure reduction.[7] However, the author did not specify whether the infants treated initially with topiramate were the symptomatic ones or whether some of the cryptogenic patients also received topiramate as a first-line antiepilepsy drug. Because most of our patients had symptomatic infantile spasms, they received vigabatrin and/or clonazepam (sometimes with pyridoxine) prior to ACTH, in accordance with current practice in Europe.[15] We used topiramate in cases of refractory infantile spasms. It was efficacious in reducing spasms in 7 of the 8 patients. Moreover, topiramate monotherapy was attained in 3 cases.

Reports on topiramate efficacy in young infants with partial seizures are anecdotal.[16] Although the number of patients with predominantly partial-onset seizures in our study is small, half of them responded to topiramate therapy. Because all of our patients and the two cases reported by Kugler and Sachdeo[16] had refractory or catastrophic epilepsy, the true efficacy of topiramate in more benign forms of partial-onset epilepsy in infancy remains to be established.[17] Although the number of patients is small, it appears that combining topiramate with another γ-aminobutyric acid (GABA)ergic antiepilepsy drug was particularly effective in reducing partial seizures. Recently, it has been shown that antiepilepsy drug polytherapy based on mechanisms of action may enhance effectiveness. When monotherapy fails and two antiepilepsy drugs are needed, combining a sodium channel blocker with a drug that enhances GABA inhibition or combining two GABA mimetic drugs may be particularly useful.[18] Two of the known mechanisms of action of topiramate involve sodium channel blocking and enhancement of GABA inhibition. Hence, the increased effectiveness noted in our patients after adding topiramate to another GABAergic antiepilepsy drug may support these observations.

Response to topiramate appeared, in part, to be related to the etiology of epilepsy. Ten of the 14 patients in whom a chromosomal/structural cause was found showed more than 50% reduction in seizure occurrence after adding topiramate to their antiepilepsy drug treatment. Of the four patients who did not improve with topiramate, one patient had sustained multiple subdural hematomas months before, one patient had a right temporal lesion and experienced seizure aggravation on addition of topiramate, a third patient had congenital microcephaly of unknown cause, and the remaining patient had hemimegalencephaly. On the other hand, only about 50% of those patients with no established epilepsy etiology improved with topiramate. Of the two patients with severe myoclonic epilepsy of infancy, one patient had an excellent response to topiramate monotherapy, whereas the other patient had no benefit from the eight different antiepilepsy drugs, including topiramate.

In adults, topiramate may have a negative effect on cognition, particularly related to verbal abilities. This complication may be reduced or prevented by gradual introduction of the drug.[19] Although cognitive symptoms are the most common reason to discontinue topiramate, no specific patient population appears to be at a higher risk for these symptoms. However, most adult patients will continue topiramate therapy beyond 6 months.[20] On the other hand, children with a previous history of behavioral and cognitive problems are more likely to depict behavioral and cognitive deterioration during topiramate therapy. Moreover, the rate of dosage increase does not relate to the incidence of these abnormalities.[21] Most data on topiramate in children relate to its use in refractory epilepsy, which is frequently associated with cognitive deterioration (or primary disability) prior to topiramate prescription. Hence, the true quantitative and qualitative effects of topiramate on cognition in intellectually normal children are unknown. Our study also fails to address this issue, inasmuch as the vast majority of our patients were developmentally delayed. Although cognitive function was not assessed in this retrospective series, adverse psychomotor effects were uncommon and did not lead to topiramate discontinuation.

Topiramate was generally well tolerated. Anorexia/weight loss and central nervous system symptoms are the most common adverse effects described in children.[22] In our series, however, the incidence of central nervous system complications (one case of drowsiness and one case of irritability) was low and did not lead to topiramate dosage reduction. There are, nevertheless, important questions regarding the true central nervous system effect of topiramate on our study population: because most patients were cognitively impaired, it is possible that, in some cases, mild to moderate changes in alertness may have been missed or misinterpreted. Furthermore, the fact that most children were receiving antiepilepsy drug polytherapy, which may induce central nervous system changes, may have masked topiramate-related central nervous system symptoms.

Seizure aggravation during topiramate therapy was not described in prospective, long-term studies in adults and children.[12,23–25] Uldall and Buchholt reported 4 cases of seizure aggravation during topiramate therapy in a retrospective

series of 39 children with intractable epilepsy. However, the authors provided no clinical details on these 4 children.[8] Seizure aggravation by antiepilepsy drugs is a well-known complication of drug therapy in epileptic patients. It is more likely to go unrecognized in patients with refractory epilepsy and multiple seizure types and in those receiving antiepilepsy drug polytherapy. Reasons for seizure aggravation include antiepilepsy drug overdosage, encephalopathy induced by the antiepilepsy, inappropriate indication, paradoxical reaction, and polytherapy. Moreover, some seizure types are more prone to be worsened by certain antiepilepsy drugs, such as absence seizure aggravation by carbamazepine or phenytoin.[26,27] Because the only reported cases of topiramate-associated seizure worsening involve patients in retrospective series, it is possible that some of these cases may actually represent an unrelated clinical deterioration in these patients. Nevertheless, in our two infants with seizure aggravation, abrupt discontinuation of topiramate was followed by disappearance of the new seizure type in one case and reduction in myoclonic jerks in the second patient. Hence, we believe that topiramate did worsen seizures in these children.

Topiramate was safe, well tolerated, and efficacious in this series of 28 infants. In concordance with available clinical data, topiramate was effective against a broad range of seizure types. In particular, it was useful in refractory infantile spasms. Because this is a retrospective study, our conclusions, however, cannot be considered definitive. Prospective, controlled studies on topiramate use in infancy are necessary to corroborate these observations. Furthermore, most data available on topiramate involve its use in refractory epilepsy and, in children in particular, patients with developmental or cognitive disabilities. Therefore, its role in developmentally normal children with less malignant epilepsies remains to be established.

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