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Topiramate in the treatment of severe myoclonic epilepsy in infancy

M. NIETO-BARRERA, R. CANDAU, M. NIETO-JIMENEZ, A. CORREA & L. RUIZ DEL PORTAL

Paediatric Neurology Unit, Hospital Infantil Universitario "Virgen del Rocio", Sevilla, Spain

The aim of this study was to assess the effectiveness of topiramate (TPM) as an add-on regimen in reducing seizure rate in a population sample of patients diagnosed with severe myoclonic epilepsy in infancy (SME). Eighteen patients were evaluated. The mean observation time was 10.5 months (range, 6–18 months). Seizure frequency and type were recorded. Topiramate was administered as an add-on regimen at a starting dose of 1 mg kg^{-1} and titrated to a maximum of 6–8 mg per kg per day. Different escalation rates were used, mainly weekly or fortnightly increments of dose. Three patients (16.6%) became seizure free, and 10 (55.6%) had a >50% reduction in seizure frequency: six of them (22.2%) achieved a reduction greater than 75%. Side-effects were observed in nine patients, eight with a weekly titration schedule and one with a fortnightly schedule. TPM is effective as adjunctive therapy for SME. Side-effects were mild and transient, generally related to rapid dosage titration.

Key words: severe myoclonic epilepsy; epilepsy of infancy; topiramate; antiepileptic drugs.

INTRODUCTION

Severe myoclonic epilepsy in infancy (SME) is a rare epileptic syndrome first defined by Dravet *et al.* in 1982[1] and included as a syndrome in the International Classification of Epilepsy and Epileptic Syndromes (ICE) in 1989 under the heading of epileptic syndromes undetermined as to whether they are focal or generalized[2]. This type of epilepsy is very resistant to all forms of treatment including steroids. A transient response was observed with intravenous immunoglobulin (IVIG) therapy[3]. Topiramate (TPM) is a new antiepileptic drug with multiple mechanisms of action and a broad therapeutic spectrum[4–6]. Data from a recent meta-analysis suggested that TPM was possibly one of the most potent new drugs[7]. Indeed, TPM is effective in the treatment of partial refractory epilepsies[8–10], and in severe epileptic syndromes such as Lennox–Gastaut syndrome[11,12] and Infantile Spasms[13]. We report our observations of TPM therapy in a group of patients with SME refractory to various treatments.

MATERIALS AND METHODS

From October 1984 to October 1998 we collected 18 patients. The group of patients included eight males and 10 females with ages ranging from 2 to 22 years (mean age, 13.3 years) diagnosed with SME according to the following criteria[14]: (1) no past medical history, (2) seizure onset in the first year of life, usually as atypical febrile convulsions, or generalized clonic seizures, (3) myoclonic, and/or partial and/or atypical absence seizures between 2 and 4 years of age, (4) a normal interictal EEG at the beginning, (5) EEG recordings within the second year of life showing interictal generalized spike-and-wave complexes and/or photosensitive generalized polyspikes. Focal background anomalies may be present as well, and (6) normal initial psychomotor development which became delayed from the second year. Family history of epilepsy or refractoriness to anticonvulsant therapy also contributes to the diagnosis. Diagnosis was made retrospectively in seven patients and prospectively in 11.

All patients were considered refractory having been treated with a mean of 6.7 AEDs (range, 3–8). Eight patients were treated with IVIG and the other two with adrenocorticotropic hormone (ACTH). All patients were in pharmacological treatment at the time of the study with one or several antiepileptic drugs (AEDs) (median, 2.2 AEDs). Three patients were on single-drug therapy, nine on double therapy, five on triple therapy, and one received four drugs. During a 3-month period this treatment was unchanged and

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Table 1: Demographics. Seizure number, types, and previous treatments.

No	Age	S	Age 1st Seizure	1st seizure type	Actual seizures	Neuropsychological status	Previous AEDs
1	4 yr 4 mo	M	6 mo	FS unilateral	GTCS	MR moderate	VPA
2	5 yr 2 mo	F	6 mo	FS GTC prolonged	GTCS ABS	MR moderate	VPA CLB
3	14 yr	M	7 mo	FS GTC prolonged	GTCS	MR mild	VPA CLB
4	12 yr	F	5 mo	FS unilateral	GTCS	MR severe Hypotonia	VPA PRM LTG
5	15 yr	F	5 mo	FS unilateral	CPS	MR mild	VPA CLB
6	17 yr	M	5 mo	GTC prolonged	GTCS MYOCL	MR severe Hypotonia	PB LTG DPZ
7	3 yr 10 mo	M	6 mo	FS unilateral	GTCS ABS	MR moderate	VPA
8	22 yr	F	4 mo	FS unilateral	GTCS	MR severe	PRM LTG
9	3 yr 9 mo	M	5 mo	FS GTC prolonged	GTCS CPS	MR mild	VPA CZP
10	22 yr	F	3 mo	FS unilateral	GTCS SPS unilateral ABS MYOCL	MR moderate Hypotonia	VPA PB CBZ
11	18 yr	F	5 mo	GTC prolonged	GTCS ABS	MR severe	VPA CLB
12	2 yr 8 mo	M	7 mo	FS GTC prolonged	GTCS	MR mild	VPA
13	17 yr	F	4 mo	FS unilateral	GTCS CPS	MR severe	PRM VGB CLB
14	22 yr	M	4 mo	FS unilateral	GTCS CPS	MR moderate	VPA CLB
15	22 yr	F	5 mo	FS unilateral	CPS	MR severe Hypotonia	VPA LTG CZP PB
16	2 yr 3 mo	M	4 mo	FS unilateral	GTCS	MR mild	VPA PRM
17	14 yr	F	5 mo	FS GTC prolonged	GTCS CPS	MR severe	VPA PRM CZP
18	9 yr 5 mo	F	7 mo	FS GTC prolonged	CPS ABS	MR moderate	VPA PRM

Abbreviations: ABS, absence seizure; CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure; CZP, clonazepam; DZP, diazepam; F, female; FS, febrile seizure; GTCS, generalized tonic–clonic seizure; LTG, lamotrigine; M, male; MYOCL, myoclonic seizure; MR, mentally retarded; PRM, primidone; PB, phenobarbital; SPS, simple partial seizure; VPA, valproate; VGB, vigabatrin.

seizure frequency and type were recorded. Treatment was optimized when TPM was initiated. Demographics and clinical situation prior to TPM are shown in Table 1.

Three types of titration schedules were performed. In five cases the schedule was started with 0.5–1 mg kg^{-1}, and the dose was doubled every week. In four cases a starting dose of 1 mg kg^{-1} was followed by weekly increments of 1 mg kg^{-1}. In nine cases the schedule was started with 1 mg kg^{-1} and increased by 1 mg kg^{-1} every 2 weeks for 12 weeks. The maximum dosage in all cases was 6–8 mg kg^{-1}. Seizure rate and types, adverse effects and EEG findings were noted during the titration stage and the subsequent follow-up ranging from 6 to 18 months (mean, 10.5 months). Assessment of efficacy is essentially based on a reduction in seizure rate greater than 50%, but seizure suppression and reductions greater than 75% were separate for the analysis.

RESULTS

Before treatment eight patients presented only one type of seizure, 10 had two types and one patient had four seizure types. Generalized tonic–clonic seizures were the most frequent type being present in 15 patients, eight patients had partial seizures (mainly partial motor seizures), five patients had atypical absences and three patients had myoclonic seizures. Seizure frequency varied between 1 and 32 per month. Table 2 specifies seizure type, number, and EEG find-

Table 2: Observation period pre-topiramate treatment.

No	Weight (kg)	Actual seizures	No seizures in prior 3 mo	EEG before TPM	AEDs prior to TPM
1	22	GTCS	4	Generalized slow S-W	VPA 41 mg kg^{-1}
2	24.5	GTCS	11	Generalized slow S-W &	VPA 30 mg kg^{-1}
		ABS	>100	PS	CLB 0.5 mg kg^{-1}
3	36.5	GTCS	90	Generalized slow S-W &	VPA 75 mg kg^{-1}
				PS	CLB 1 mg kg^{-1}
4	46	GTCS	4	Generalized slow S-W &	VPA 18 mg kg^{-1}
				PS	PRM 8 mg kg^{-1}
					LTG 4.5 mg kg^{-1}
5	43	CPS	7	Generalized slow S-W &	VPA 30 mg kg^{-1}
				PS	CLB 0.3 mg kg^{-1}
6	59	GTCS	30	Generalized slow S-W&	PB 5 mg kg^{-1}
		MYOCL	>100	PS	LTG 5 mg kg^{-1}
					DPZ 0.5 mg kg^{-1}
7	22.5	GTCS	3	Generalized slow S-W &	VPA 66 mg kg^{-1}
		ABS	12	PS	
8	45	GTCS	83	Slow S-W predominantly	PRM16 mg kg^{-1}
				left hemisphere	LTG 9 mg kg^{-1}
9	14	GTCS	7	Slow S-W predominantly	VPA 10 mg kg^{-1}
		CPS	30	right hemisphere	CZP 0.1 mg kg^{-1}
10	55	GTCS	20	Generalized slow S-W &	VPA 18 mg kg^{-1}
		SPS unilateral	3	PS	PB 1.8 mg kg^{-1}
		ABS	10		CBZ 12 mg kg^{-1}
		MYOCL	90		
11	53	GTCS	78	Slow S-W predominantly	VPA 38 mg kg^{-1}
		ABS	6	right hemisphere	CLB 0.25 mg kg^{-1}
12	14	GTCS	9	Generalized slow S-W	VPA 40 mg kg^{-1}
13	48	GTCS	3	Slow S-W predominantly	PRM 10 mg kg^{-1}
		CPS	15	left hemisphere	VGB 52 mg kg^{-1}
					CLB 1 mg kg^{-1}
14	82	GTCS	12	Generalized slow S-W	VPA 18.2 mg kg^{-1}
		CPS	3		CLB 0.2 mg kg^{-1}
15	80	CPS	9	Generalized slow S-W	VPA 22 mg kg^{-1}
					LTG 5 mg kg^{-1}
					CZP 0.1 mg kg^{-1}
					PB 2 mg kg^{-1}
16	12	GTCS	6	Generalized slow S-W	VPA 30 mg kg^{-1}
					PRM 15 mg kg^{-1}
17	54	GTCS	90	Slow S-W predominantly	VPA 30 mg kg^{-1}
		CPS	5	left hemisphere	PRM 5 mg kg^{-1}
					CZP 0.1 mg kg^{-1}
18	42	CPS	6	Generalized slow S-W	VPA 38.5 mg kg^{-1}
		ABS	>100		PRM 6 mg kg^{-1}

Abbreviations: ABS, absence seizure; CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure; CZP, clonazepam; DZP, diazepam; FS, febrile seizure; GTCS, generalized tonic–clonic seizure; LTG, lamotrigine; MYOCL, myoclonic seizure; PB, phenobarbital; PRM, primidone; PS, polyspikes; SPS, simple partial seizure; S-W, spike-and-wave; VPA, valproate; VGB, vigabatrin.

ings in every case.

When topiramate was added, 14 patients were on valproate, three on monotherapy. At the end of the study, 72% of patients reached a >50% reduction in seizure rate, 50% had a reduction rate >75% and 16.6% were seizure free. Table 3 shows results during TPM therapy. All these patients started to improve from the titration period. Figure 1 presents response rate by seizure type. Response was slightly better in partial than in generalized seizures. The most dramatic response was with atypical absence seizures in which a total response rate was achieved. A better response rate was observed if the patient had one type of seizure or a combination of partial or generalized with atypical absence seizures. Response to TPM has no apparent relationship with the titration schedule, the maximal dose or time since diagnosis.

Adverse effects were observed mainly during the fourth and sixth weeks of treatment. Usually these were minor and lasted 10–14 days except for weight loss, which persisted longer. These occurred in most cases with a weekly increase and exceptionally when the dose was increased every fortnight. In no case was TPM withdrawn.

Table 3: Topiramate treatment. Results.

No.	TPM start dose	Scalation type	No seizures during first 2 months	Maintenance doses	AEDs associated	Follow-up time	Actual state	Adverse effects
1	25 mg 1 mg kg^{-1}	A	0	200	VPA 41 mg kg^{-1}	12	1 per 3 mo Red >75%	Somnolence Weight loss Motor incoordination
2	25 mg 1 mg kg^{-1}	A	5 GTCS >100 ABS	200	VPA 40 mg kg^{-1}	12	1 per mo Red >50%	Somnolence Weight loss Midriasis
3	25 mg 0.7 mg kg^{-1}	A	5 GTCS 39 CPS	200	VPA 27 mg kg^{-1}	12	30 per mo No effect	Anorexia Restlessness Impulsivity
4	25 mg 0.5 mg kg^{-1}	A	4 GTCS	400	PRM 8 mg kg^{-1} LTG 4.5 mg kg^{-1}	12	1 per day Increment seizure rate	Anorexia Weight loss Somnolence
5	25 mg 0.5 mg kg^{-1}	A	0	400	VPA 30 mg kg^{-1}	12	Seizure free	Drooling Apathic
6	50 mg 1 mg kg^{-1}	B	20 GTCS 60 MYOCL	400	PB 5 mg kg^{-1} DPZ 0.5 mg kg^{-1}	12	10 per mo No effect	Anorexia Somnolence Sphincter incontinence
7	25 mg 1 mg kg^{-1}	B	2 GTCS	150	VPA 66.6 mg kg^{-1}	12	Seizure free	Weight loss Anorexia
8	50 mg 21 mg kg^{-1}	B	36 GTCS	600	PRM 16 mg kg^{-1}	10	13 per mo Red >50%	Apathic
9	12.5 mg 1 mg kg^{-1}	B	10 GTCS 7 CPS	150	VPA 15 mg kg^{-1} CZP 0.1 mg kg^{-1}	8	1–2 per mo Red >75%	—
10	50 mg 1 mg kg^{-1}	C	5 GTCS 10 MYOCL	500	VPA 18 mg kg^{-1} CBZ 16 mg kg^{-1}	18	3–4 per mo Red >50%	—
11	100 mg 2 mg kg^{-1}	C	6 GTCS 8 ABS	500	VPA 38 mg kg^{-1} CLB 0.25 mg kg^{-1}	18	1–2 per mo Red >75%	—
12	12.5 mg 1 mg kg^{-1}	C	2 GTCS	100	VPA 40 mg kg^{-1}	14	1–2 per mo Red >75%	—
13	50 mg 1 mg kg^{-1}	C	3 GTCS 0 CPS	350	PRM 10 mg kg^{-1} CLB 1 mg kg^{-1}	7	1 per 7 mo Red >75%	—
14	50 mg 0.6 mg kg^{-1}	C	1 GTCS 2 CPS	400	VPA 18.2 mg kg^{-1} CLB 0.2 mg kg^{-1}	7	1 per wk Red >25%	—
15	50 mg 0.75 mg kg^{-1}	C	3 CPS	400	VPA 20 mg kg^{-1} LTG 2.5 mg kg^{-1}	6	1–2 per mo Red >50%	—
16	12.5 mg 1 mg kg^{-1}	C	3 GTCS	100	VPA 25 mg kg^{-1} PRM 15 mg kg^{-1}	6	1 per mo Red >25%	Somnolence
17	50 mg 1 mg kg^{-1}	C	20 GTCS 2 CPS	400	VPA 30 mg kg^{-1} PRM 5 mg kg^{-1}	6	1–2 per mo Red >75%	—
18	25 mg 0.6 mg kg^{-1}	C	1 CPS 25 ABS	200	VPA 38.5 mg kg^{-1} PRM 6 mg kg^{-1}	6	Seizure free	—

Titration schedule: A, doubling starting dose every week; B, increasing dose by 1 mg per kg of body weight every week; C, increasing dose by 1 mg per kg of body weight every 2 weeks.
Abbreviations: ABS, absence seizure; CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure; CZP, clonazepam; DZP, diazepam; GTCS, generalized tonic–clonic seizure; LTG, lamotrigine; MYOCL, myoclonic seizure; PB, phenobarbital; PRM, primidone; SPS, simple partial seizure; VPA, valproate.

DISCUSSION

Virtually all AEDs have been used in the treatment of SME usually with no clear results. Generally, valproic acid (VPA) is considered to be the most effective, though its actual efficacy has not been confirmed. Among newer AEDs, vigabatrin increased myoclonic seizures and lamotrigine has no significant effects, though it has been reported that it can increase seizures[15]. The use of IVIG at 100–200 mg kg^{-1} every 15 days to a total of six doses substantially improved the outcome of seizures in 30% of cases[3]. Improvement after puberty has been described[16] but not found in our series. Topiramate is the first oral AED that achieved a significant reduction in the number of seizures. Burkart *et al.*[17] reported 10% of patients becoming seizure free and 60% of patients showing a 50% reduction in seizure rate. These results were slightly worse than ours (16% and 72%, respectively).

Improvement was evident during dose escalation in 30% of the cases and in the stabilization stage in the

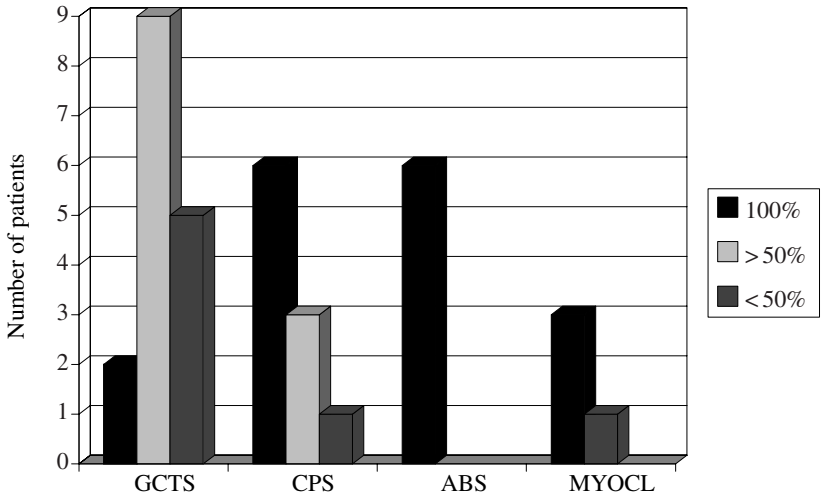

Fig. 1: Response rate by seizure type. Abbreviations: ABS, absence seizure; CPS, complex partial seizure; GTCS, generalized tonic–clonic seizure; MYOCL, myoclonic seizure; SPS, simple partial seizure.

rest. Adverse effects were moderate and transient.

This retrospective study suggests that TPM may be effective in the treatment of SME in infancy and has a specific role in the management of this epilepsy syndrome.

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