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Sulthiame add-on therapy in children with Lennox-Gastaut syndrome: A study of 44 patients

Roberto H. Caraballo[a,*], Santiago Flesler[a], Gabriela Reyes Valenzuela[a], Sebastian Fortini[b], Santiago Chacón[c], Lucas Ross[d], Daniel Noli[e]

[a] Hospital de Pediatría "Prof. Dr. Juan P Garrahan", Buenos Aires, Argentina
[b] Hospital del Niño Jesús, Tucuman, Argentina
[c] Hospital Centenario, Gualeguaychú, EntreRios, Argentina
[d] Sanatorio Allende Cerro, Córdoba, Argentina
[e] Hospital de Pediatría A Fleming, Mendoza, Argentina

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ABSTRACT

Purpose: The aim of this study was to evaluate efficacy and tolerability of sulthiame as an add-on treatment in 44 patients with Lennox-Gastaut syndrome (LGS) refractory to other antiepileptic drugs and/or non-pharmacological treatment.

Methods: Patients were selected according to the following criteria: (1) age 4 years or older, (2) a diagnosis of LGS refractory to at least four previous antiepileptic drugs, alone or in combination.

Neurologic examinations, brain magnetic resonance imaging, and repeated prolonged electroencephalography (EEG) or video-EEG studies were performed in all cases. Data on school achievements and/or neuropsychological evaluations were obtained during the follow-up of 1–3 years. Sulthiame was added in doses ranging from 5 to 30 mg/kg/day.

Results: Twenty-seven of 44 patients (61%) who received sulthiame as add-on therapy had a greater than 50% seizure decrease after a mean follow-up period of 20 months. Complete seizure freedom was achieved in one patient (2%). Four patients (9%) had a 25–50% seizure decrease, while seizure frequency remained unchanged in 12 (25%), and was increased in one (2%). Hyperpnoea and dyspnoea were observed in four patients, and nausea, drowsiness, and headache were seen in one patient each; however, these manifestations were transient and discontinuation of sulthiame was not necessary. Two other patients had decreased appetite, skin rash, and irritability. The adverse effects were mild and transient in these nine cases.

Conclusion: Sulthiame as an adjunctive therapy achieved a more than 50% seizure reduction in 27 of 44 patients with LGS with only mild or moderate adverse effects.

1. Introduction

Lennox-Gastaut syndrome (LGS) is a paediatric epilepsy syndrome described as a triad consisting of multiple seizure types, such as tonic –mostly occurring at night–, atonic, and atypical absence seizures, intellectual disability or regression, and abnormal electroencephalography (EEG) findings with a symptom onset before 12–24 months of age [1]. The EEG abnormalities consist primarily of an interictal pattern of diffuse, slow spike-wave complexes at 2.5 Hz during wakefulness and paroxysmal fast rhythms (10–20 Hz) during sleep, mainly in the non-rapid eye movement phase, which is the hallmark of tonic seizures [1].

There is no biological marker for LGS and its aetiology may be genetic, structural, or of unknown cause in around 25–30% of the cases [2,3].

Valproic acid is still considered as the first-line treatment for patients with *de novo* LGS. If ineffective, clobazam, lamotrigine or rufinamide may be added as adjunctive therapy. If seizure control remains inadequate, the choice of the next adjunctive antiepileptic drug (AED) should be evaluated for each case [3].

AEDs can be used together with non-pharmacological therapies, including the ketogenic diet (KD), callosotomy, and vagus nerve stimulation (VNS). The KD has been found to work particularly well in patients with LGS of unknown cause [4]. Recently, cannabidiol has been shown to be effective as an adjunctive therapy in LGS patients [5].

Sulthiame (STM) acts as a membrane-permeant carbonic anhydrase

* Corresponding author at: Neurology Department, Hospital de Pediatría "Prof. Dr. Juan P Garrahan, Combate de los Pozos 1881, Buenos Aires, Argentina.
E-mail address: rhcaraballo@arnet.com.ar (R.H. Caraballo).

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inhibitor with a beneficial effect on epileptiform activity, which results, at least in part, from a modest intracellular acidosis of central neurons [6]. STM has also been shown to inhibit voltage-gated sodium channels [6].

In the 1980s, the German child neurologist Hermann Doose found STM to be effective in benign focal epilepsies of childhood [7] and since then the drug has been used in sporadic cases [8,9]. Subsequently, STM was used in epileptic encephalopathies with continuous spikes and waves [10].

LGS is one of the childhood epileptic encephalopathies known to be particularly refractory to AEDs and non-pharmacological therapies. Based on the efficacy of STM in focal as well as other types of seizures, in 2010 our group started to use the drug in patients with refractory LSG.

The aim of this study was to evaluate efficacy and tolerability of STM as add-on treatment in 44 patients with LGS, who were refractory to other AEDs and/or non-pharmacological treatment.

2. Material and methods

Medical records of 53 patients with LGS treated with add-on STM seen at six paediatric neurology centres in Argentina between May 2015 and March 2018 were retrospectively analysed. The patients were enrolled at each centre on an intention-to-treat basis and entered into their respective databases.

Inclusion criteria were: (1) age 4 years or older, and (2) a diagnosis of LGS refractory to at least four previous AEDs, alone or in combination. Informed consent was obtained from the parents and/or caregivers of all the patients. The study was approved by the Institutional Review Board of each centre.

Exclusion criteria were other epileptic encephalopathies (e.g., epileptic encephalopathy with continuous spikes and waves) and focal epilepsy with secondary bilateral synchrony that did not fulfil criteria for LGS, as well as progressive neurological or systemic disease. Patients with abnormal liver, kidney, or blood laboratory tests were also excluded.

The diagnosis of LGS was made based on the ILAE classification considering polymorphous seizures including tonic–axial, atonic, and absence seizures, as well as other seizure types such as myoclonic, generalized tonic–clonic, or partial seizures, (2) abnormal background activity, slow spike-wave discharges, and episodic fast activity during sleep on the EEG, and (3) intellectual disability [11,12].

The parents and/or caregivers had kept an epilepsy diary to record seizures occurring at home and at school. At each follow-up visit, seizure frequency, type, and duration were evaluated. The seizures were classified according to the International League against Epilepsy Revised Classification of Seizures [13,14]. Improvements on the EEG was evaluated by the treating neurologist based on a more or less than 50% reduction of the slow spike-waves, diffuse fast rhythms, and multifocal spikes, mainly during the maximum sleep stage on a video-EEG recording of at least 2 h. EEG abnormalities were quantitatively assessed before and after STM initiation; however, due to the retrospective nature of the study, no systematic mathematical and statistical analysis could be performed [15].

All patients had received more than four other AEDs before STM was added in doses ranging from 5 to 30 mg/kg/day. STM was titrated over a period of 3 to 8 weeks starting at a dose of 100 mg/day up to a maximum dose of 800 mg/day. The average STM dose was 20 mg/kg/day in patients with a structural and 15 mg/kg/day in patients with an unknown aetiology. The dose was established based on the initial clinical and EEG response and tolerability. After STM initiation, concomitant AEDs were not modified and no other AEDs were started. In the 16 patients with VNS, setting parameters remained unchanged.

Efficacy was assessed by comparing seizure frequency before and after initiating STM therapy. Response to treatment was defined as (1) seizure freedom, (2) a 50%–99% decrease in seizure frequency, (3) a 25%–50% decrease in seizure frequency, (4) increase in seizure frequency, and (5) no change.

Computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed in all patients. Brain MRIs were performed with a General Electric Sigma Horizon LX, 1.5 T equipment (General Electric, Milwaukee, WI, USA). EEG and Video-EEG were repeated several times a year according to the evolution of the patients. Data on school achievements and neuropsychological evaluations (Terman & Merrill, or WISC III or IV) were obtained during the follow-up.

Blood chemistry and liver and kidney function were carefully assessed before STM was introduced and during the follow-up period. Molecular biology studies were not performed.

For statistical analysis the two-tailed Wilcoxon rank-sum and the Fisher exact tests were used and a $p < 0.05$ was considered significant.

3. Results

3.1. General characteristics

We evaluated 44 patients (28 males, 16 females), aged between 4 and 16 years with a mean and median age of 9 and 10 years, respectively. The patients were treated with STM for a mean period of 20 months (range, 12–60 months).

Fifteen patients were diagnosed as having an unknown aetiology and 29 as structural LGS. Of the latter patients, 12 had malformations of cortical development, 11 brain atrophy, three tuberous sclerosis, and three others encephalitis. All patients had intellectual disability, which was found to be mild in 10, moderate in 19, and severe in 15.

CT scan and MRI showed abnormal findings in 29/44 patients (66%); brain atrophy was observed in 11, brain malformations in 12, tuberous sclerosis in three, and a **destructive** lesion in three others.

Mean and median age at seizure onset was 2.5 and 3 years, respectively. Mean duration of epilepsy was 4 years. Seizure types observed before STM initiation were atypical absences in 15 (34%), atonic and/or myoclonic seizures in 37 (82%), tonic seizures in 35 (76%), focal seizures in 20 (45%), and tonic-clonic seizures in 15 patients (34%). Before STM initiation, the patients had a mean of 13 seizures per day (range, 2–26).

All patients had received more than four AEDs before STM was added, in doses ranging from 10 to 35 mg/kg/day. The mean number of AEDs tried before STM was 8.5. The mean STM dose was 25 mg/kg/day. The mean and median number of concomitant AEDs was 2.5 and 2, respectively. Concomitant AEDs were valproic acid in 80%, levetiracetam in 66%, clobazam in 34%, topiramate in 34%, rufinamide in 34%, and lamotrigine in 23%. Four (9%) and 16 (36%) patients were on the KD or VNS, respectively.

3.2. Efficacy

Twenty-seven of 44 patients (61%) who received STM as add-on therapy had a greater than 50% decrease in seizures after a mean follow-up of 20 months. One patient (2%) became seizure free. Four patients (9%) had a 25–50% seizure reduction, while seizure frequency remained unchanged in 11 (23%) and increased in one patient (2%).

Considering seizure type, 21 of the 27 responders (78%) had a greater than 50% reduction in drop attacks (atonic and/or myoclonic seizures), 17/27 (63%) had a greater than 50% decrease in tonic seizures, 9/27 (33%) had a greater than 50% decrease in atypical absences, 6/27 had a greater than 50% decrease in focal, and 6/27 others had a greater than 50% decrease in generalized tonic-clonic seizures.

No statistical difference was found between responders and non-responders regarding age at seizure onset, epilepsy duration, and age at STM initiation. When evaluating the patients with a greater than 50% decrease in seizure frequency, there was no difference between the patients with an unknown aetiology and those with a structural aetiology. A better control of the drop attacks was seen in the patients