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Lacosamide use in the treatment of refractory epilepsy in tuberous sclerosis complex

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Abstract Lacosamide (LCS) was approved by the United States Food and Drug Administration (FDA) in 2008 as adjunctive therapy to other anti-epileptic drugs (AEDs) to treat focal-onset seizures, with or without secondary generalization. Its role in the treatment of epilepsy in individuals with tuberous sclerosis complex (TSC) has yet to be determined. This study evaluates LCS treatment of focal-onset refractory epilepsy in patients with TSC. From November 2009 to June 2014, 46 TSC patients followed by a single neurologist were treated with LCS. Forty-eight percent were responders (seizure reduction ≥50%). No significant differences between responders and non-responders in demographic characteristics were found. LCS appears to be an effective and safe treatment of refractory focal onset seizures in TSC. Determining the long-term tolerability and efficacy of LCS in TSC patients requires additional clinical experience.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder, characterized by benign hamartomas in various organ systems, including the brain, heart, lungs, skin, eyes, and kidneys (Leung and Robson, 2007). TSC results from a mutation in tumor suppressor genes *TSC1* or *TSC2*. Phenotypes vary widely among patients and mutations of *TSC2* tend to result in a more severe phenotype than mutations of *TSC1* (Lyczkowski et al., 2007; Dabora et al., 2001). The most common symptom of TSC is epilepsy, which occurs in 75—90% of patients, about 60% of whom experience seizure onset in their first year of life (Chu-Shore et al., 2010). In the general epilepsy population, about a third of people have refractory epilepsy; however, in the TSC epilepsy population, about two thirds have refractory

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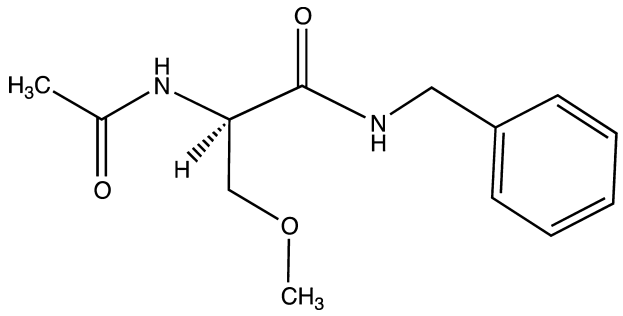

Fig. 1 Molecular structure of lacosamide.

epilepsy, most of which is characterized by multiple seizure types (Chu-Shore et al., 2010).

Seizures in TSC have a focal onset, with and without secondary generalization (Kwiatkowski et al., 2010). LCS was first approved by the United States Food and Drug Administration (FDA) in October of 2008 as an adjunctive therapy to other anti-epileptic drugs (AEDs) to treat focal-onset seizures, with or without secondary generalizations.

LCS ($C_{13}H_{18}N_2O_3$) is (*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide, a functionalized amino acid (Fig. 1). It has a half-life of 13 h and a bioavailability of 100% (Doty et al., 2007). LCS is thought to reduce spread of seizure activity through voltage-gated sodium (NaV) channels. LCS selectively enhances slow inactivation of NaV channels, preventing excessive firing of action potentials. In prolonging the inactivation of NaV channels, LCS decreases the ability of these channels to depolarize, stabilizing hyperexcitable neuronal membranes and minimizing repetitive, synchronous neuronal firing (Doty et al., 2013). In this manner, LCS only affects neurons with action potential firing of high frequency or duration, typical of neurons at the focus of epilepsy. Simultaneously, LCS binds to the CRMP-2, which partakes in a neurotrophic signal transduction. This is hypothesized to produce a neuroprotective effect to neuronal plasticity from seizures, preventing the formation of abnormal neuronal connections in the brain (Wilson and Khanna, 2014).

The purpose of this retrospective study is to evaluate the efficacy and response to LCS for treating focal seizures in people with TSC and refractory epilepsy.

Materials and methods

Patient selection

A retrospective review of patients with a definite diagnosis of TSC who had been evaluated at the Herscot Center at Massachusetts General Hospital (MGH) from January 2005—June 2014 (448 patients) was performed; 46 patients with refractory epilepsies due to TSC were identified who had been treated with LCS (November 2009—June 2014).

Data collection

Charts of TSC patients treated with LCS were reviewed for clinical data including seizure history, neuropsychological evaluation, genetics, and TSC data in accordance with institutional review board (IRB) approval. Therapeutic response and adverse reactions to LCS and number of concurrent and ineffective (previous) AEDs were also noted. Cognitive impairment was defined as an intellectual quotient (IQ) of <70 when indicated in available psychometric tests from clinical records. Diagnoses of autism were made based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. A patient was considered to have refractory epilepsy if two or more antiepileptic treatments had not effectively controlled seizures and seizures persisted after a minimum of one year.

LCS was used as an adjunctive therapy to other AEDs to treat TSC patients presenting with refractory epilepsy. Patients were monitored with regular EEGs, MRIs, and clinical assessment as part of standard clinical practice in TSC. Initial doses for children were either 5 mg of Elixir (10 mg/ml liquid formulation) or 12.5 mg of a 50 mg Vimpat tablet (1/4 of the tablet), ranging from 1.42 to 10.64 mg/kg/day (mean = 4.37, median = 3.93 mg/kg/day). Children increased doses by 5 mg/week of Elixir or 12.5 mg/week of the Vimpat tablet, up to 1.42—15.69 mg/kg/day. Initial doses for adults were 25 or 50 mg/day, depending on number of concurrent AEDs and seizure severity; most adults started on doses of 50 mg/day. Titration step was 50 mg/week or slower, up to about 400 mg/day. Variations in initial doses and titration steps were determined based on individual histories and clinical response. If LCS was deemed ineffective or not tolerated, it was tapered slowly.

Seizure frequencies before and after initiation of treatment were used to determine the efficacy of LCS for each patient. Baseline and post-treatment periods were at least a month (range ~1—3 months), unless LCS was stopped earlier due to adverse events. Other AEDs were not changed during these periods. Patients were divided into two groups according to response. A responder had a 50% or greater decrease in seizure frequency, while a non-responder had less than a 50% decrease seizure frequency. Patients with only electrographic seizures (no electroclinical seizures) ($n = 2$) or inconclusive records ($n = 2$) were not categorized as a responder or non-responder.

Statistical analysis

Responders and non-responders were compared using two-tailed *t*-tests, with a significance set at $p < 0.05$. A Kaplan—Meier curve was performed for retention of LCS.

Results

Forty-six patients with TSC and refractory epilepsy were treated with LCS. In children, LCS doses ranged from 1.42 to 15.69 mg/kg/day. In adults, LCS doses ranged from 2.09 to 8.90 mg/kg/day. Patient demographics can be found in Table 1. About half the patients were female ($n = 25$, 56%). The majority of this cohort were pediatric patients ($n = 27$, 59%); ages ranged from 1 to 54 years old (mean = 20, median = 15). Most of the patients ($n = 40$, 87%) were cognitively impaired. Twenty-five patients had previously had epilepsy surgery. There was no significant difference between responders and non-responders with