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Original Article

Efficacy and Tolerability of Lacosamide as an Adjunctive Therapy in Children With Refractory Partial Epilepsy

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ABSTRACT

BACKGROUND: A unicentre, prospective study was performed to investigate the efficacy of lacosamide as adjunctive therapy in children with refractory partial epilepsy. **METHODS:** The study was performed at a tertiary care hospital over a period of 30 months between November 2011 and May 2014. Seventy-nine children with refractory partial epilepsy (age 5-15 years) who had failed two or more antiepileptic drugs and in whom lacosamide was used as an add-on drug were enrolled. Lacosamide tablets were administered orally, at a dose of 25 mg for 1 week followed by 50 mg twice daily for the remaining period. Efficacy and tolerability evaluation was performed at every visit of titration, maintenance period (3 months), and two follow-up visits at monthly interval. Electrocardiogram and liver function tests were performed before enrollment and at the end of 3 months of lacosamide therapy. Patient's caregiver or investigator observed adverse events were recorded in a predesigned pro forma. **RESULTS:** A total of 79 patients with uncontrolled partial epilepsy screened from 531 epileptic children were enrolled, after they satisfied the inclusion and exclusion criteria. The mean age of children enrolled was 8.8 ± 3.1 years (range 5-15 years); 53 children (67.0%) were boys. Mean weight of the patients was 24.2 ± 9.8 kg. The mean age at the onset of seizures was 6.4 ± 3.5 years. The mean dose of lacosamide administered was 4.1 mg/kg. Three patients (3.8%) dropped out of the study, because of vomiting, aggressive behavior, and poor response, respectively. Of 76 patients (96.2%) entering the maintenance period, 35 patients (44.3%) were seizure free, 32 patients (40.6%) indicated ≥50% reduction in seizure frequency, 3 patients (3.8%) indicated 25-49% seizure reduction, and 9 patients (11.4%) either had no change in seizure frequency or experience increase in seizure frequency. **CONCLUSION:** Lacosamide is an effective add-on antiepileptic drug for children with refractory partial epilepsy and is well tolerated.

Keywords: lacosamide, tolerability, refractory epilepsy, children, antiepileptic drug

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Introduction

Epilepsy is a chronic neurological disorder complicated by neurobehavioral comorbidities and social consequences.[1] In spite of the introduction of several new antiepileptic drugs (AEDs) over the past 20 years, about 30% of patients with epilepsy become refractory to current treatments or experience significant adverse events.[2-4] Therefore, attempts are being made to identify novel drugs and/or therapies that reduce the seizure frequency and may improve patients' quality of life.

In October 2008, United States Food and Drug Administration and in August 2008, European Commission approved lacosamide (LCM) as an adjunct drug in the treatment of epilepsy patients with partial-onset seizures aged ≥16 years and older. LCM, the single (R)-enantiomer, is (R)-2-acetamido-N-benzyl-3methoxypropionamide, is a functionalized amino acid, with a novel mechanism of action, synthesized for use as an AED.[5-7] It was suggested

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that LCM may have two novel mechanisms of action: increase of the slow inactivation of the voltage-gated sodium channels and interference with collapsing response mediator protein 2.[8-10] Later, the collapsing response mediator protein 2 component has recently been repudiated based on new experimental evidence.[11] A pharmacokinetic-pharmacodynamics (efficacy) analysis was performed based on the pooled data from the three efficacy trials for partial-onset seizures. LCM exposure was correlated with the reduction in seizure frequency.[7] LCM indicated 100% oral absorption with linear pharmacokinetics, low protein binding (<19%), good renal clearance, and a low potential for drug-drug interactions and is thus well suited for polytherapy and use in children.[5] Based on large Phase III studies, in adults, it was demonstrated that the proportion of patients with at least a 50% reduction in seizure frequency (50% responder rate) with LCM 400 and 600 mg/day were statistically significant compared with placebo in the primary intent-to-treat population.[12] Although it is not approved for use in children, it has been suggested that it may have a role in the management of pediatric epilepsy because focal seizures are the most common type of seizures in children; this drug is found to be safe in adults and has favorable pharmacokinetic properties.[13] Four small reports on efficacy and tolerability of LCM as an adjunctive treatment in pediatric patients with refractory focal epilepsy have demonstrated the usefulness of LCM in pediatric patients.[14-16] We wanted to study the efficacy and tolerability of this newer AED with novel mechanism of action in a larger group of children with refractory partial epilepsy and hence planned this study. We here present the results of our study on use of LCM in 79 refractory epileptic patients aged between 5 and 15 years.

Materials and Methods

Patients and assessments

This study is a prospective, open-label treatment study performed between November 2011 and May 2014. Prior approval from the institutional human ethics committee was obtained. All patients or their legal representatives gave written informed consent before trial participation. Children, aged between 5 and 15 years, with uncontrolled focal epilepsy were eligible for the study. Diagnosis of seizures and epileptic syndromes was based on the Classification of Epileptic Seizures (Commission on Classification and Terminology of the International League Against Epilepsy 2011)[17] after going through their electroencephalography (EEG) reports and neuroimaging findings.

Patients were enrolled based on inclusion criteria of those who have had at least 3 months duration of epileptic seizures and not controlled after either sequential or additive use of at least two AEDs. Patients who were included had to have at least two seizures in 4 weeks before enrollment and during baseline.

Patients were excluded if they were <5 years of age or were >15 years at enrollment. Those children who had underlying metabolic and systemic disorders, those with a history of poor drug compliance, those who refused informed consent, those with pseudo seizures (non-epileptic seizures) and a history of progressive neurological disorder that was not stable, and those who had used an investigational drug within 1 month before the study were excluded from the study.

Seizure frequency during the 4 weeks preceding LCM initiation was used as baseline. LCM was added to a stable dosage of baseline AEDs and administered orally in the form of tablets with increment dose of 25 mg twice daily for 1 week followed by 50 mg twice daily for the remaining period. During the study period, in case of any adverse event, patients were asked to report or call the principal investigator.

After enrollment, plasma samples were drawn to estimate transaminase serum glutamate oxaloaceate transaminase and serum glutamate pyruvate transaminase levels, and an electrocardiogram was recorded. After the titration period, patients entered into a 3-month maintenance period. Later, they were called on monthly intervals for 2 months for follow-up visits. No change in the dose of LCM was permitted during the maintenance period. Patients who were unable to tolerate protocol medication and those experiencing adverse effects were allowed to discontinue treatment.

The efficacy was based on change in frequency of seizures per 28 days. The number of children experiencing ≥50% reduction in seizure frequency from baseline to maintenance period and patients who achieve seizure-free status were observed separately. Tolerability was assessed by an investigator and patients at the last visit on a point scale. In our study, we measured tolerability based on global 5-point scale (a score of 5 was given when there was decrease in side effects, 4 when there were no new side effects, 3 when there was one new side effect, 2 when there were two to three side effects, and 1 when there were more than three side effects).

Patients were categorized based on etiologic classification as idiopathic or genetic, structural or metabolic and cryptogenic or unknown. Seizure type was based on the semiology and EEG findings (temporal lobe epilepsy, focal lobe epilepsy, occipital lobe epilepsy, centrotemporal epilepsy, multifocal, and others). Caretakers were provided with diary card, which captures the details of per month treatments days, seizure occurrence, loss of consciousness, total number of seizure for 24 hours, duration of seizure, and medication taken in morning and evening from the beginning of titration period till last evaluation.

Routine examination of vital signs, body weight, height measurements, and physical and neurological examination findings was performed at every visit. Liver function tests, electrocardiogram, and EEG were also performed. The assessment of tolerability was performed at every visit of 1 month period and consisted of collecting data on adverse events reported by the patient or their caregiver or observed by the investigator.

SPSS 20.0 for Windows (IBM Corporation, Armonk, NY) was used for the statistical analyses. Continuous clinical variables were analyzed using Wilcoxon signed rank test. The response to LCM treatment was analyzed using repeated measure Kruskal-Wallis test. Statistical significance was set at $P < 0.05$.

Results

Demographics

Of 531 screened patients, 79 were enrolled based on inclusion and exclusion criteria. Of 79 patients who entered the study, all patients completed the titration phase, and 76 patients (96.2%) completed the maintenance phase. Three patients (3.8%) dropped out from the study. Of these three patients, one patient (1.3%) developed severe hyperactivity and behavioral changes, and the other two patients (2.5%) withdrew from the study because of vomiting and lack of seizure control, respectively.

The clinical characteristics of 79 patients with refractory partial epilepsy are presented in Table 1. Patient's mean age was 8.8 ± 3.1 years (age range 5-15 years); 53 of 79 patients were boys. The mean weight was 24.4 ± 9.5 kg (range 11-55 kg), and the mean age at epilepsy onset was 6.4 ± 3.5 years. The mean dose of LCM administered was 4.1 mg/kg. Forty-one patients (51.9%) had normal developmental milestone, whereas delayed milestones (includes significant delay in any one or two of following milestones: head control; sitting; walking; crawling) were evident in the remaining 38 patients (48.1%).

As listed in Table 2, among the study population, most of the 30 patients (38.1%) had occipital lobe epilepsy,