



ORIGINAL ARTICLE

Safety of lacosamide in children with refractory partial epilepsy



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Abstract *Objectives:* The study was carried out to investigate the safety of lacosamide on children with refractory partial epilepsy. *Materials & methods:* The study was carried out at a tertiary care hospital after obtaining approval from the institutional ethics committee. Patients aged between 5 and 15 years taking oral lacosamide (LCM) tablets that were given orally as an adjunctive anti-epileptic drug were enrolled for assessing safety, tolerability and its effect on the behavioural life at every visit of titration, during the treatment period (3 months) and at 2 follow up visits that were done at monthly intervals. Adverse events reported by caregiver or by investigator were recorded. Patients/caregivers also completed a 25 items on Connor's behavioural rating clinical scale at every visit. *Results:* Out of 531 screened patients, 79 patients with refractory partial epilepsy were enrolled after they fulfilled the inclusion and exclusion criteria. Mean age of the children was 8.84 ± 3.09 years (5–15 years), of which 53 were males and 26 females. The mean age at onset of seizures in males was 6.46 ± 3.57 and in females, 6.38 ± 3.39 years. Seventy-six children of 79, completed 3 months of treatment period showed significant ($p < 0.001$) decrease in the frequency of seizures, significant improvement in behaviour and showed good tolerability. Three (3.79%) patients dropped out of the study due to hyperactive behaviour, vomiting and lack of seizure control respectively. *Conclusions:* Lacosamide is a well-tolerated newer antiepileptic drug that is effective in refractory partial epilepsy paediatric patients and concurrently improved patient's behaviour.

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1. Introduction

Epilepsy is one of the most frequent neurological disorders affecting 0.5–1% of the population worldwide. In epilepsy there is an enduring predisposition of the brain to generate seizures (Verrotti et al., 2012). Despite the introduction of multiple newer antiepileptic drugs (AEDs) over the past 20 years, about 30% of patients with epilepsy become refractory to

current treatments or experience significant adverse events (Kwan and Brodie, 2000; Diaz et al., 2002; Perucca, 2007). Therefore, attempts to identify novel drug therapies that reduce the seizure frequency and improves patient's behavioural life are on. Lacosamide is one of the newer AEDs which promises to be effective and has a better tolerability profile.

Based on experimental evidence it was suggested that lacosamide has a novel mechanism of action: increase of the slow inactivation of the voltage-gated sodium channels (Errington et al., 2006; Wang et al., 2010; Brandt et al., 2006; Verrotti et al., 2013). A pharmacokinetic-pharmacodynamics (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. Lacosamide exposure was correlated with the reduction in seizure frequency (Verrotti et al., 2013). Lacosamide showed favourable pharmacokinetics properties, has a low potential for drug–drug interactions and is thus well suited for polytherapy and probably for use in children (Beyreuther et al., 2007). Few studies in adults proved that the proportion of patients with at least a 50% reduction in seizure frequency (50% responder rate) with lacosamide 400 and 600 mg/day were statistically significant (Ben-Menachem et al., 2007). Though it is not approved for use in children, it may have an active role in the management of paediatric epilepsy because focal seizures are the most common seizure type in children (Berg and Shinnar, 1999). From the past 3 years, 7 published studies have reported similar efficacy and safety of lacosamide as an adjunctive treatment in infants, children and young adults with refractory epilepsy (Highlights, 2014; Fattore and Perucca, 2011; Halasz et al., 2009; Chung, 2010; Gavatha et al., 2011; Guilhoto et al., 2011; Heyman et al., 2012; Rastogi and Ng, 2012; Fernandez et al., 2012; Grosso et al., 2014; Kim et al., in press). There have been some reports of hyperactivity with lacosamide in children. We wanted to study the safety of lacosamide in children with refractory partial epilepsy. It is a part of our likely upcoming study on effect and tolerability of lacosamide in children with refractory partial epilepsy.

2. Materials and methods

2.1. Patients

In this prospective study, out of 531 screened patients, 79 patients were enrolled after they fulfilled the inclusion and exclusion criteria. Informed written consent was taken from the parents and approval from the child obtained wherever applicable.

2.2. Study design

This, open-label study was conducted over a 30 month duration, after obtaining approval from Institutional Human Ethics Committee.

2.3. Inclusion and exclusion criteria

Patients were enrolled based on inclusion criteria of age between 5 and 15 years and those who have had at least 3 month duration of uncontrolled focal epilepsy even after

use of 1–4 AEDs. One month before enrolment patients were to have at least 2 seizures. Patients were excluded from the study if they had an underlying metabolic and systemic disorder and if they were diagnosed with pseudo seizures and if they had a progressive neurological disorder. Patients with history of noncompliance and use of investigational drug within 1 month prior to the study were also excluded from the study.

Lacosamide was added to a stable regime of baseline AEDs were administered orally in the form of tablets at a dose of 25 mg twice a day for one week followed by 50 mg twice a day for the remaining period. During the study period, patients were asked to report or call principal investigator (PI) if they developed any complaint or reaction.

2.4. Study assessments

Diagnosis of epileptic seizures and syndromes was based on Classification of Epileptic Seizures (Commission on Classification and Terminology of the International League against Epilepsy, 2011) (Berg and Ingrid, 2011). After reviewing the semiology of seizures, electroencephalography (EEG) and magnetic resonance imaging (MRI) findings.

At enrolment, after detailed physical examinations, serum samples were drawn to assess transaminase (SGOT/SGPT) levels and an ECG was recorded. Later patients entered into a 3-month maintenance period and two follow up visits of one month interval. Electrocardiogram (ECG) and transaminase levels were estimated at the end of 3 months of maintenance period. No change in the dose of lacosamide was permitted during the maintenance period.

The efficacy measures were analysed based on change in seizure frequency per 28 days. Children experiencing $\geq 50\%$ or greater reduction in seizure frequency from baseline to maintenance period and also patients who were seizure free were noted.

The assessment of safety and tolerability was performed at every visit and it consisted of collecting data on adverse events reported by the patient or their caregiver or those observed by the investigator. Patients who were unable to tolerate protocol medication and those experiencing adverse effects were allowed to discontinue treatment. In our study, we measured tolerability based on global five point scale (A score of 5 was given when there was decrease in side effects; a score of 4 when there were no new side effects; score of 3 when there was one new side effect; score of 2 when there were 2–3 side effects and a score of 1, when there were > 3 side effects.).

At the same time, parents or their patients were made to complete 25 items of Connor's CBRS clinical index scale. A high score on an item indicates difficulty in that area of the patient's life. The total score can range from 10 indicating good behaviour to 75 indicating low quality behavioural life.

Caretakers were provided with diary cards, which captured the details of seizures per month, medications taken in the morning and evening, from the beginning of titration period till last evaluation.

2.5. Statistical analysis

Tolerability and effect of lacosamide on the children's behaviour outcome measured using SPSS 20.0 for Windows (IBM Corporation, Armonk, NY, USA) were used for the statistical

analysis. Continuous clinical variables were analysed using Wilcoxon signed rank test. The response to lacosamide treatment in improving children's behaviour was analysed using repeated measure ANOVA. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographics data and patient characteristics

Out of 531 screened patients, 79 patients were enrolled after they fulfilled the inclusion and exclusion criteria. Seventy-six (96.2%) patients completed 3 months of maintenance period. Three patients discontinued due to adverse events. The disposition of patients is summarized in Table 1.

The clinical characteristics of 79 patients with refractory partial epilepsy are presented in Table 2. In this study, 53 (69.7%) children were males and 23 (30.2%) were females with a mean age of 8.84 ± 3.09 years (age range 5–15 years). Mean age at seizure onset in males was 6.46 ± 3.57 years and in female, 6.38 ± 3.39 years. Out of 76, 49 (62.02%) children continued lacosamide even after the completion of treatment period while 27 (35.5%) children stopped it after treatment period.

Out of 79 enrolled patients, 3 patients were dropped from the study. The behavioural life of the remaining 76 patients was assessed using 25 item questionnaire that was filled by parents/care takers/attenders. Mean total score at baseline was 48.04 ± 10.57 ; after 3 months of maintenance period, mean behavioural life was 19.27 ± 08.03 and subsequent follow up visit was 19.05 ± 05.29 as shown in Fig. 1. Thus scores improved significantly with treatment (ANOVA test with $P < 0.001$). Thus behavioural scores remained relatively constant from baseline to treatment period to all subsequent follow up visits.

3.2. Efficacy

At the end of the study (EOS), 76 patients entered the maintenance period with a mean reduction in seizure frequency per 28 days from 13.35 ± 24.12 at baseline to 4.53 ± 13.23 at the EOS (Wilcoxon signed ranked test $p < 0.001$). At the end of the follow up period, mean reduction in seizure was 3.9 ± 11.81 as shown in Table 3.

3.3. Adverse effects

All enrolled patients were included in the safety analysis, which included study of adverse events, laboratory test results and

Table 2 Demographic data and patient characteristics.

Characteristics	Value
Age, year	8.84 ± 3.09
Sex, n (%)	
Male (53)	8.93 ± 3.09
Female (26)	8.65 ± 3.31
Follow up duration on lacosamide	
Continued	49 (62.02%)
Discontinued after treatment period	27 (35.5%)
Co-administered drugs along with lacosamide (LCM) n (%)	
1	38 (48.1%)
2	35 (44.3%)
3	05 (6.3%)
4	00 (0.0%)
5	01 (1.35%)
Onset of seizure	
Males	6.46 ± 3.57
Females	6.38 ± 3.39
Duration of seizure	
< 1 month	20 (25.3%)
1 month–1 year	15 (19.0%)
1–2 year	15 (19.0%)
> 3	29 (36.7%)

Co-administered drugs: VPA: valproic acid, CLB: clobazam, CBZ: carbamazepine, OXC: oxcarbamazepine, LMT: lamotrigine, LEV: levetiracetam, TPM: topiramate, PHT: phenytoin, ZNS: zonisamide, PB: phenobarbitone, CNZ: clonazepam, NPM: nitrazepam.

vital signs. Out of 79 patients, 40 (50.63%) experienced side effects.

The common adverse events were hyperactivity, ataxia, drowsiness, insomnia, weight gain, nausea, abdominal discomfort, giddiness, headache, and vomiting as shown in Fig. 2. Most of the reported side effects were mild to moderate in intensity and did not need discontinuation of treatment. Overall results of clinical laboratory tests as well as periodic physical examinations, neurological examinations and assessments of vital signs did not reveal any changes with lacosamide treatment.

Lacosamide was withdrawn in three patients (3.79%). Reasons for discontinuation were unsatisfactory seizure control (one patient) and adverse events during the titration and treatment period (one patient with aggressive behaviour and one with vomiting).

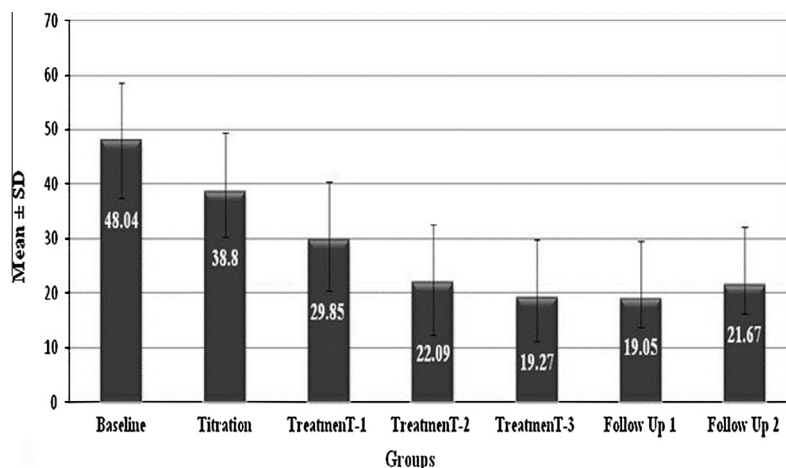
4. Discussion

This prospective, open label treatment study demonstrates that adjunctive therapy with oral lacosamide in children with uncontrolled epilepsy, not only reduces seizure frequency with better tolerability profile, there is improvement in children's behaviour and it causes fewer side effects. The study confirms the clinical efficacy and tolerability of lacosamide in refractory epilepsy in children and validates findings from previous studies.

In a multicentre prospective study by Verrotti et al. that compared lacosamide in paediatrics and adults, a total of 118 patients (59 group A, 59 group B) with uncontrolled

Table 1 Patient disposition.

Study details	Value
No. of patients enrolled	79
No. of patients completed	76 (96.2%)
No of patients completed 3 months of treatment duration	46 (58.2%)
No. of patients continued even after treatment period	30 (37.9%)
No. of patients discontinued the study	03 (3.79%)



The scores significantly improved with treatment (ANOVA test with $P < 0.001$). Thus showed maintenance of proper behaviour from baseline to treatment period.

Figure 1 LCM study: connors comprehensive behaviour rating scale.

Clinical findings	Values	
	Males	Females
<i>Seizure type</i>		
Temporal lobe epilepsy	3 (5.8%)	1 (3.84%)
Frontal lobe epilepsy	13 (25.0%)	7 (26.6%)
Occipital lobe epilepsy	24 (44.2%)	6 (23.0%)
Centrottemporal epilepsy	01 (1.9%)	3 (11.5%)
Multifocal	06 (11.5%)	9 (34.5%)
others	06 (11.5%)	0 (0.0%)
<i>Aetiology classification:</i>		
Idiopathic/genetic	16 (30.8%)	03 (11.5%)
Structural/metabolic	32 (61.5%)	18 (69.1%)
Cryptogenic/unknown	05 (9.6%)	05 (19.0%)
<i>Retention of lacosamide (months)</i>		
≤6	02 (2.5%)	
7–12	20 (25.3%)	
13–18	14 (17.7%)	
19–24	08 (10.1%)	
>24	05 (6.3%)	
Discontinued after treatment period	30 (38%)	
<i>Connors comprehensive behaviour rating scale</i>		
Baseline – mean ± SD	48.04 ± 10.57	
End of the study – mean ± SD*	19.27 ± 08.03	
Follow up*	19.05 ± 05.29	
<i>Seizure frequency per 28 days:</i>		
Mean ± SD – baseline	13.3 ± 24.11	
<i>End of the study seizure frequency:</i>		
Mean ± SD	4.53 ± 13.22	
% Reduction ($p < 0.001$)#	59.9 ± 99.9	

$p < 0.001$, showed significant difference using Wilcoxon signed ranks test.
* $P < 0.001$, showed significant difference using ANOVA test.

generalized and focal epilepsy were enrolled. At 3-month evaluation, 118 treated patients and 56 subjects (47.4% group A; 47.4% group B; $p = 0.8537$) experienced at least 50% reduction in seizure frequency respectively (Verrotti et al., 2013).

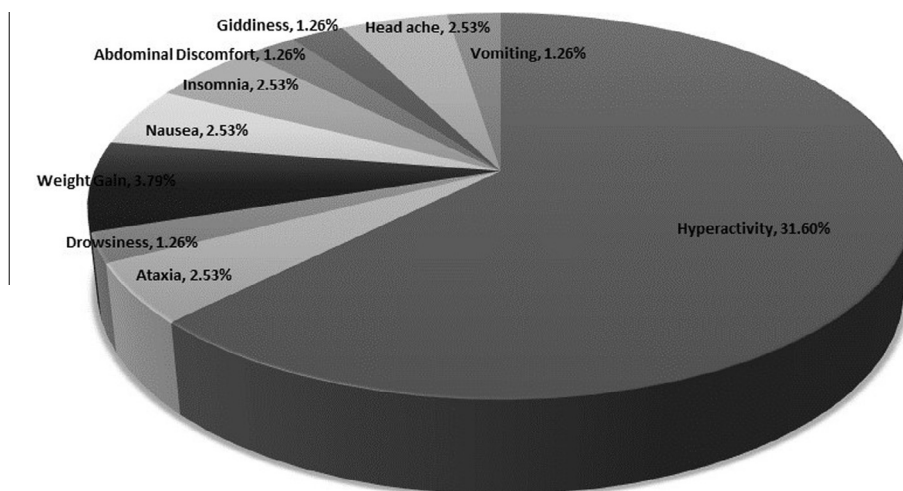
In randomized controlled trials conducted in adults, lacosamide has been shown to be an effective and safe AED in treating refractory seizures, with 30–40% of patients achieving a $\geq 50\%$ reduction in seizure frequency at doses of 400–600 mg/day (Fattore and Perucca, 2011; Halasz et al., 2009; Chung, 2010; Berg and Ingrid, 2011; Chung et al., 2010).

In the last 3 years, 7 published studies have reported similar efficacy and safety of lacosamide in infants, children and young adults with refractory epilepsy that had shown greater reduction in seizure frequency and few children with seizure free status (Gavatha et al., 2011; Guilhoto et al., 2011; Heyman et al., 2012; Rastogi and Ng, 2012; Fernandez et al., 2012; Grosso et al., 2014; Kim et al., in press).

Lacosamide has been reported to be a well-tolerated and relatively safe drug (Buck and Goodkin, 2012). Mild adverse reactions, such as dizziness, headache, diplopia, nausea and somnolence, drowsiness, dizziness have been observed in paediatric case reports and case series (Guilhoto et al., 2011; Heyman et al., 2012; Fernandez et al., 2012; Buck and Goodkin, 2012). The most common adverse event observed in our study (50.63%) was almost congruent with those reported by Gavatha et al., 2011 Adverse effects seen with lacosamide in adults are dose-related (Buck and Goodkin, 2012) and same was seen in paediatrics. Many of them are reversible upon discontinuation or dose reduction.

The effect of lacosamide on behaviour in 76 patients was measured using mean scores. The behavioural scores improved significantly with treatment (ANOVA test with $P < 0.001$) using Conner’s Comprehensive Behavior Rating Scales (Connors, 2007). The scores remained relatively constant from baseline to treatment period to all subsequent follow up visits. The possible reasons for a favourable effect of lacosamide on behavioural scores could be attributed to improved adherence of children to twice-daily dose of LCM leading to better seizure control and that in turn helped to sustain behavioural improvements.

In our study population, lacosamide showed greater efficacy and was well tolerated with no relationship between dose and adverse effects development. Most adverse effects seen with lacosamide in adults are dose-related and are reversible



Pie chart shows 31.6% cases had hyperactivity after giving the drug followed by 3.8% of cases each had weight gain and hyperactivity. 2.5% of cases had nausea, insomnia and ataxia each.

Figure 2 LCM study – adverse effect.

upon discontinuation or dose reduction (Grosso et al., 2014). One of the literature stated that patient who received the highest lacosamide dose (20 mg/kg/day) did not experience any adverse effects (Buck and Goodkin, 2012; Vishwanath and Miller, 2012). Plasma drug levels were not determined in our study. The literature suggests that adverse effects associated with lacosamide therapy are generally mild-to-moderate in severity.

Lacosamide was discontinued in one patient (1.26%) because of severe hyperactivity, aggression and inattention for one week after starting the drug. These symptoms persisted for one month till the drug was continued and the behavioural symptoms reverted back to normal status after the drug was stopped (Ismail et al., 2014a,b). Two (2.53%) others withdrew from study due to vomiting and instability in seizure control respectively.

5. Conclusions

In conclusion, lacosamide is one of the newest additions to the AED category and represents a possible option, currently available for refractory partial epilepsy. To the best of our knowledge, this is the first prospective study in a large sample of children (> 55 subjects). Results from our prospective, open label, hospital based study confirm the usefulness of LCM for adjuvant treatment in patients with refractory partial epilepsy. Lacosamide showed favourable safety, tolerability profile and improved behavioural life scores with no increase in seizure frequency. A few more multi-centre randomized controlled trials are required to validate our study results.

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