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ORIGINAL ARTICLE

Safety of lacosamide in children with refractory partial epilepsy

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KEYWORDS

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Hyperactivity

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

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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 whereever 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 $\geqslant 50\%$ 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