Original article

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Efficacy and safety of lacosamide as an adjunctive therapy for refractory focal epilepsy in paediatric patients: a retrospective single-centre study

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ABSTRACT – *Aim*. Lacosamide is an antiepileptic drug approved for the treatment of focal epilepsy in adult patients. The aim of this observational study was to review our centre's experience with lacosamide and to characterize its effectiveness and tolerability as an adjunctive antiepileptic drug in a retrospective cohort of children with refractory focal epilepsy.
Methods. We retrospectively reviewed the medical records of 22 patients who received lacosamide from November 2009 to April 2014 at the CHU Ste-Justine, University of Montreal. Treatment responders were defined as children with a ≥50% reduction in seizure frequency compared to baseline, and this was determined three months after the initiation of treatment and at the last follow-up visit.
Results. We included 14 boys and eight girls with a mean age of 12.9 years (SD: 5.2; range: 5.2-20.7 years) at the initiation of treatment. The average length of follow-up was 11.9 months. Patients had previously received an average of 7.5 antiepileptic drugs. The mean number of concomitant antiepileptic drugs was 2.3. The mean initial and maintenance doses were 2.9 and 8.4 mg/kg/d, respectively. Thirteen (59%) and ten (45%) patients were responders after three months of treatment and at the last follow-up visit, respectively. One became seizure-free. Adverse effects were reported in 11 patients and none were severe. Responders and non-responders were identical with respect to all studied parameters except gender, with the proportion of responders being greater in girls than in boys (75% vs 29%; p=0.035).
Conclusion. Our study adds evidence that lacosamide appears to be a safe and effective adjunctive therapy for children with refractory focal epilepsy.

Key words: lacosamide, antiepileptic drug, refractory epilepsy, treatment, pediatric patients

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Epilepsy is one of the most common chronic neurological disorders, affecting up to 0.5% to 1% of the general population (Keränen and Riekkinen, 1988; Diaz-Arrastia *et al.,* 2002). Administration of antiepileptic drugs (AEDs) is the mainstay of treatment for most patients. Despite the introduction of multiple new AEDs over the past 20 years, 30% of patients remain refractory to medical treatment (Kwan and Brodie, 2000; Diaz-Arrastia *et al.,* 2002), which imposes a significant burden on families and society (Bjornaes *et al.,* 2001). Therefore, new effective AEDs with novel mechanisms of action, better tolerability and pharmacokinetic properties to effectively treat refractory epilepsy in children are still needed.

Lacosamide (LCM) was approved by Health Canada in 2010 and the US Food and Drug Administration (FDA) in 2008, as an adjunctive therapy for focal epilepsy in adult patients (Health Canada Drug Product Database. Lacosamide, 2014). LCM ([R]-2-acetamido-N-benzyl-3-methoxyproprionamide) is a functional amino acid that reduces neuronal excitability by selectively enhancing the slow inactivation of voltage-gated sodium channels (Curia *et al.,* 2009), which participate in the generation and propagation of action potentials. Because of this novel mechanism of action, it may be effective in patients who are refractory to other AEDs. Pharmacokinetic properties of LCM make it well suited for polytherapy in a paediatric population. The drug has 100% oral absorption with linear pharmacokinetics, low protein binding (<19%), a 13-hour half-life, renal clearance with limited hepatic metabolism, and a very low potential for drug interactions (Chu-Shore and Thiele, 2010).

LCM was found to be effective in adults with focal-onset seizures in three randomized, double-blind, placebo-controlled studies (Ben-Menachem *et al.,* 2007; Halasz *et al.,* 2009; Chung *et al.,* 2010). These studies have shown that daily administration of 400 to 600 mg of LCM for around three months is associated with a 50% reduction in seizure frequency in around 40% of patients as compared to 18-25% for those taking placebo.

These studies have also shown a favourable adverse effects profile of LCM, with mild or moderate events reported in around 50% of patients. The most frequent dose-related adverse effects involved the nervous and gastrointestinal system and included dizziness, headache, nausea and diplopia. Only about 10% of patients discontinued treatment due to the adverse events. Caution is advised when using LCM in adults with severe cardiac disease or conduction problems as high doses of the drug have been shown to slightly prolong PR interval (de Biase *et al.,* 2014).

Although the potential usefulness of LCM is apparent, it has not been well studied in the paediatric population. No randomized clinical trials have been conducted. Observational studies reported encouraging results, showing a more than 50% reduction in seizure frequency in 30 to 50% of children with focal epilepsy, with the maintenance dose ranging between 2 and 20 mg/kg/day, with minor adverse effects reported in only 30% of patients (Gavatha *et al.,* 2011; Guilhoto *et al.,* 2011; Heyman *et al.,* 2012; Rastogi and Ng, 2012; Kim *et al.,* 2014; Yorns *et al.,* 2014). Yet, the optimal dose of LCM in the paediatric population and the profile of patients who will benefit most from treatment still remain to be clearly determined.

The aim of this observational study was to review our centre's experience with LCM and to characterize its effectiveness and tolerability as an adjunctive therapy for children with refractory focal epilepsy.

Methods

Study population and data collection

We retrospectively reviewed the medical records of 25 consecutive patients who initiated treatment with LCM at the CHU Sainte-Justine, at the University of Montreal, between November 2009 and April 2014. All these patients were under 21 years of age and had focal epilepsy refractory to multiple therapies including medications, the ketogenic diet (three patients), vagal nerve stimulation (three patients), and surgery (one patient). All patients treated with LCM at our institution were included, independent of the status of response to treatment, thus excluding the possibility of a selection bias.

We collected data on age, sex, developmental/cognitive level and other comorbidities, epilepsy syndrome, seizure type and aetiology, duration of epilepsy before the initiation of LCM treatment, number and types of previous and concomitant AEDs used, previous or concomitant use of other therapies (ketogenic diet, vagal nerve stimulator, or surgery), EEG findings before (available in all 22 patients) and after initiation of LCM treatment (available in 16 out of 22 patients), initial and maximal daily dose of LCM, treatment response, reported adverse events, reasons for treatment discontinuation if any, and duration of treatment and of follow-up after the initiation of treatment. In patients who discontinued treatment, follow-up was considered to end at the time of discontinuation, although all patients continued to be followed by our neurology team.

Response to LCM treatment was quantified using the data on seizure frequency before and after the initiation of treatment, as determined by the neurologist at each follow-up visit according to the parental report and seizure diaries, when available. Children with 50% or more reduction in seizure frequency were considered responders, while those with unchanged,

Table 1. Patient clinical characteristics and response to treatment with lacosamide.

Patient	Age	Sex	Epilepsy classification / aetiology	Number of failed AEDs	Concomitant AEDs[a]	Other treatment[b]	Maximum Dose (mg/kg/d)	Response ≥50% at 3 months	Response ≥50% at last follow-up visit
1	17	M	Unknown	14	ESM, FBM, VPA, LTG	VNS	12.5	No	No
2	6	M	Structural / Neurofibromatosis	6	CBZ , TPM		6.9	Yes	No
3	14	F	Unknown	9	PB		16.6	Yes	Yes
4	18	M	Structural / Herpes encephalitis	8	LEV, VPA	KD, VNS	2.1	No	No
5	18	M	Structural / Mesial temporal sclerosis	10	LEV, OXC	VNS	8.0	No	No
6	14	M	Unknown	9	LEV, CBZ	KD	5.9	No	No
7	20	F	Structural / Lissencephaly	8	LTG		4.7	Yes	Yes
8	16	F	Unknown	5	CLB, VPA		3.8	No	No
9	11	F	Unknown	10	CLB, LEV	KD	11.0	Yes	No
10	15	F	Structural / Focal atrophy	5	TPM, CBZ		7.1	Yes	Yes
11	8	M	Unknown	3	CLB, LEV		8.8	Yes	Yes
12	17	F	Structural / Neonatal anoxia	8	LTG, CBZ , GBP		3.0	Yes	Yes
13	18	M	Unknown	9	TPM, LEV, CLB	Surgery	2.9	Yes	Yes
14	5	M	Metabolic / Creatine Transporter Defect	4	CBZ , LTG		8.2	No	No
15	18	F	Structural / Megalencephaly / hypoglycaemic coma	6	LTG, VPA		3.7	Yes	Yes
16	13	M	Structural / Periventricular leukomalacia	10	VPA, LEV, PB, CZP		8.9	No	No
17	8	M	Unknown	7	LTG		13.4	Yes	Yes
18	5	M	Structural / Herpes encephalitis	5	NZP, CBZ, TPM		12.9	Yes	Yes
19	7	F	Unknown	5	CBZ, VPA		10.6	Yes	Yes
20	5	M	Structural / Tuberous sclerosis	9	LTG, PB		15.0	No	No
21	6	M	Structural / Tuberous sclerosis	6	LTG, PRP		7.8	No	No
22	11	M	Unknown	8	VPA, PHT		10.3	Yes	No

[a]antiepileptic drugs: CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESM: ethosuximide; FBM: felbamate; GBP: gabapentin; LTG: lamotrigine; LEV: levetiracetam; NZP: nitrazepam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; TPM: topiramate; VPA: valproic Acid.
[b]KD: ketogenic diet; VNS: vagal nerve stimulation.

less than 50% reduction, or increase in seizure frequency, were considered non-responders. The treatment response was determined for each patient at two time points: three months after the initiation of treatment (short term) and at the last follow-up visit.

Statistical analysis

We used descriptive statistics to characterize our population of patients. Comparison between responders and non-responders was performed using chi-square test and student's *t* test for categorical and quantitative variables, respectively. Statistical significance was set to $p<0.05$.

Results

We identified 25 children with refractory focal epilepsy treated with LCM. Three patients were excluded from the analysis because of insufficient clinical information in the medical records. We included 14 (64%) boys and 8 (36%) girls with a mean age of 12.9 years (SD: 5.2; range: 5.2-20.7 years) at the initiation of treatment with LCM. The mean age at onset of seizures was 4.2 years (SD: 4.1; range: birth to 12.1 years). Fourteen (64%) patients had developmental delay. All patients had undergone MRI scans of the brain. The putative aetiology of their epilepsy was found to be structural in 11 patients, metabolic in 1 patient and of unknown aetiology in 10 patients (*table 1*). All patients had focal onset epilepsy and the majority of them had multiple seizure types (*table 2*). Twenty out of 22 patients had lateralizing EEG findings (focal onset electrographic seizures, epileptiform discharges or focal slowing) and two of them additionally had generalized epileptiform activity.

Patients had previously received an average of 7.5 AEDs (SD: 2.5; range: 4-14). At the initiation of treatment with LCM, the average number of concomitant AEDs was 2.3 (SD: 0.9; range: 1-4). Three patients (14%) had tried but none benefited from vagal nerve stimulation. Three patients (14%) had tried the ketogenic diet: two did not tolerate the diet, one benefited for one year with a >90% control of seizures and then relapsed. Only one patient had undergone neurosurgery which helped to partially control epilepsy by reducing the frequency of seizures. The mean initial dose of LCM was 2.9 mg/kg/d (SD: 1.4; range: 0.9-5.4) and the mean maintenance dose was 8.4 mg/kg/d (SD: 4.2; range: 2.1-16.6). The average length of follow-up after starting LCM was 11.9 months (SD: 11.0; range: 3 to 35 months).

A total of 13 patients (59%) had more than 50% reduction of seizures at the three-month follow-up visit, and 10 patients (45%) still had a ≥50% reduction of seizures at the last follow-up visit (*figure 1*). Moreover, a significant proportion of patients had more than 90% seizure reduction: 23% and 14% at the three-month and last follow-up visits, respectively, with one being seizure-free. Six patients in the study have been on lacosamide for over two years and four were still responding to treatment. The patients' characteristics according to treatment response at the last follow-up visit are presented in *table 3*. Responder and non-responder groups were identical with respect to the patients' age, the maximal maintenance dose attained, the number of previous and of concomitant AEDs, as well as the occurrence of interictal epileptiform discharges noticed on the regular EEG recording preceding LCM treatment initiation. The only statistically significant difference was observed with respect to gender, the proportion of girls that responded to treatment being greater than the proportion of boys (75% vs 29%; $\chi^2=4.43$, df=1, $p=0.035$). Girls were not different from boys with respect to patient age, maximal maintenance dose attained, number of previous and concomitant AEDs, or the aetiology of epilepsy.

Among the six non-responders with interictal epileptiform discharges noticed on the last regular EEG preceding treatment initiation (*table 3*), four had EEG recordings before their last follow-up visit. The frequency of discharges decreased in two of them and remained unchanged in the remaining two. Only two out of three responders with interictal discharges had follow-up EEGs and their frequency remained

Table 2. Seizure characteristics and lacosamide adverse effects in our population of patients (*n*=22).

Items	*n* (%)
Seizure types:	
Generalized:	
Atonic	1 (5%)
Tonic	1 (5%)
Myoclonic	5 (23%)
Atypical absence	3 (14%)
Focal:	
Without impairment of consciousness	5 (23%)
With impairment of consciousness	17 (77%)
Evolving to bilateral convulsive seizure	13 (59%)
Lacosamide adverse effects:	
Dizziness	5 (23%)
Drowsiness	5 (23%)
Incoordination	3 (14%)
Irritability	2 (9%)
Insomnia	2 (9%)
Headache	1 (5%)
Blurred Vision	1 (5%)
Nausea	1 (5%)

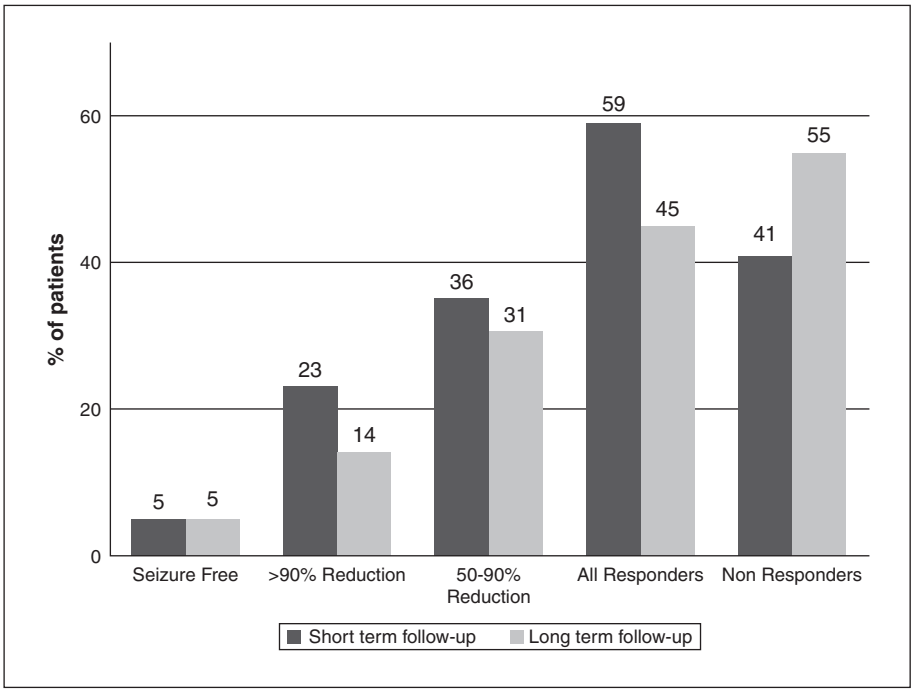

Figure 1. Reduction in seizure frequency and overall response to lacosamide treatment after the short-term (three months) and long-term (mean: 11.9 months) follow-up period.

Table 3. Patient characteristics according to response to lacosamide treatment at the last follow-up visit.

Item	Responders (*n*=10)	Non-Responders (*n*=12)	*p* Value
Age, years (mean [SD])	13.6 (5.6)	12.3 (5.0)	0.28
Gender (*n* [%]) Male (*n*=14) Female (*n*=8)	 4 (29%) 6 (75%)	 10 (71%) 2 (25%)	 0.035
Maximal maintenance dose, mg/kg/d (mean [SD])	8.3 (4.9)	8.4 (3.6)	0.5
Number of previous AEDs[a] (mean [SD])	6.5 (2.0)	8.3 (2.7)	0.054
Number of concomitant AEDs (mean [SD])	2.0 (0.8)	2.3 (0.8)	0.11
Interictal epileptiform discharges on the regular EEG preceding LCM treatment initiation (n [%])	3 (30%)	6 (50%)	0.4

[a]antiepileptic drugs

unchanged. No patients had increase in the frequency of epileptiform discharges post-treatment.

The proportion of patients who responded to treatment was similar between patients treated with a combination of LCM and sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine, phenytoin) and those treated with a combination of LCM and AEDs with a different mechanism of action (50% and 38%, respectively; p=0.57). Finally, treatment response was not significantly different between the patients with symptomatic (structural or metabolic) or cryptogenic (unknown) aetiology of epilepsy, with 50% (5/10) and 42% (5/12) of patients respectively having responded to treatment.

At three months after initiation, four patients (18%) had discontinued treatment with LCM. Reasons for interruption were mild but persistent adverse effects in three patients and lack of efficacy in one patient. At

the last follow-up visit, a total of nine patients (41%) had discontinued treatment. Reasons were persistent adverse effects in six patients and lack of efficacy in three patients.

Adverse effects (*table 2*) were observed in 11 patients (50%), dizziness and drowsiness being the most frequently reported adverse effects in our population. No severe adverse events were reported. The average maximal doses reached by patients with and without adverse effects were similar (8.6 and 8.1 mg/kg/d, respectively; p=0.38).

Discussion

In three previous adult randomized, double-blind, placebo-controlled studies (Ben-Menachem *et al.,* 2007; Halasz *et al.,* 2009; Chung *et al.,* 2010), LCM was shown to be safe and effective with as many as 40% of patients showing ≥50% seizure reduction by the end of a three-month follow-up period. Data regarding the experience with LCM in the paediatric population is limited, but five retrospective studies have shown so far that the proportion of children that respond to treatment varies between 30 and 50% (Heyman *et al.,* 2012; Gavatha *et al.,* 2011; Guilhoto *et al.,* 2011; Rastogi and Ng, 2012; Yorns *et al.,* 2014), indicating that the efficacy in children appears to be equivalent to that in adults. The present study, showing ≥50% seizure reduction in 59% of children after the short-term three-month follow-up, adds more evidence toward this finding. Our data also indicate a minor decrease in the proportion of patients responding to LCM with longer duration of follow-up, due to both loss of effectiveness and treatment discontinuation due to adverse effects. Nevertheless, the effectiveness of LCM was maintained in as many as 45% of patients even after an average of one year of treatment.

Our study does not show significant difference between responders and non-responders with respect to the patients' age, maximal maintenance dose attained, number of previous and concomitant AEDs, EEG findings, or the aetiology of epilepsy. The only statistically significant difference noticed between the two groups was the treatment response by gender, with females (75%) responding better than males (29%). This finding is surprising as no previous study reported a gender effect on the LCM treatment response and, to our knowledge, no such reports exist for other AEDs. However, knowing that girls are more likely to benefit from treatment than boys would be of great clinical importance and is worth being validated by larger trials.

The maximal maintenance dose of LCM in our population of patients was quite variable (2.1 to 16.6 mg/kg/d), partially due to the lack of clear dosing recommendations in children. However, the mean dose was identical in responders and non-responders (8.3 and 8.4 mg/kg/d, respectively), which suggests that the lack of efficacy in non-responders was most probably not accounted for by insufficient dosing.

Our study population included only patients with refractory focal epilepsy, reflecting the current practice at our hospital, in accordance with the FDA and Health Canada recommendations. However, LCM has been shown effective in a rat model of generalized epilepsy (Stöhr *et al.,* 2007). Moreover, paediatric studies that included patients with refractory generalized epilepsy reported a similar efficacy to focal epilepsy (42.5%) or slightly lower (25% *vs* 62.5%) (Heyman *et al.,* 2012; Rastogi and Ng, 2012; Yorns *et al.,* 2014). Nevertheless, a substantial proportion of patients responding to treatment with LCM suggests that the indications of use of LCM could be extended to a larger population of paediatric patients. Future studies could investigate the spectrum of patients with generalized epilepsies responding to LCM treatment.

Another important avenue of LCM use is the utility of the intravenous formulation for the emergency treatment of status epilepticus. Numerous case reports and case series described LCM effectiveness in adults with various types of status epilepticus. A systematic review of 19 studies (136 patients) demonstrated an overall success rate of 54% (Höfler and Trinka, 2013). The data for paediatric status epilepticus is scarce, but an Italian multicentre study of nine patients with refractory status epilepticus has shown a success rate of LCM as high as 45% (Grosso *et al.,* 2014). Although we began using LCM for treating status epilepticus in our centre, our experience is still limited.

It has been suggested that LCM, acting via the slow inactivation of voltage-gated sodium channels, would be more effective when combined to AEDs with different pharmacodynamic properties (Villanueva *et al.,* 2012). Our study results, similar to those of Kim *et al.* (2014), could not find greater effectiveness of LCM when combined to AEDs with a mechanism of action other than sodium channel blockers. In fact, although the difference was not statistically significant, we found more responders among patients using another sodium channel blocker than AEDs with other mechanisms of action (50% vs. 38%, respectively). This could suggest that blockade of the sodium channel in different states might improve seizure outcome. Prospective studies with larger sample size are, however, needed to explore the role of LCM in polytherapy.

Common adverse effects reported in the adult trials and paediatric studies were dizziness, nausea, drowsiness, diplopia, and headaches (Ben-Menachem *et al.,* 2007; Halasz *et al.,* 2009; Chung *et al.,* 2010; Gavatha *et al.,* 2011; Guilhoto *et al.,* 2011; Heyman *et al.,* 2012; Rastogi and Ng, 2012; Kim *et al.,* 2014; Yorns

et al., 2014). In our study, similar adverse effects were noted, with dizziness and drowsiness being the most common. No severe adverse effects were reported. As previously reported (Yorns *et al*., 2014), these adverse effects tended to happen early on and often limited the increase of LCM to optimal doses. A total of 12 (55%) patients reported persistent adverse effects, and in six of them this was the reason for treatment discontinuation. At the end of our study, a total of 41% of patients had discontinued treatment because of adverse effects or lack of effectiveness which is within the range from other paediatric studies (mean: 30%; range: from 14% to 50%) (Heyman *et al*., 2012; Gavatha *et al*., 2011; Guilhoto *et al*., 2011; Kim *et al*., 2014; Rastogi and Ng, 2012; Yorns *et al*., 2014).

In conclusion, our study adds evidence that LCM appears to be an effective and safe adjunctive treatment in paediatric patients with refractory epilepsy. The profile of patients who are most likely to benefit from treatment is still unknown. In this respect, our study is the first to suggest the possibility of a better response to treatment in girls compared to boys. Larger studies are needed to identify the best combinations of LCM and other AEDs that will allow for rationale polytherapy. Innovative clinical trials will help obtain further evidence on the safety and efficacy of LCM in paediatric patients with epilepsy and will validate hypotheses generated by previous observational studies (Registry and results database of publicly and privately supported clinical studies of human participants conducted around the world, 2014). □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
Dr. Carmant has received investigator initiated funding from UCB to study vigabatrin in humans and brivaracetam in animal models. Dr Carmant is on the advisory boards and speaker bureaus of UCB Canada, Eisai Canada, Baylis Canada and on the safety committee of UCB International for the study of clobazam. Dr Major is on advisory boards for Novartis and UCB Canada.

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TEST YOURSELF

(1) Is lacosamide safe and effective for treating paediatric patients with refractory focal epilepsy?

(2) What is the lacosamide mechanism of action?

(3) What are the most common adverse events of treatment with lacosamide?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".