Abstract

Aim: To assess effectiveness and tolerability of lacosamide in paediatric clinical practice.

Methods: Search of our hospital's pharmacy database yielded all children <16 years old dispensed lacosamide for drug-resistant epilepsy between January 2011 and June 2016. Medical records were reviewed for clinical and drug details. Continued treatment for ≥ 12 months was considered an indicator of effectiveness and tolerability.

Results: 107 children (61 boys) satisfied inclusion criteria. Median age at lacosamide commencement was 9.9 years (IQR 6.7 – 13.7). 57 (53%) children had focal epilepsy, with focal motor or impaired awareness seizures most commonly. 50 (47%) children had generalised epilepsy, most with tonic-clonic seizures, tonic seizures or epileptic spasms. 83 (78%) children had an intellectual disability, 24 (22%) had a physical disability and 22 (21%) had an autism spectrum disorder. 69 (65%) children continued lacosamide for ≥ 12 months. Reasons for discontinuation before 12 months in 38 (35%) children included ineffectiveness in 25 (66%), adverse events in 7 (18%) and worsening of seizures in 2 (5%). The most common adverse events were drowsiness, behavioural changes, unsteadiness, nausea and vomiting. Epilepsy type and comorbidities were not associated with continuation or reasons for discontinuation.

Conclusion: Most children continued treatment with lacosamide, suggesting effectiveness and tolerability. Lacosamide may prove to be a useful, "broad spectrum" antiepileptic medication in children, for focal and generalised epilepsies and in association with comorbidities.

Key words: Children; drug-resistant epilepsy; refractory epilepsy; lacosamide

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What is already known on this topic

1. Lacosamide is a newer antiepileptic-drug with a favourable pharmacokinetic profile and a novel mechanism of action.
2. Lacosamide is approved for use in patients age 16 years and older with drug-resistant focal epilepsy.
3. In adults with refractory epilepsy lacosamide has been shown to be effective and well tolerated.

What this paper adds

1. Most children with drug-resistant focal and generalised epilepsy continue treatment with lacosamide, suggesting a degree of effectiveness and tolerability.
2. Adverse drug events on lacosamide are reported infrequently.
3. The presence of comorbidities does not affect effectiveness or tolerability.

1. Introduction

The long-term prognosis for seizures in children with epilepsy is favourable in most.^{1,2} However, about 30% of patients with epilepsy have an incomplete response to drug therapy.⁴

Lacosamide is a newer AED, approved for the use in patients age 16 years and older with drug-resistant focal epilepsy. Lacosamide has a novel mechanism of action, selectively enhancing slow inactivation of voltage-gated sodium channels.⁵ Efficacy and tolerability of lacosamide have been shown in randomised controlled trials in adults with refractory focal seizures.⁶⁻⁸ Open label studies in adults with generalised epilepsy suggest a similar profile.⁹ Lacosamide is widely used off-label in children with drug-resistant epilepsy, though there is limited paediatric data available. Several open-label studies¹⁰⁻¹² and a recently completed randomised controlled-trial¹³ have shown favourable efficacy and tolerability of lacosamide in children with drug-resistant epilepsy.

There is only one report of Australian experience with lacosamide in children. Forty children, mostly with focal epilepsy, were included. They reported a responder rate (proportion of children with a 50% or greater reduction in seizure frequency) of 20%, with 5% children becoming seizure free and lacosamide being well-tolerated.¹⁴

We assessed the effectiveness and tolerability of lacosamide in real-world paediatric clinical practice in a large cohort of hospital patients with drug-resistant epilepsy.

2. Patients and Methods

2.1 Patient selection and data collection

We searched our hospital's pharmacy database for children younger than 16 years with epilepsy who were dispensed oral lacosamide between January 2011 and June 2016. Lacosamide was available from our hospital's pharmacy for children with drug-resistant epilepsy treated by a neurologist, lacosamide not being listed on the Pharmaceutical Benefits Scheme in Australia for subsidised prescription to children. Only children with a minimum 12-months clinic follow-up were included; children treated with lacosamide for brief periods were not excluded by this criterion. We extracted clinical data from medical records up to June 2017, including type of epilepsy and seizures, comorbidities, age at commencement of lacosamide, number of concomitant AEDs, duration of lacosamide treatment, reason for cessation and adverse events while on lacosamide. Data on quality

of life, cognition, behaviour, sleep, use of rescue medications and EEG were not reliably recorded or systematically collected.

2.2 Definition of primary and secondary outcomes

Continued treatment with lacosamide for 12 months or longer was considered a proxy indicator of effectiveness and tolerability. This was chosen because it allowed group analysis of children with variable periods of observation. Furthermore, prospective seizure diaries were not kept, so responder rates could not be assessed. Reported changes in seizure frequency were categorised as decreased, seizure free, unchanged, increased or uncertain. We assessed if type of epilepsy and presence of comorbidities affected the proportion of children who stayed on lacosamide for 12 months or longer. We determined reasons for cessation and adverse drug reactions. Finally, we also looked at the presence of concomitant sodium channel blocking (SCB) antiepileptic drugs and if there was a relationship to the continuation rate of lacosamide. Phenytoin, carbamazepine, oxcarbazepine and lamotrigine were denoted as SCB.

2.3 Classification of epilepsy and comorbidities

Types of epilepsy and seizures were defined according to the latest classification of the International League Against Epilepsy (ILAE) 2017.^{15,16} Children were classified broadly as having either focal or generalised epilepsy, based on their seizure semiology and EEG findings, recognising that children with a focal lesion as the basis for their epilepsy can manifest with generalised seizures (usually tonic seizures or epileptic spasms) and EEG abnormalities, and that children with a generalised (often genetic) predisposition to seizures can also have focal seizures. Comorbidities studied were intellectual disability, physical disability (e.g. cerebral palsy, dystonia) and autism spectrum disorder, as these were readily determined from chart review. Behaviour and learning disorders were more difficult to determine and characterise, and therefore not studied.

2.4 Statistical analysis

Statistical analyses were performed using STATA software (Intercooled V.14, StataCorp, College Station, Texas, USA). Demographic data and clinical characteristics were reported as frequency for categorical variables and median with interquartile range (IQR) for continuous variables. Continuous

variables were compared using *t*-test and categorical variables using chi-square analysis. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Demographics

The pharmacy search identified 112 children who were dispensed oral lacosamide during the study period from January 2011 until June 2016. Five children were excluded, of whom three had follow-up less than 12 months, one was dispensed lacosamide in error and one did not have epileptic seizures in retrospect. A total of 107 children were included in the study. Demographic data and clinical characteristics are summarized in Table 1.

3.2 Epileptic seizures and syndromes

The underlying aetiologies of epilepsy are listed in Table 1. The 57 children with focal epilepsy had focal motor seizures (31), focal seizures with impaired awareness (29), epileptic spasms (6), focal to bilateral tonic-clonic seizures (6) and focal sensory seizures (4). The 50 children with generalised epilepsy, of whom seven had Lennox-Gastaut Syndrome, four had idiopathic generalised epilepsy and two had Dravet Syndrome, had tonic seizures (31), generalised tonic-clonic seizures (21), epileptic spasms (13), myoclonic seizures (3), absence seizures (1), focal motor seizures (12) and focal seizures with impaired awareness (9). Seizure types in the four children with idiopathic generalised epilepsy were generalised tonic-clonic (4), myoclonic (2), tonic (1) and absence (1) seizures.

3.3 Change in seizure frequency

In the children with focal epilepsy, one child became seizure free, 27 (47%) had a decrease in seizure frequency, 23 (40%) had unchanged seizure frequency, and two (4%) had an increase in seizure frequency; in four (7%) seizure frequency was uncertain. In the children with generalised epilepsy, 23 (46%) had a decrease in seizure frequency and 22 (44%) had unchanged seizure frequency; in four (9%) seizure frequency was uncertain. Of the children with focal epilepsy whose seizures reportedly worsened, one had tonic seizures and the other had spasms and focal sensory seizures.

3.4 Lacosamide effectiveness and tolerability

The duration of lacosamide treatment (date of commencement of lacosamide to date of lacosamide discontinuation or last follow-up on lacosamide) was 1.2 – 66 months (median 12, IQR 5.5 – 40). Fifty-two (49%) children continued lacosamide at last follow-up and 55 (51%) discontinued lacosamide during the study period. Sixty-nine (65%) children continued treatment with lacosamide for 12 months or longer, while 38 children (35%) discontinued treatment with lacosamide before 12 months.

Continued treatment with lacosamide for 12 months or longer was not associated with type of epilepsy and comorbidities (Table 2). All four children with idiopathic generalised epilepsy continued lacosamide for 12 months or longer.

3.5 Reasons for cessation and adverse drug reactions

Reasons for discontinuing lacosamide before 12 months included lack of effectiveness in 25 (66%) children, adverse drug reactions in 7 (18%), worsening seizures in 2 (5%), seizure freedom following surgery in 3 (8%), and cost in one (3%). Adverse drug reactions that led to discontinuation included, lethargy, unsteadiness, fatigue, vomiting, pruritus, rash and aggression. An additional seven children reported minor side effects such as nausea, vomiting, behaviour change, irritability and drowsiness. Overall, adverse effects were reported in only 14 (13%) children. Adverse drug reactions were related to increasing doses of lacosamide in eight children (57%).

Forty (43%) children were taking a concomitant SCB antiepileptic drug. Discontinuation of lacosamide before 12 months was seen in 16 children taking a concomitant SCB antiepileptic drug compared to 22 not (p=0.45). Seven (50%) children with reported adverse effects on lacosamide were treated with a concomitant SCB antiepileptic drug.

4. Discussion

In this retrospective, observational study of effectiveness and tolerability of lacosamide as add-on therapy in children with drug-resistant epilepsy, 65% children continued treatment with lacosamide for 12 months or longer. Similar continuation rates were seen in children with focal and generalised epilepsies, various seizure types, various comorbidities and a diverse range of aetiologies. There was a 100% continuation rate in the four children with idiopathic generalised epilepsy. Lacosamide was

discontinued mainly due to ineffectiveness; in only 18% children was lacosamide discontinued due to adverse events. Overall, adverse events were infrequent (13%).

Retention rate is used as a measure of efficacy and tolerability in retrospective epilepsy studies and in long-term extension phases of clinical trials where seizure counts may not be reliably obtained.¹⁷⁻

¹⁹ Retention rate has gained importance in measuring primary outcome in studies with antiepileptic drugs, since it encompasses the time to treatment discontinuation for any reason and can be applied in clinical practice.^{20,21} In our study, retention rate was easily determined from clinic and pharmacy records, and acted as a substitute for prospective seizure diary and adverse event monitoring that is used in formal clinical trials. Twelve-month retention rates for lacosamide in our study are lower than reported for other AEDs.^{22,23} Frew et al reported that at 12 months, between 80-90 % remained on gabapentin, oxcarbazepine, carbamazepine, lamotrigine and topiramate.²²

Until recently, evidence for lacosamide use in children with drug-resistant focal and generalised epilepsies was based on retrospective^{10,11,14,24-26} and observational studies.²⁷⁻³² Retrospective case series of 16-40 children reported responder rates between 35-67%. Adverse events were reported in 18-59% and up to 25% of patients discontinued treatment due to adverse events. Prospective observational studies of 18-130 children reported 13-62% responder rates, with adverse events reported in 30-51%, leading to discontinuation of treatment in 3-14%. The most commonly reported adverse events in these studies were drowsiness, dizziness, nausea, vomiting, behavioural problems, visual disturbances and gait instability.

The results of the first multi-centre, randomized, double-blind, placebo-controlled trial of add-on lacosamide in children and adolescents with uncontrolled focal seizures were presented at the Annual Meeting of the American Society of Epilepsy in December 2017.¹³ 302 patients aged 4-16 years completed the trial. The responder rate was 52.9% for the lacosamide group and 33.3% for placebo group (odds ratio 2.17; p=0.0006). Sixty-eight percent patients on lacosamide and 58% on placebo reported drug-related adverse events, somnolence and dizziness being reported most commonly.

There is evidence that lacosamide may be better tolerated in patients not receiving concomitant SCB antiepileptic drugs, such as carbamazepine, oxcarbazepine, phenytoin or lamotrigine.³³⁻³⁶ In our

study, with 37% children taking a concomitant SCB drug, there was no difference in the duration of treatment between the group with a concomitant SCB drug and the group without.

Our study has several limitations due to its retrospective nature, variable periods of treatment and reliance on clinical reporting rather than prospective patient seizure diaries, prompting us to evaluate effectiveness and tolerability with retention rate. An additional limitation is that lacosamide doses in mg/kg/day could not be accurately determined due to uncertainty or change in exact doses prescribed and frequent lack of contemporaneous weights. Finally, adverse effects may be underreported due to the absence of a standardized inquiry and reporting. Nevertheless, the study does provide real-world evidence for effectiveness and tolerability of lacosamide in children, which will supplement the findings from the recent randomised controlled trial when published.

5. Conclusion

In summary, most children with drug-resistant epilepsy due to a variety of underlying aetiologies continued treatment with lacosamide for 12 months or longer, regardless of the type of seizures and the presence of comorbidities. Lacosamide was well-tolerated, with adverse effects reported in a minority. Lacosamide is likely to become a widely prescribed antiepileptic drug for different types of epilepsy and seizures in paediatric clinical practice.

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Table 1 Demographic and clinical data of patients included (n = 107)

Characteristics	N (% or range)
Male	61 (57%)
Median age at commencement of LCM[†]	9.9 years (IQR 6.7 – 13.7)
Median number of concomitant drugs	2 (IQR 2 – 3)
Number on concomitant sodium channel blockers	40 (37%)
Type of epilepsy	
Focal	57 (53%)
Generalised	50 (47%)
Comorbidities	
Intellectual disability	83 (78%)
Movement disorder	24 (22%)
Autism spectrum disorder	22 (21%)
Median number of concomitant AEDs[‡] at commencement of LCM[†]	2 (0 – 4)
Aetiologies	
Brain malformation	21 (20%)
Chromosomal anomaly	15 (14%)
Dravet syndrome	2 (1.9%)
Focal cortical dysplasia	16 (15%)
Perinatal stroke	5 (4.7%)
Tuberous sclerosis	4 (3.7%)

Metabolic disorder	4 (3.7%)
Neonatal hypoglycaemia	3 (2.8%)
Meningitis, encephalitis	4 (3.7%)
FIRES	1 (0.9%)
Neonatal hypoxic ischaemic encephalopathy	3 (2.8%)
Rasmussen encephalitis	2 (1.9%)
Hippocampal sclerosis	2 (1.9%)
Acute demyelinating encephalomyelitis (ADEM)	1 (0.9%)
Dysembryoplastic neuroepithelial tumour (DNET)	1 (0.9%)
Idiopathic generalised epilepsy	4 (3.7%)
Unknown (negative history, normal imaging)	19 (18%)

† Lacosamide, ‡ antiepileptic drug

Table 2 Treatment duration of lacosamide overall and in subgroups

	≥ 12 months	< 12 months	<i>P</i>
Overall, n (%)	69 (65%)	38 (35%)	
Type of epilepsy			
Focal, n (%)	34 (60%)	23 (40%)	0.26
Generalised, n (%)	35 (70%)	15 (30%)	0.26
Comorbidities			
Intellectual disability, n (%)	55 (66%)	28 (34%)	0.47
Movement disorder, n (%)	17 (71%)	7 (29%)	0.46
Autism spectrum disorder, n (%)	13 (59%)	9 (41%)	0.55

Title page

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