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A case series of lacosamide as adjunctive therapy in refractory Sleep-related Hypermotor Epilepsy (previously Nocturnal Frontal Lobe Epilepsy).

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Summary

To evaluate the efficacy and tolerability of open label lacosamide in patients with refractory Sleep-related Hypermotor Epilepsy (SHE).

Case review of eight patients with refractory SHE treated with lacosamide. Seizure diaries compared the mean baseline seizure frequency with the most recent three months of follow-up.

Five (62.5%) patients were responders, defined as ≥50% reduction in seizure frequency, over a mean duration of exposure of 21.5 months. The mean maintenance dose of lacosamide was 400mg/day. None reported worsening of seizures. Lacosamide was well tolerated with initial fatigue being the main side effect.

Lacosamide is a potentially efficacious adjunctive therapy in patients with refractory SHE. A double-blind placebo-controlled study would determine its efficacy.

Key Words: Lacosamide, antiepileptic drugs, sleep-related hypermotor epilepsy**Introduction**

Sleep Related Hypermotor Epilepsy (SHE), previously Nocturnal frontal lobe epilepsy (NFLE), is a sleep-related disorder characterised by clusters of motor seizures during sleep. The disorder was renamed SHE to recognise the pattern of seizures- occurring during day and night-time sleep, their localisation- which may be extra-frontal and their motor manifestations (Tinuper, Bisulli et al. 2016). Seizures may vary, from brief paroxysmal arousals to paroxysmal dystonia and hypermotor phenomena (Provini, Plazzi et al. 1999). SHE varies markedly in severity and pharmacoresponsiveness; patients typically experience many seizures a night.

Seizures typically respond to carbamazepine (Scheffer, Bhatia et al. 1995) although a third of patients are refractory (Oldani, Zucconi et al. 1998, Provini, Plazzi et al. 1999). Since patients are

often non-lesional, without localizing abnormalities on EEG or structural MRI (Provini, Plazzi et al. 1999)(Scheffer *et al.* 1995), novel pharmacotheraputic options are required.

Lacosamide is an antiepileptic drug licensed for focal seizures. It was reported as efficacious in two patients with SHE (Liguori, Romigi et al. 2015). We also observed a marked response to lacosamide in one patient with SHE which led us to review our experience of lacosamide as adjunctive treatment in eight patients with SHE.

Methods

Following the response of Patient 4 to lacosamide during trial SP774: An open-label extension trial to determine safety and efficacy of long-term oral SPM 927 in patients with partial seizures, we undertook a case review of patients with refractory SHE who were treated with lacosamide. Patients were recruited from the epilepsy clinic at Austin Health and the private practices of the investigators. A diagnosis of SHE was made following clinical characterisation of the seizures, supported by video-EEG monitoring. No patient had a causative lesion on MRI brain.

Patients were reviewed at regular intervals in the clinic. Seizure frequency was serially documented in seizure diaries. Where patients had not been reviewed in the previous three months at the time of study, telephone consultations were performed to ascertain current seizure frequency.

Treatment outcomes with lacosamide were defined as:

Responder: ≥50% reduction in seizure frequency (last three months of follow up compared with the three months pre-treatment)

Partial responder: 25-50% reduction.

Non-responder: no change or increase in seizure frequency.

Molecular analysis

All patients underwent sequencing of *CHRNA4* and *CHRNB2*, the genes encoding the α4 and β2 subunits of the neuronal nicotinic acetylcholine receptor, as previously described (Steinlein, Mulley et al. 1995, Phillips, Scheffer et al. 1998, Phillips, Favre et al. 2001). Patients 2, 4, 5, 6 and 7 were also sequenced for the sodium-gated potassium channel gene *KCNT1* associated with severe autosomal dominant SHE (Heron, Smith et al. 2012) . Patient 3 underwent whole exome sequencing which lead to the identification of a *KCNT1* mutation (Heron, Smith et al. 2012).

All patients, or their parents or legal guardians in the case of minors or those with intellectual disability, gave informed research consent.

Results

The 8 patients (5 males) had a mean age of 36 years (range 21-54) (table). Mean age at seizure onset was 9 years (range 1-25). Three patients had intellectual disability and psychiatric features of psychosis (2) and autism spectrum disorder (2).

Patients experienced a range of sleep-related seizure phenomena, including stereotyped arousals and more prolonged hypermotor attacks, occurring both during daytime naps and night-time sleep.

Prior to lacosamide, all patients received a minimum of six antiepileptic drugs including carbamazepine. Whilst taking lacosamide, five patients continued with additional antiepileptic drugs (AEDs) (table). The mean length of exposure to lacosamide was 21.5 months (range 6-37); mean maintenance dose of 400mg/day (range 300-600 mg/day). During the period of exposure to lacosamide, all doses of other AEDs remained unchanged. Of the six patients who responded to lacosamide, five were responders, defined as a >50% seizure reduction, and one (patient 3) showed a 25% response (Table). Of the non-responders, one withdrew lacosamide after two months (patient 7) and one after 24 months (patient 8). No patient experienced seizure exacerbation.

Tolerability

Two patients complained of transient fatigue within the first six months of commencing lacosamide. Patient 7 felt 'spaced out' on 300mg/day and subsequently stopped lacosamide.

Patient 4 experienced diplopia on 500mg/day, which resolved when the lacosamide dose was reduced. Following a dramatic improvement in seizure frequency, patient 4 experienced a gradual return to baseline seizure frequency after 31 months of lacosamide treatment. The drug was subsequently withdrawn.

Discussion

Refractory SHE is challenging to manage despite an increasing armamentarium of AEDs. SHE has a major impact on the lives of patients and their families with poor sleep having a major impact on their quality of life (Provini, Bisulli et al. 2012). Many patients do not have causative structural lesions and the mainstay of management is AED therapy. Here we show in a small retrospective observational series that lacosamide was effective in 5 of 8 patients. This was a highly refractory population who had failed six prior AEDs at least including first line agents such as carbamazepine.

The gold standard in AED trials is a randomized double blind placebo controlled trial. For lacosamide, these show a 40% responder rate in focal epilepsy and a 36-40% median reduction in seizure frequency when it used as adjunctive therapy at doses of 200-600mg/day (Ben-Menachem, Biton et al. 2007) (Flores, Kemp et al. 2012, Weston, Shukralla et al. 2015). No studies to date have examined the efficacy of LCM in SHE specifically, although two cases were reported showing dramatic reduction in seizure frequency following the introduction of lacosamide and seizure freedom at 12 months with lacosamide monotherapy (Liguori, Romigi et al. 2015).

Limitations

Our study strengthens the case for the use of Lacosamide in SHE . Results need to be interpreted in the context of the limited sample size and the inherent difficulty in obtaining accurate long term data regarding seizure frequency in this population; many seizures are subtle and escape detection without video-EEG monitoring (Provini, Bisulli et al. 2012). Three of our patients had a long-term bed partner. Diaries recorded by the remaining five patients and their carers are likely to be a conservative estimate of seizure frequency as many more seizures were captured during video-EEG monitoring. Serial video-EEG monitoring would have been preferable, nevertheless seizure diaries remain the most practical way of monitoring seizure frequency. Data collection was undertaken for three months as this was considered to be a reasonable time frame during which a sustained change in seizure frequency could be captured.

Five patients received lacosamide with carbamazepine or oxcarbazepine (Table). Lacosamide, then licenced for use as adjunctive therapy in focal epilepsy, was only used as monotherapy in those patients participating in a clinical trial. Limited data has suggested that efficacy and adverse event rate are improved if lacosamide is combined with a non-sodium channel blocker AED (Villanueva, Lopez-Gomariz et al. 2012). A recent study of lacosamide in temporal lobe

epilepsy did not reflect this (Borzi, Di Gennaro et al. 2016). Our numbers are too small to draw conclusions regarding the optimal combination of AEDs.

This case series adds support to a recent study of two cases of SHE who benefited from lacosamide. There is a need for randomized placebo controlled studies to determine if lacosamide is indicated for specific syndromes, such as SHE.

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References

Ben-Menachem, E., V. Biton, D. Jatuzis et al (2007). "Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures." Epilepsia **48**(7): 1308-1317.

Borzi, G., G. Di Gennaro, F. C. Schmitt, et al (2016). "Lacosamide in patients with temporal lobe epilepsy: An observational multicentric open-label study." Epilepsy Behav **58**: 111-114.

Flores, L., S. Kemp, K. Colbeck et al (2012). "Clinical experience with oral lacosamide as adjunctive therapy in adult patients with uncontrolled epilepsy: A multicentre study in epilepsy clinics in the United Kingdom (UK)." Seizure **21**(7): 512-517.

Heron, S. E., K. R. Smith, M. Bahlo et al (2012). "Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy." Nat Genet **44**(11): 1188-1190.

Liguori, C., A. Romigi, F. Placidi et al (2015). "Effective treatment of nocturnal frontal lobe epilepsy with lacosamide: a report of two cases." Sleep Med.

Oldani, A., M. Zucconi, R. Asselta et al (1998). "Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome." Brain **121 (Pt 2)**: 205-223.

Phillips, H. A., I. Favre, M. Kirkpatrick, S. et al (2001). "CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy." Am J Hum Genet **68**(1): 225-231.

Phillips, H. A., I. E. Scheffer, K. M. Crossland et al (1998). "Autosomal dominant nocturnal frontal-lobe epilepsy: genetic heterogeneity and evidence for a second locus at 15q24." Am J Hum Genet **63**(4): 1108-1116.

Provini, F., F. Bisulli and P. Tinuper (2012). "Nocturnal Frontal Epilepsies: Diagnostic and Therapeutic Challenges for Sleep Specialists." Sleep Medicine Clinics **7**(1): 105-112.

Provini, F., G. Plazzi, P. Tinuper et al (1999). "Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive cases." Brain **122 (Pt 6)**: 1017-1031.

Scheffer, I. E., K. P. Bhatia, I. Lopes-Cendes et al (1995). "Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder." Brain **118 (Pt 1)**: 61-73.

Steinlein, O. K., J. C. Mulley, P. Propping, et al (1995). "A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy." Nat Genet **11**(2): 201-203.

Tinuper P[1], Bisulli F[1], Cross JH[1] et al (2016). " Definition and diagnostic criteria of sleep-related hypermotor epilepsy**."** Neurology 86(19):1834-4

Villanueva, V., E. Lopez-Gomariz, J. Lopez-Trigo et al (2012). "Rational polytherapy with lacosamide in clinical practice: results of a Spanish cohort analysis RELACOVA." Epilepsy Behav **23**(3): 298-304.

Weston, J., A. Shukralla, A. J. McKay and A. G. Marson (2015). "Lacosamide add-on therapy for partial epilepsy." Cochrane Database of Systematic Reviews(6).

							Mean seizure freq/month			
	Age	Gender	Age at onset	Genes	Comorbid condition	Concurrent AEDs	Initial	24 months	% change	LCM dose (mg/day)
1	45	M	6	*CHRNA4*		CBZ	450	40	91	300
2	33	F	25			none	40	10	75	600
3	54	M	25			OXC TOP	10	3	70	400
4	21	F	1		ID ASD	TOP	25	[8*]	68	300
5	26	M	7			PHT CBZ ZNS	100	40	60	400
6	28	F	3	*KCNT1*	ID psychosis	PHT VPA	400	300	25	400
7	52	M	7			none	300	300	0	300
8	28	M	1	*DEPDC5*	ID ASD	CBZ	15	15	0	300

*6 month follow-up ASD autism spectrum disorder LCM lacosamide

Clinical features and seizure frequency outcomes at 24 months.