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Original article

A clinical efficacy experience of Lacosamide on sleep quality in patients with Nocturnal Frontal Lobe Epilepsy (NFLE)

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Summary. *Background:* Nocturnal frontal lobe epilepsy (NFLE) is a focal epilepsy with seizures arising mainly during sleep and characterized by complex motor behavior or sustained dystonic posturing. First described in 1981, it was considered a motor disorder of sleep and was indicated as nocturnal paroxysmal dystonia (NPD). The debated on epileptic origin of this condition was demonstrated in 1990 and the term NFLE was introduced. Since then it has been demonstrated that the heterogeneous aspects of morpheic seizures were responsive to antiepileptic drugs (AED's) with sodium blocking action mechanism, especially the carbamazepine (CBZ). *Aim of Work and Methods:* We report a clinical experience of NFLE patients associated with sleep disorders treated with Lacosamide, AED's with a novel mechanism of action. In vitro electrophysiology studies have shown that lacosamide selectively boosts the slow inactivation of the sodium-voltage-dependent channels, resulting in a stabilization of the hypersensitive neuronal membranes. *Results and Conclusion:* On the treated patients we observed a positive clinical response to lacosamide therapy without significant side effects. In particular, the effective clinical response to the pharmacological treatment was obtained at a dose of 200 mg/day. (www.actabiomedica.it)

Key words: Nocturnal frontal lobe epilepsy, sleep disorders, Lacosamide

Introduction

Nocturnal Frontal Lobe Epilepsy (NFLE) is a form of focal epilepsy with heterogeneous clinical presentation of morpheic seizures that tend to cluster overnight (1).

Genetically the NFL is inherited in dominant autosomal manner. The genetic defect was first isolated to the gene CHRNA4 coding for the alpha4 subunit of the neuronal nicotinic acetylcho-line receptor (nAChR) and afterwards mutations in genes CHRNA2 and CHRNB2 coding for other subunits (alpha2 and beta2) of the nAChR have been identified (2, 3). Often recording EEG, both in the ictal and interictal stages, is negative for epileptiform activities. In most cases a good response to carbamazepine (CBZ) was described but not to other AEDS. Related to the clinical presentation (stereotyped dystonic/dyskinetic features of attacks), the almost absence of EEG abnormalities and the recurrence of episodes during sleep, the authors debated the epileptic origin of the NFLE, considering it as a sleep motor disorder with an unclear pathophysiology (4).

Furthermore, due to the recurrence of the motor events during sleep, NFLE patients may complain of daytime sleepiness and/or other sleep disorders (5, 6) .

Below we report our clinical experience in five patients of both sexes and ages between 26 and 43 years affected by NFLE and sleep disorders successfully treated with lacosamide (LCM).

LCM present a novel mechanism of action: the active principle, lacosamide (R-2-acetamido-N-benzyl-

3-methoxypropionamide) is an aminoacid to which other functional groups have been added. Although the precise mechanism of action by which lacosamide has an antiepileptic effect in humans has not yet been fully explained, in vitro electrophysiology studies have shown that lacosamide selectively boosts slow inactivation of sodium-dependent voltage-dependent channels , resulting in a stabilization of the hypersensitive neuronal membranes (7).

Methods

In our study, we observed five patients with multiple-frequency night-time seizures episodes, men and women aged between 26 and 43 years. In all of our patients, night-time seizures were stereotyped (ballistic upper right and chewing gait movements, explosive vocalization, scratch movements, dystonic posturing of the left toe, etc.) with multiple frequency and short duration. Only in three of the five patients described, partial epileptic seizures have been sometimes followed by secondary generalization.

Family history and brain magnetic resonance imaging (MRI) was negative in all patients, except for one patient who had a positive history for febrile seizures.

Ictal and interictal scalp EEG revealed nonspecific anterior slow discharges in everyone.

Video-polysomnography showed an increase in sleep fragmentation and high percentage of waking with a simultaneous decrease in the percentage of deep sleep and the REM phase in four out of five patients; bilateral frontal slow waves that arise during the transition phases between NREM and REM sleep, was registered on ictal video-polysomnography in only one patient.

Mutations in nAChR were undetected.

All patients were administered the Epwort Sleepiness Scale (ESS) to assess the degree of daytime sleepiness and the score was greater than 10 in all five of our patients. In particular, 3 patients scored between 11 and 15 (moderate daytime sleepiness), and 2 patients scores above 16 (severe daytime sleepiness).

At the time of enrollment in the study, patients underwent antiepileptic therapy with high doses of carbamazepine/oxacarbazepine (1200mg/600mg day), which however was ineffective in night-time seizures control or ill tolerated for many side effects.

Therefore, the patients slowly withdrew from carbamazepine/ oxacarbazepine and started Lacosamide until the dosage of 100mg BD.

After 6 months of follow-up on Lacosamide treatment, 3 patients had still about two or three nocturnal seizures per month.

After 12 months follow-up, all patients were seizures free without significant side effects, and the daytime sleepiness disappeared (ESS score<10).

Conclusion

Nocturnal Frontal Lobe Epilepsy (NFLE) is a form of focal nocturnal epilepsy that due to its heterogeneous clinical presentation, the almost absence of EEG abnormalities and the recurrence of episodes during sleep, was renamed Sleep-Related Hypermotor Epilepsy (SHE) (4).

Although epileptic seizures are non-disabling since they occur at night and controlled by CBZ, these patients showed a reduced sleep quality that is negatively reflected on the activities of daily life.

The night-time awakenings, sleep fragmentation and parasomnias, induce an excessive daytime sleepiness and paradoxical insomnia.

This report has shown how lacosamide can be effective not only in the treatment of nocturnal seizures, but also in sleep disorders associated with them in SHE, probably due to the multiple action mechanisms of this drug (slow inactivation of voltage-gated sodium channels, inhibitions of carbonic anhydrases) (7,8).

Although in the literature has recently described some cases of NFE patients successfully treated with lacosamide (9), further studies will be needed to confirm these data and to investigate the positive effects of the drug on heterogeneous sleep disorders in this category of patients.

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