

Clinical management of elderly patients with epilepsy; the use of lacosamide in a single center setting

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Abstract

Introduction:

Lacosamide (LCM) is a third-generation anti-epileptic drug (AED) for which there is limited experience in the treatment of elderly epileptic patients. This study was performed to evaluate the use of LCM in this particular patient group, focusing on its tolerability and effectiveness. This is a retrospective, single-center study, in patients over 60 years old treated with LCM during 1/2010-5/2015. Altogether 233 elderly patients receiving LCM were identified; of these, 67 fulfilled the inclusion criteria, i.e. LCM administered for at least two weeks.

Results:

LCM was initiated for acute seizure disorders (prolonged complex partial seizures, recurrent seizures or status epilepticus) in 54 patients (81%) and for chronic epilepsy in 13 patients in an outpatient setting. The mean follow-up period for LCM treatment was 14 months. The mean daily dose of LCM at the end of follow-up was 368 mg (range 100-600) for those 57 patients that continued treatment. Ten patients (15%) stopped LCM treatment but none due to lack of efficacy and only three patients (4 %) because of side effects. The most frequent side effects were dizziness, fatigue and tremor.

Conclusions:

LCM was well tolerated even at relatively high doses even in combination therapy.

1. Introduction

Epileptic seizures are the third most common neurological disorder in the elderly after cerebrovascular disorders and dementias [1]. The commonest etiologies of new-onset epilepsy in older aged subjects include stroke, dementia, brain tumor and traumatic head injury [2, 3] but there is also a population of elderly patients with chronic epilepsy who have been receiving AED treatment for many decades. The incidence of epilepsy is highest among the elderly in comparison with other age groups [2, 4]. As the population of elderly citizens increase, we can expect to encounter more elderly patients with epilepsy.

When treating elderly patients, special attention should be made to selecting an AED that undergoes no interactions with other medications, especially with other AEDs [4]. Furthermore, tolerability issues are of major importance in this patient group.

Lacosamide (LCM) is a third-generation AED that acts by slow inactivation of voltage gated sodium channels. It has been available in Europe since 2008 and in Finland since 2009 as either an intravenous (i.v.) or an oral formulation. The oral formulation is approved in Europe as an adjunctive treatment for partial onset seizures with or without secondary generalization [5]. The intravenous formulation is approved for as replacement therapy for oral LCM, but it has been used also in emergency situations [6, 7]. LCM has a favorable pharmacokinetic profile with minimal drug-drug interactions and neither inducing nor inhibiting the CYP450 enzyme system. These are important features when treating elderly patients. At present, there is limited data on the use of LCM in elderly

patients with epilepsy. This study was performed to evaluate the use of LCM in this particular patient group, especially focusing on its tolerability and effectiveness.

2. Materials and methods

This was a retrospective study to analyze the outcome for patients aged sixty years or more treated with LCM in the Neurological Unit of Tampere University Hospital between January 2010 and May 2015. The hospital patient registry was used to identify the patients.

Altogether 233 patients who had been treated with LCM were found and their clinical data reviewed.

Sixty-six patients had started LCM in acute settings as treatment for an acute seizure disorder and received LCM for less than 2 weeks and they were therefore excluded from this evaluation. In

another 100 patients, there was a lack of sufficient follow-up data after the initiation of LCM in an acute situation. The majority i.e. 67/100 of these patients had died soon after the acute situation,

mostly due to serious comorbidities but only 1 of them because of status epilepticus. Our hospital serves as a tertiary center for difficult to manage neurological patients and also as the only

neurosurgical center for a larger population. Therefore additional 33 patients in whom there was insufficient follow-up data had originated outside our core hospital district and were treated in our hospital only for the acute emergency situation which had involved the initiation of LCM treatment.

Thus, in a total of 54 patients who had initiated LCM in the acute setting, there was reliable follow-up data and these were included in the study as well as 13 patients being treated in the outpatient clinic.

After the acute treatment period, patients from our own hospital district were transferred for follow-

up of epilepsy to our outpatient neurology clinic, but the overall monitoring of their general health was conducted in health centers by general practitioners.

This study was a non-interventional, retrospective study, which does not require ethical committee approval according to the Finnish Law on Research. Access to patient records was based on the statement provided by the Head of Science Centre, Tampere University Hospital Research and Innovation Services, Science Center.

3. Results

3.1 Patients

We had reliable follow-up data for at least 2 weeks for a total of 67 patients and these individuals were included in this analysis. The demographics of the patients are presented in table 1. About every third patient (23/67) had started LCM treatment within 2 weeks of the initial diagnosis of epilepsy but overall LCM had been initiated for acute seizure disorders (prolonged complex partial seizures, acute repetitive seizures or status epilepticus) in 54 patients (81%). Most of these patients started LCM therapy with an i.v. loading dose of 200-400 mg. Forty-one patients had received a previous epilepsy diagnosis and also previous AED treatment before the initiation of LCM therapy. The mean duration of epilepsy before LCM treatment was 8.8 years (range 0.9-60).

3.2 Tolerability and efficacy

During the follow-up period, 10 patients discontinued LCM; three were preplanned to terminate the LCM treatment after the acute situation but had actually continued medication for longer than 1 month, four had stopped treatment on their own volition, and only three had discontinued LCM use due to side effects. Of those who had discontinued LCM themselves, two patients had used also previously several other AEDs and also discontinued these drugs by their own volition, one patient who had taken LCM for 17 months then decided to stop using not only that drug but also any other AEDs and one patients had discontinued LCM, probably due to some misunderstanding in primary health care but continued to take oxcarbazepine (OXC). None of the patients who stopped LCM after a consultation with a neurologist, stated that a lack of efficacy was the reason for discontinuation. Side effects leading to discontinuation were fatigue, dizziness and tremor which were also the most common side effects reported at the follow-up visits. Even in patients with dizziness as a side-effect, there were no reported falls. None of the patient records reported falls, but if a fall was mild and not clinically significant, it is possible that they were not presented on hospital records but were evaluated in primary health care or were assumed to be a result of something else than LCM. About every third patient (34%) described some side effect, but no serious treatment-related adverse effects were reported and in many cases, adverse effects were present only at the beginning of treatment. It should also be noted that many patients were using polytherapy and therefore the side effect profile was not only attributable to LCM. In our patients there were no reported cardiac side-effects or significant changes in PQ-intervals in normal follow-up

protocol. This does not rule out minor changes with no clinical significance or need for changes in medication.

3.3 Follow up

The mean follow-up period for those who had stopped LCM treatment was 5.7 months (0.6-17), whereas for those who continued LCM treatment it was 16 months (1.5-48). The mean daily dose of LCM at the end of follow-up was 368 mg for the 57 patients continuing treatment. The dose range was extensive i.e. 100-600 mg/ day; the most common dose was 400 mg/day which was being taken by 32 patients whereas 11 patients were being treated with 200 mg/day.

At the end of follow-up, 13 patients were using LCM as monotherapy. The most commonly used combinations were LCM and levetiracetam (LEV) in 14 patients and LCM + topiramate (TPM) in 9 patients, other combinations were more random. The full data is presented in Table 2.

4. Discussion and conclusions

When treating elderly patients with epilepsy, often comorbidities and concomitant medications cause concerns in terms of tolerability. Our study indicated that LCM was well tolerated in elderly patients, even when LCM treatment was initiated in acute situations with relatively high doses as one component of combination therapy. The purpose of the present study was to evaluate long-term use of LCM in elderly, not its use in acute settings for which we are undertaking another study which will

address this issue. The most common combinations with LCM in our patients can be explained by patient selection i.e. the vast majority, over 80%, of patients started to receive LCM in an emergency situation. LCM has become a standard AED for the treatment of acute seizure disorders in our hospital, together with LEV and TPM. These AEDs are also commonly administered in combination therapy in refractory cases.

The safety and effectiveness of i.v. loading doses of LCM have been reported earlier in several studies evaluating more general populations [8, 9, 10, 7]; in the one small study focusing on the elderly [6] there was only sixteen patients. Intravenous dosing of LCM has been shown to cause rather similar side effects as orally administered LCM. Previously, Balcastro et al [6] reported that there were no significant side effects associated with i.v. LCM in the treatment of acute non-convulsive status epilepticus in elderly patients over the age of 65 years. There is also a recent study including elderly patients with 82 patients older than 60 years. None of these patients required any reduction in the rate of infusion and there were no cardiac side effects [11]. This is in agreement with the results of our study where no cardiac side effects were observed.

In our patients, the most common daily dose of LCM was 400 mg but doses up to 600 mg/day were used and tolerated. Even with these relatively high doses, only 4% of patients discontinued LCM due to adverse effects (AE). It is worth noting that none of the patients that started LCM in out-patient settings terminated LCM therapy due to AE. In the VITOBA study, which involved a significant number of elderly patients, assessing the effectiveness and safety of LCM add-on treatment, AEs were stated as the reason for discontinuation in 11% of patients [12]. The incidence of adverse effects with LCM has been reported to be similar in elderly patients as in their younger counterparts [12]. In the

VITObA study, a lack of efficacy was the reason for discontinuation of LCM in 3% of patients [12] but none of our patients discontinued treatment for this reason.

Our study found LCM to be beneficial in the clinical follow-up of 45 patients; 12 became seizure-free and the other 33 reported only occasional seizures. The change in seizure frequency after initiation of LCM treatment was gathered during control visits either by asking patients or by examining their seizure diary, and therefore the absolute count of seizures was not registered in patient records for all patients. In a recent study by Baulac et al [13], LCM was found to be as effective but better tolerated than carbamazepine-controlled release (CBZ-CR) in patients over the age of 65 years as monotherapy.

The main finding from our single-center real life retrospective study was that LCM displayed good tolerability even with relatively high doses often initiated with loading doses. The main limitation of our study is its retrospective nature and the lack of quantitative data on seizure frequencies before LCM treatment in most of the patients that started LCM in acute settings. Nonetheless, we were still able to include 67 elderly patients in the present study, making it one of largest study populations of LCM usage in this age group.

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All authors meet the International Committee of Medical Journals Editors (ICMJE) criteria for authorship and have given final approval to the manuscript to be published.

Conflict of interest and sources of funding statement

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Jussi Mäkinen has received support for travel congresses from Biogen-Idec, Boehringer-Ingelheim, Eisai, and Orion Pharma; received speaker honoraria from Boehringer-Ingelheim; received research funding from Finnish Epilepsy Association; and participated in an advisory board for Eisai.

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Table 1. Demographics of the patients

Number of patients	67
Sex (M/F)	37/30
Mean age when epilepsy was diagnosed (years)	60 (3-83)
Diagnosed > 60 years old	49
Diagnosed < 60 years old	18
Mean age at onset of LCM treatment (years)	68 (61-84)
Number of previous AEDs	
0	7
1	18
2	18
3 or more	24
Etiology of epilepsy, number (%)	
Post-stroke	24 (36)
Brain tumor	12 (18)
CNS infection	5 (7)
Other	13 (19)
Unknown	13 (19)

Table 2. AEDs at follow-up

AEDs including LCM	Number of patients
LCM	13
LCM+ LEV	14
LCM+TPM	9
LCM+CLB	4
LCM+TPM+CLB	3
LCM+LEV+TPM	2
LCM+LEV+CLB	2

LCM=lacosamide, LEV=levetiracetam, TPM=topiramate, CLB=clobazam

