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Short communication

Switching from traditional sodium channel blockers to lacosamide in patients with epilepsy

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ABSTRACT

Purpose: Lacosamide (LCM) is a recently developed sodium channel blocker (SCB), which acts mainly on the slow activation state in sodium channels. Although LCM shares a range of dose-dependent adverse effects with traditional SCBs, it has several advantages in that it does not induce hepatic drug metabolizing enzymes and has less risk of drug interactions and idiosyncratic adverse effects.

Methods: We retrospectively analyzed the efficacy and tolerability of switching from traditional SCBs to LCM. The reason for the switch was classified as insufficient efficacy, adverse effects, or concern about metabolic derangement, resulting in conditions such as atherosclerosis and osteoporosis, with long-term use of traditional SCBs.

Results: Seventy-five patients were switched to LCM from traditional SCBs. The overall rate of successful switching was high (81.3%, 61/75 patients). However, the success rate was strongly dependent on the reason for the switch; patients with insufficient efficacy on SCBs had less chance of a successful switch (71.8%, 28/39 patients) than those with adverse effects (89.5%, 17/19) or concerns about metabolic derangement (94.1%, 16/17, $p = 0.038$). Patients with insufficient efficacy were significantly younger ($p = 0.004$) and had a higher chance of drug-resistant epilepsy ($p = 0.004$) than those in the other two groups.

Conclusions: Our study shows that switching from traditional SCBs to LCM is usually successful and the likelihood of a successful switch is higher in patients when the reason for the switch is adverse effects or concerns about metabolic derangement on traditional SCBs.

1. Introduction

Sodium channel blockers (SCBs) have been the mainstay for pharmacological management of focal and generalized tonic-clonic seizures for more than 70 years. Lacosamide (LCM) is a recently developed SCB that acts primarily on the slow activation state of sodium channels, whereas traditional SCBs, such as phenytoin, carbamazepine, oxcarbazepine, and lamotrigine, act by inhibiting fast inactivation of these channels. Although LCM shares a range of dose-dependent adverse effects with traditional SCBs, including dizziness, drowsiness, and ataxia, it has several advantages over traditional SCBs in that it does not induce hepatic drug metabolizing enzymes and has less risk of drug interactions and idiosyncratic adverse effects [1].

Although some studies have suggested that combining traditional SCBs with LCM has an additive or synergistic effect [2], randomized controlled trials and subsequent observational studies have shown that efficacy and tolerability may be better when LCM is combined with non-SCBs than when it is combined with traditional SCBs [3–5]. Therefore, it would be reasonable to switch to LCM in patients in whom traditional SCBs have insufficient efficacy or are poorly tolerated. We hypothesized that switching from traditional SCBs to LCM would be effective in adult patients with focal seizures. We also attempted to identify the reasons for the switch, which might predict a successful switch to LCM in these patients.

2. Methods

The protocol for this 18-month, single-center, observational study was approved by our institutional review board. The need for informed consent was waived in view of the retrospective nature of the study. LCM has been licensed for the treatment of focal seizures in South Korea since 2011, but its use has only been fully covered by the National

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Health Insurance program in South Korea since February 2017. Patients with epilepsy who switched to LCM from other traditional SCBs between March 2017 and February 2018 were enrolled in the study. Traditional SCBs were defined as phenytoin, carbamazepine, oxcarbazepine, and lamotrigine. The following exclusion criteria were applied: insufficient follow-up, concomitant use of traditional SCBs, use of LCM as an initial monotherapy or adjunctive therapy; and a switch from non-SCBs. Efficacy and tolerability were evaluated for at least six months after switching to LCM. Eslicarbazepine was not available in South Korea during the study enrolment period, and drugs with multiple mechanisms of action including an effect on sodium channels, such as valproic acid, topiramate, and zonisamide, were not considered to be traditional SCBs in this study.

All patients underwent electroencephalography (EEG) and epilepsy-dedicated magnetic resonance imaging. Video-EEG monitoring was performed in selected patients. Patients were classified as having focal or generalized seizures on the basis of a thorough clinical assessment and the clinical correlation between the EEG and magnetic resonance imaging findings.

LCM was administered at a starting dose of 100 mg a day (in two divided doses), and was increased by 100 mg every two weeks to reach the maximum tolerable dose that provided good to excellent seizure control. The usual target dose was 200–400 mg/day, but the dose could be adjusted based on the physician's judgment of the clinical response. Physicians were fully responsible for any treatment modification during follow-up, including adding a further anti-epileptic drug (AED) or switching to other AEDs. After the titration period, patients usually visited the clinic at two-month intervals and their clinical responses were assessed at every visit for at least six months.

The reason for the switch was classified as insufficient efficacy, adverse effects (either dose-dependent or idiosyncratic), and concerns about metabolic derangements caused by long-term use of traditional SCBs, such as atherosclerosis and osteoporosis. In patients with insufficient efficacy, dose-dependent adverse effects, and concerns about metabolic derangement, traditional SCBs were tapered off at the same time as uptitration of LCM, but were stopped immediately in patients with idiosyncratic adverse effects. All patients were provided with a seizure diary, and the changes in seizure frequency were calculated based on analysis of the diary. The responsiveness to AED therapy was classified as seizure freedom or drug-resistant epilepsy. At least 6 months' seizure freedom before the introduction of LCM was necessary to define seizure freedom. Patients who had occasional seizures but did not meet the clinical criteria for drug-resistant epilepsy were classified as an intermediate group [6]. Successful switch was defined as no worsening of seizure frequency or adverse effects on LCM at least 6 months after discontinuation of traditional SCBs. Changes in seizure frequency were measured by comparing the numbers of seizure, 3 months before and after the introduction and the titration of LCM, respectively.

The patients' clinical characteristics were compared using the Student's *t*-test or analysis of variance, for continuous variables and the chi-square test for categorical variables with post hoc Bonferroni correction. We used the Mann-Whitney *U* test for nonparametric comparison of the number of AEDs. All statistical analyses were performed using SPSS for Windows software (version 21; IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

3. Results

During the study period, 195 patients (129 men, 66 women; mean age, 49.1 ± 16.8, range [18–84] years) started treatment with LCM for the first time; 75 of these patients were switched to LCM from traditional SCBs (Fig. 1), with a mean follow-up period of 14.7 ± 3.3 months (range 6–18 months). The traditional SCBs administered before the switch to LCM were carbamazepine in 10 patients, oxcarbazepine in 15, lamotrigine in 38, and phenytoin in 12. The reason for switching from traditional SCBs was insufficient efficacy in 39 patients, dose-dependent or idiosyncratic adverse effects in 19 patients (eight for dizziness or ataxia, eight for an allergic skin reaction, and three for hair loss) and concerns about metabolic derangement in 17 patients (Fig. 1). The chances of successful switching from traditional SCBs to LCM were generally high overall (81.3%, 61/75 patients), but were strongly dependent on the reason for the switch. Patients in whom traditional SCBs were insufficiently effective had a lower likelihood of a successful switch (71.8%, 28/39) than those in whom the reason was adverse effects (89.5%, 17/19) or concern about metabolic derangement (94.1%, 16/17). Additionally, patients in the insufficient efficacy as the reason for switch were younger than those in whom the switch was due to concern about metabolic derangement ($p = 0.02$). They also had a higher baseline seizure frequency ($p = 0.038$) and a chance of drug-resistant epilepsy than those in adverse effects constituted the reason for the switch ($p = 0.001$). The patients with adverse effects and concern about metabolic derangement were combined for the purposes of analysis because the reason for the switch was neither an 'efficacy' issue nor an 'adverse effects' issue. Patients in the insufficient efficacy group were younger than those in the other groups ($p = 0.004$), have a higher baseline seizure frequency ($p = 0.029$), and were more likely to have drug-resistant epilepsy ($p = 0.004$) and lower chance of a successful switch ($p = 0.038$) (Table 1). Twenty-nine of the 75 patients in the study achieved or maintained seizure freedom. The eight patients who achieved seizure freedom with traditional SCBs did not experience recurrence after the switch. Fourteen of 19 patients in the intermediate group and seven of 48 with drug-resistant epilepsy achieved seizure freedom after the switch to LCM. A further 11 patients (two in the intermediate group and nine in the drug-resistant epilepsy group) achieved at least a 50% reduction in seizure frequency. There was no significant change in seizure frequency in 21 patients, and 14 patients failed to switch successfully to LCM and returned to traditional SCBs (11/39 in patients with insufficient efficacy, 2/19 in patients with adverse effects, and 1/17 in patients with concerns about metabolic derangement). The causes of an unsuccessful switch to LCM were worsening of seizures in most cases (13/14 patients) and an adverse effect (dizziness) in one case.

4. Discussion

In this study, switching from traditional SCBs to LCM was usually successful, with more than 80% of patients being maintained by LCM after at least six months of follow-up. The likelihood of a successful switch was higher in patients with adverse effects or concerns about metabolic derangement (89.5% and 94.1%, respectively) on traditional SCBs; however, the lower likelihood of a successful switch in patients with insufficient efficacy was not considered disappointing (71.8%), given that the efficacy rate of an alternative AED is lower in patients who had discontinued a previous AED because of poor efficacy [7] and the higher proportion of patients with drug-resistant epilepsy in this group. The different mode of action of LCM may account for the high success rate when patients with insufficient efficacy on traditional SCBs switch to LCM.

Although LCM shares many dose-dependent adverse effects with the traditional SCBs, our study showed that most patients who experienced intolerable dose-dependent adverse effects on traditional SCBs could be switched successfully to LCM. The reason for this difference in tolerability is not clear, but may reflect individual susceptibility to adverse effects on different SCBs. It is also possible that this result reflects the relatively lower maximum dose of LCM used in our study (400 mg/day) considering that few patients in the randomized controlled trials discontinued LCM at this dose because of dose-dependent adverse effects [3,8]. Our study suggests that LCM may be a good therapeutic option for patients who have idiosyncratic adverse effects on traditional SCBs, because none of the 11 patients who discontinued traditional SCBs for idiosyncratic adverse effects (eight with allergic skin reaction and three

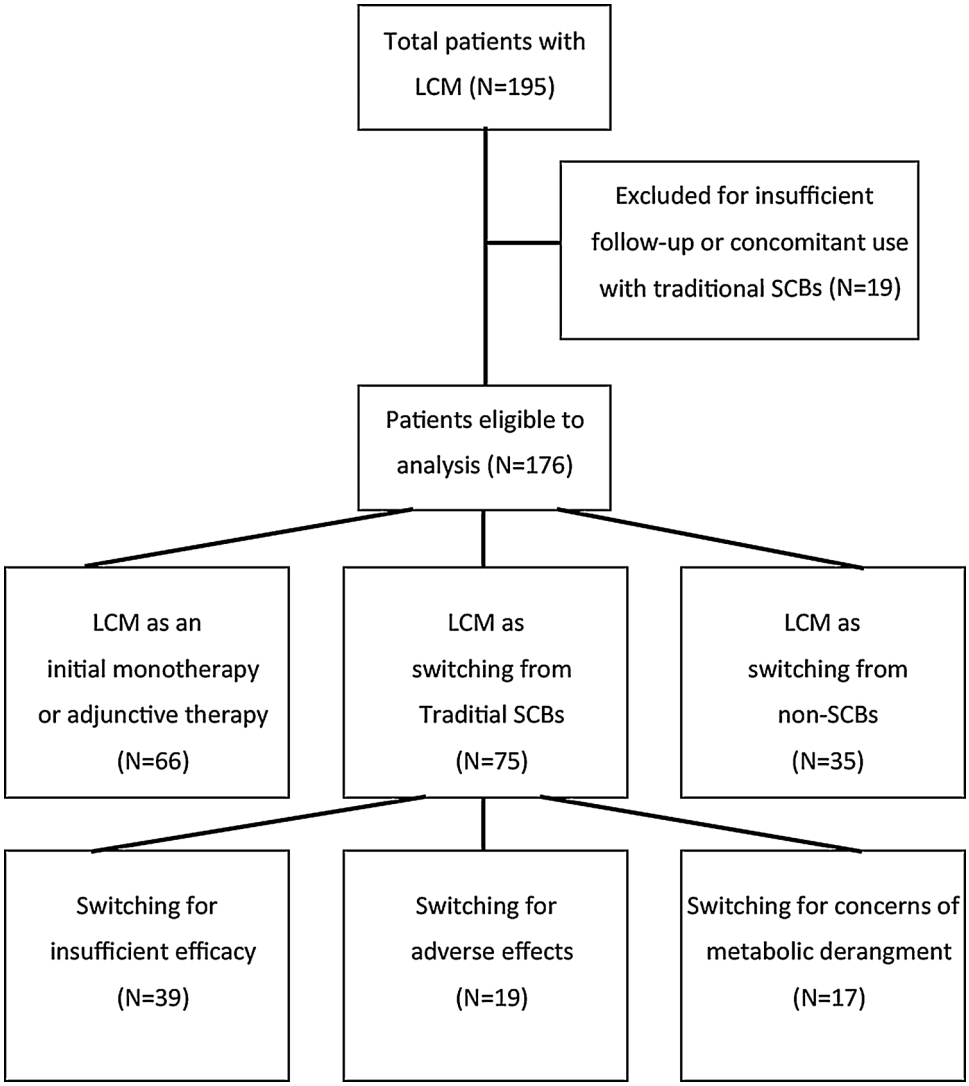

Fig. 1. Schematic representation of LCM as switching from traditional SCB/non-SCB AED, antiepileptic drug; LCM, lacosamide; SCB: sodium channel blocker.

Table 1
Reasons for switching from traditional sodium channel blockers to lacosamide in 75 patients with epilepsy.

Reason for switch	Insufficient efficacy (n = 39)	Adverse effects (n = 19)	Concern about metabolic derangement (n = 17)
Sex (M: F)	22 (56.4%): 17 (43.6%)	11 (57.9%): 8 (42.1%)	13 (76.5%): 4 (23.5%)
Age, years	45.4 ± 14.9*	53.6 ± 14.2	57.6 ± 15.4*
Underlying number of AEDs	1.97 ± 1.2	1.58 ± 1.0	2.47 ± 1.2
Previous number of AEDs	4.18 ± 1.8	3.78 ± 1.8	4.82 ± 1.8
Drug-resistant epilepsy	31/39 (79.5%)**	6/19 (31.6%)**	11/17 (64.7%)
Baseline seizure frequency	5.94 ± 7.8/month***	1.55 ± 2.2/month***	4.12 ± 4.3/month
Successful switch	28/39 (71.8%)	17/19 (89.5%)	16/17 (94.1%)
Reason for switch	Insufficient efficacy (n = 39)	Adverse effects or concern about metabolic derangement (n = 36)	P-value
Sex (M: F)	22 (56.4%): 17 (43.6%)	24 (66.7%): 12 (33.3%)	0.48
Age, years	45.4 ± 14.9	55.4 ± 14.7	0.004
Underlying number of AEDs	1.97 ± 1.2	2.0 ± 1.2	0.93
Previous number of AEDs	4.18 ± 1.8	4.28 ± 1.8	0.82
Drug-resistant epilepsy	31/39 (79.5%)	17/36 (47.2%)	0.004
Baseline seizure frequency	5.94 ± 7.8/month	2.77 ± 3.6/month	0.029
Successful switch	28/39 (71.8%)	33/36 (91.7%)	0.038

* Patients with the insufficient efficacy on traditional SCBs were younger than those with the concern about metabolic derangement ($p = 0.02$).
** Patients with insufficient efficacy had a higher chance of drug-resistant epilepsy than those with adverse effects (p = 0.001).
*** Patients with insufficient efficacy had a higher seizure frequency than those with adverse effects (p = 0.038), AEDs, antiepileptic drugs.

with hair loss) had a recurrence of these adverse effects. It seems that the risk of idiosyncratic adverse effects is lower for LCM than for traditional SCBs, perhaps because of the different structure of LCM [9].

Several traditional SCBs, including phenytoin, carbamazepine, and oxcarbazepine, can induce hepatic enzymes that lead to metabolic derangement after long-term use [10]. LCM has no known effect on hepatic drug metabolizing enzymes, so may be a good therapeutic option for patients with epilepsy who are concerned about long-term metabolic derangement and for those who have established osteoporosis or atherosclerotic cardiovascular disease. However, a careful benefit-risk assessment should be performed before switching AEDs, because there is a small risk of seizure recurrence when patients who are well-controlled on one AED are switched to another AED [11]. We also observed a small risk of seizure recurrence in patients who were switched to LCM because of concern about metabolic derangement on traditional SCBs.

Our study has several limitations, mainly related to its retrospective design, rather small patient population, along with short and variable follow-up duration. Therefore, it is difficult to generalize our results to the wider epilepsy population. The short follow-up duration in our study may have resulted in selection bias owing particularly to the long period of uptitration in our study protocol with a higher proportion of patients with rare seizures in the 'intermediate group'. Although other researchers have documented the efficacy of switching to LCM monotherapy in patients with epilepsy [12], one recent study reported rapid loss of efficacy of LCM in a pediatric epilepsy population [13]. We used retention of LCM after at least 6 months of follow-up as a marker of successful switching. Although the retention to drug is considered to be a composite of drug efficacy and drug safety and reflects the willingness of patients to continue drug treatment, a higher retention rate does not directly indicate better efficacy or tolerability. In addition, it is debatable that a successful switch occurs in patients with insufficient efficacy even when continued LCM administration did not yield a significant reduction in the seizure frequency. Finally, we could not use a structured questionnaire to investigate the occurrence of adverse events, so the incidence and clinical implications of adverse events while on LCM may have been underestimated (Table 1).

In summary, our study shows that switching from traditional SCBs to LCM in patients with epilepsy is usually successful, especially in patients with adverse effects and concern about metabolic derangement. When compared with the traditional SCBs, LCM has similar efficacy and a lower risk of hepatic enzyme induction and idiosyncratic adverse effects, so switching from traditional SCBs to LCM can be a useful therapeutic option in selected patients.

Conflicts of interest

None

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