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Lacosamide tolerability in adult patients with partial-onset seizures: Impact of planned reduction and mechanism of action of concomitant antiepileptic drugs

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ABSTRACT

Objective: We evaluated the impact of planned dose reduction and mechanism of action of concomitant AEDs on tolerability in adults with partial-onset seizures undergoing lacosamide (LCM) titration.
Methods: Data were collected at baseline and 3–6 and 12–24 months post-LCM initiation. Subjects were categorized as having planned reduction of concomitant AEDs or not; AEDs were categorized as traditional sodium channel blockers (TSCB) or non-TSCB (NTSCB). Groups with/without planned reduction were compared on the presence and number of treatment-emergent adverse events (TEAEs) using chi-square tests or logistic regression and on time to LCM discontinuation with time-to-event methods controlling for standardized (STD) AED dose, a measure of concomitant AED load. Similar analyses were performed comparing subjects taking TSCB and NTSCB agents and used to identify relationships with ≥50% decreases in seizure frequency.
Results: One hundred six adults (mean age 41.4 ± 13.4; 50% male) underwent LCM titration from June 2009–2011 with complete data. Reduction of concomitant AEDs was planned at the time of LCM initiation in 59 (55.7%) subjects. Fewer subjects with planned reduction had TEAEs (49.2% vs. 68.1%; $p = 0.05$), and these subjects had a lower risk of TEAEs (OR 0.36; $p = 0.019$) after adjusting for STD AED dose. The hazard ratio (95% CI) for LCM discontinuation was 0.46 (0.23, 0.94) in subjects with planned reduction of concomitant AEDs vs. others ($p = 0.033$) and 3.29 (1.01, 10.70) in subjects taking TSCB vs. NTSCB agents ($p = 0.048$). Among all cases, those who ever had TEAEs had significantly higher STD dose at both follow-up visits ($p = 0.033$ and $p = 0.023$, respectively). Seizure outcomes were not significantly different between groups at the last follow-up assessment.
Significance: Planned reduction of concomitant AEDs during LCM initiation and the use of NTSCB agents only are associated with a reduced risk of TEAEs and LCM discontinuation in adults with partial-onset seizures. This study extends prior observations by considering total AED load in the assessment of tolerability and supports the benefits of early reduction of concomitant AEDs during LCM initiation.

1. Introduction

Lacosamide (LCM) is the first of the third generation antiepileptic drugs (AEDs) approved as adjunctive therapy for the treatment of partial-onset seizures in the U.S. in 2008 and monotherapy in 2014. Unlike traditional sodium channel blocking (TSCB) agents that affect fast sodium channel inactivation, LCM acts through selective enhancement of sodium channel slow inactivation [1]. In the management of pharmacoresistant epilepsy, AEDs having different, presumably complimentary, mechanisms of action are often combined in hopes of optimizing effectiveness and tolerability. In a post hoc exploratory analysis involving patients with partial-onset seizures from three, randomized, double-blind, placebo-controlled LCM clinical trials [2–4], in contrast to patients taking TSCB agents, those not taking TSCB agents had fewer treatment-emergent adverse events (TEAEs) resulting in a lower rate of LCM discontinuation [5]. We performed a retrospective analysis studying the impact of planned reduction and mechanism of action (at least one TSCB vs. NTSCB) of concomitant AEDs on tolerability and effectiveness of adjunctive LCM in adults with partial-onset seizures in a tertiary care epilepsy center.

2. Methods

This was a retrospective study involving adult patients treated in the Cleveland Clinic Epilepsy Center. The study was approved by the Cleveland Clinic Institutional Review Board. Queries of the electronic

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medical record (EMR) and the Cleveland Clinic Knowledge Program (KP) Epilepsy Center database were performed to identify patients meeting inclusion criteria. The KP is an electronic patient-reported data collection system consisting of disease-specific standardized assessments completed at each outpatient clinic encounter.

2.1. Sample characteristics

Inclusion:

- at least 18 years of age;
- partial-onset seizures based on clinical history, semiology, and/or EEG incompletely controlled on current AED regimen;
- initiated on oral LCM as part of standard clinical care following the manufacturer's recommended titration (starting dose of 50 mg bid, increasing by 100 mg per week as needed based on the discretion of the prescribing provider); and
- Completed KP assessment at baseline (at or within three months prior to LCM initiation; Visit 1), 3–6 months post-LCM initiation (Visit 2) and 12–24 months post-LCM initiation (Visit 3).

Exclusion:

- inadequate historical data such as questionable reporting of TEACs or seizures due to impaired mental status and/or inadequate caretaker observations and
- uncertain dosing of LCM and/or concomitant AEDs.

2.2. Data collection

- Demographic data
- Epilepsy-related characteristics including monthly seizure frequency, total daily dosage, and dose adjustments (increase, increase and decrease, or no change vs. decrease) of concomitant AEDs at each visit.
- Type and number of TEAEs
  - CNS: dizziness, headache, drowsiness, insomnia, ataxia, blurred vision, diplopia, coordination abnormalities, somnolence
  - Cardiovascular: hypotension, bradycardia, cardiac arrhythmia, cardiovascular collapse
  - Gastrointestinal: nausea, vomiting
  - Dermatologic: rash
  - Other
- Duration of LCM treatment and median LCM dose at follow-up visits
- Reason for LCM discontinuation
  - TEAE
  - lack of effectiveness
  - cost
  - other
  - unknown

2.3. Data analysis

Concomitant AEDs were classified as:

- traditional sodium channel blockers (TSCB): carbamazepine, lamotrigine, oxcarbazepine, phenytoin;
- nontraditional sodium channel blockers (non-TSCB): valproic acid, topiramate, zonisamide, felbamate; and
- nonsodium channel blockers (NSCB): gabapentin, pregabalin, levetiracetam, rufinamide, primidone, phenobarbital, benzodiazepines.

Subjects were grouped based on whether or not their concomitant AED regimen included a TSCB agent regardless of the number and type of additional AEDs taken. Subjects taking one or more of the TSCB agents were assigned to the TSCB group. Because of the small number of subjects taking NSCB only, the NSCB and non-TSCB groups were combined and referred to as NTSCB.

Subjects were categorized as having planned reduction of concomitant AEDs or not based on documentation by the epilepsy provider. A standardized variable of the amount of concomitant AED(s) taken daily at each visit was determined for each subject based on the Defined Daily Dose (DDD), a measure of the average maintenance dose needed for adults obtained from the World Health Organization website [6]. The ratio of the each concomitant AED daily dose to the DDD was determined and then summed over all drugs in a given regimen to produce a standardized AED dose (STD dose). Values >1 indicate that dose regimens are higher than average.

Categorical variables were summarized using frequencies and percentages. The relationship between planned AED reduction and TEAE (presence/absence) was described using Pearson chi-square tests, while the relationship between planned reduction and number of TEAEs was described using Wilcoxon rank sum tests. Logistic regression models and proportional odds models were used to evaluate whether relationships between planned reduction or LCM discontinuation and TEAEs were affected by STD dose of concomitant AEDs. These methods were also used to identify relationships with ≥50% decreases in seizure frequency (responder rate). Analyses were performed for the entire sample and the TSCB subgroup.

Kaplan–Meier estimates and Cox proportional hazards models were used to evaluate the effect of planned reduction on time to LCM discontinuation unadjusted and adjusted for baseline STD dose of concomitant AEDs. For cases where the overall tests were significant, multiple comparisons using a Bonferroni-corrected significance level of 0.017 (0.05/3) were performed. Results of the multiple comparisons are included as footnotes where appropriate. Analyses were performed using SAS software (version 9; Cary, NC).

3. Results

A total of 106 adults seen in the Cleveland Clinic Epilepsy Center who underwent oral LCM titration between 6/9/2009 and 6/9/2011 out of 422 patients with prescriptions for LCM written during this period were included. Excluded cases did not have outpatient clinic data at the required time points. Sample characteristics are shown in Table 1. Baseline characteristics of subjects with and without planned AED reduction were similar with the exception of race; a higher percentage of subjects with planned reduction were white (98.3 vs. 85.1%; $p = 0.021$). Subjects on multiple AEDs including TSCBs had significantly higher median baseline STD dose and were more likely to have a STD dose greater or equal to the mean compared with those on TSCBs only or NTSCBs ($p < 0.001$).

Visit 2 and Visit 3 occurred 177 ± 32 (122–242) and 372 ± 49 (253–486) days, respectively, after LCM initiation. The median [P25, P75] LCM dosage at Visit 2 and Visit 3 was 300[150,400] and 300[0,400], respectively. At Visit 2, LCM daily dosage was as follows: 30 (28%): 400 mg, 11 (10%): >400 mg, 46 (44%): <400 mg, and 19 (18%) had discontinued LCM. At Visit 3, LCM daily dosage was: 24 (23%): 400 mg, 20 (18%): >400 mg, 30 (29%): <400 mg, and 32 (30%) had discontinued LCM. In total, 61 (56%) subjects had at least one TEAE. A single TEAE was reported in 37 (60.7%) subjects with TEAEs. The TEAEs were classified as CNS-related in 86.4% and CNS/GI-related in 6.8% of cases. The majority of TEAEs (55/61; 90.2%) were reported at Visit 2. The reason for LCM discontinuation was TEAE in 25 (78.1%) and lack of effectiveness in 9 (28.1%) subjects (groups not mutually exclusive). Subjects who ever had TEAEs had a significantly higher median STD dose of concomitant AEDs at Visit 2 than those who had never had a TEAE (2.5 vs. 2.0; $p = 0.031$) and Visit 3 (2.7 vs. 1.9; $p = 0.021$). However, the difference between groups (TEAE vs. no TEAE) in STD AED dose when including LCM was not significant at Visit 2 (3.3[2.3,4.6] vs. 3.0[2.5,4.3]; $p = 0.74$) by which time the majority of TEAEs had been reported, suggesting that the change in concomitant AED dose was related to the reduction in TEAEs, not the overall drug burden including LCM.