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ORIGINAL PAPER

Therapeutic Drug Monitoring of Lacosamide in Norway: Focus on Pharmacokinetic Variability, Efficacy and Tolerability

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Abstract Lacosamide (LCM) is a new antiepileptic drug (AED). Experience from therapeutic drug monitoring (TDM) in clinical practice is limited. The purpose of this study is to evaluate the pharmacokinetic variability of LCM in relation to efficacy and tolerability in patients with refractory epilepsy in a real-life setting. Variables included age, gender, daily doses and serum concentrations of LCM and other AEDs from the TDM-database at the National Center for Epilepsy in Norway. Clinical data regarding efficacy and tolerability were collected from medical records. The Norwegian Prescription Database (NorPD) was used to include population-based numbers of users. TDM-data from 344 patients were included. The median dose, serum concentration, and concentration/dose (C/D)-ratio of LCM was 350 (range 25–700) mg/day, 19.7 (range 8.1–56.2) µmol/L, and 0.06 (0.02–0.82) µmol/L/mg, respectively. Serum concentrations were reduced by 28% by concomitant use of enzyme inducers and increased by 30% in patients aged >65 years. Efficacy and tolerability were assessed in 227 patients: 29% had >50% seizure reduction (eight seizure free), 30% had no effect, and 44% reported adverse effects. In Norway, there were on average 500 patients per year using LCM in this period based on NorPD. The study demonstrated pharmacokinetic variability and use of TDM of LCM in Norway. Data were collected from multiple sources for improved pharmacovigilance. Serum concentrations were influenced by enzyme inducers and ageing, indicating the usefulness of TDM. Effect and tolerability were favorable within a suggested reference range of 10–40 µmol/L given drug-fasting conditions.

Keywords Antiepileptic drugs · Efficacy · Epilepsy · Lacosamide · Pharmacokinetic variability · Therapeutic drug monitoring · Tolerability

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Introduction

Lacosamide (LCM) is a third-generation antiepileptic drug (AED) approved for use in focal epilepsy since 2009. In contrast to the majority of sodium-blocking AEDs, LCM inhibits slow-activated sodium channels rather than fast-acting [1–4]. About 40% of LCM is eliminated unchanged in the urine, whereas 60% is subject to metabolic degradation by several cytochrome P450 (CYP) enzymes (CYP2C19, CYP2C9 and CYP3A4) as well as CYP-independent mechanisms [5]. Pharmacokinetic studies of LCM in patients with epilepsy have demonstrated a linear dose–concentration relationship and reduced serum concentrations when used in combination with strong enzyme inducers [6–8]. Patients with refractory epilepsy often try the newest drugs as add-on to other AEDs soon after approval by the authorities. Documentation of pharmacokinetic variability,

efficacy and tolerability is usually limited based on pivotal clinical studies of new drugs. Post-marketing data from TDM-databases provide important information of new AEDs in clinical practice which can be used for assessment of suitable reference ranges [9–12].

The purpose of this study was to evaluate the pharmacokinetic variability of LCM in relation to efficacy and tolerability in patients with refractory epilepsy.

Materials and Methods

Study Material

Patients using LCM, 2013-16, were retrospectively identified from the TDM service at the Section for Clinical Pharmacology, National Center for Epilepsy, Oslo University Hospital. Additional clinical data from medical records at the National Center for Epilepsy, Lillehammer Trust Hospital and St. Olav's University Hospital, Trondheim were collected and evaluated. Initiation of therapy was from 2009 to 2016. Date of termination of medication or last visit was used as endpoint for treatment in the study.

Clinical data regarding gender, age, seizure onset, use of AEDs, time of start and discontinuation, and efficacy/tolerability were collected. The most recent dose and serum concentration were used from the TDM-database. Data on doses and steady state conditions retrieved from the medical records served as quality assurance of the TDM data. Based on clinical information efficacy was categorized using a modified Likert scale: (1) no effect, (2) some effect (modest reduction of seizure frequency and/or severity), (3) good effect (>50% reduction of seizure frequency) and (4) complete seizure control for at least one year. Tolerability was evaluated by the treating clinician, and reported adverse effects were recorded as mild, moderate or severe (i.e. leading to discontinuation). When discontinued, the reason was categorized as lack of effect, adverse effects, both or other.

To relate our findings to population data, the total number of patients using LCM in Norway in the period 2009–15 was retrieved from the Norwegian Prescription Database (NorPD) [13]. NorPD consists of data on prescriptions dispensed from all pharmacies in Norway [14, 15].

Drug Analysis

The analyses were routine measurements of validated methods at the Section for Clinical Pharmacology, National Center for Epilepsy, Oslo University Hospital, as measured by HPLC-UV. The measuring range was 10–250 µmol/L, on an Ultimate 3000 HPLC, Dionex, with a 125 × 3 mm, 3 µm Hypersil BDS C-18 column based on Greenway et al. [16]. A preliminary reference range of 10–40 µmol/L was used based on the results from drug-fasting samples by Contin et al. [7]. Results below the lower linear limit of 10 µmol/L were reported as <10 µmol/L to the clinicians. The most recent measurement of serum concentrations of LCM and concomitantly used AEDs at assumed steady-state conditions were included. Blood samples were drawn drug fasting before intake of the morning dose, otherwise excluded. Anonymized data regarding gender, age, serum concentration measurements and concomitant AEDs in use were collected. The study was approved by the Regional Ethics Committee.

Calculations

Serum Concentration and Dose Relationships

Serum concentrations, doses and concentration/dose (C/D) ratios were calculated as arithmetic means or medians with standard deviation (SD)/ minimum–maximum range to express variability. The C/D-ratio is the inverse expression of clearance, and thus a decrease in the C/D-ratio reflects an increase in clearance, based on the following equation: CL/F (mL/kg/min) = daily dose (mg/kg)/C_{ss} (mg/L × 1000) × 1440 as utilized in a previous publication [17] where oral clearance is CL/F; CL = clearance, F = oral bioavailability, C_{ss} = serum concentration at steady-state, and 1440 = minutes per 24 h.

The use of concomitant AEDs was categorized as follows for comparisons of possible effects on C/D-ratios of comedication:

1) Strong enzyme inducers (carbamazepine, phenobarbital, or phenytoin), even in combination with other AEDs mentioned below.
2) Valproate, which is known to inhibit several CYPs and UGT, and no concomitant use of strong inducers or category 3.
3) Oxcarbazepine or eslicarbazepine acetate, and none of the drugs mentioned in 1) or 2), since these drugs may inhibit CYP2C19 [18], and we wanted to further explore this possible interaction.
4) Neutral drugs, also including weak enzyme inducers/inhibitors (acetazolamide, clobazam, clonazepam, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, perampanel, pregabalin, retigabine, rufinamide, topiramate, zonisamide, vigabatrin, or other benzodiazepines) [17] but no AEDs categorized in 1,2,3 or monotherapy.

The C/D-ratios of each group were calculated and compared among the groups and for comparison with neutral drugs, monotherapy or no listed concomitant medication.

Statistical Analyses

For statistical analyses IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL, USA) was used. Students' two-sided t-test with unequal variance was used to calculate significant pair-wise differences. Comedication groups were compared to the neutral group by One-Way Anova post hoc test by Dunnett (2-sided) to compare multiple groups. Simple linear regression analysis was used to define the relationship between dose and concentration. P-values of <0.05 was considered statistically significant in all analyses.

Results

Patient Characteristics

Altogether 361 patients had LCM concentrations measured within the study period (2013–16); 17 patients were excluded due to lack of information regarding dose or time of intake, and the remaining 344 patients were included for further analysis. Details regarding the patients are presented in Table 1. Additional clinical data were available for 227 (66%) out of the 344 patients. Age and gender distribution were similar in the total group and the sub-group with clinical data (Table 1). The overall median age was 40 years (range 4–86), and most patients (82%) were adults. In 136 patients LCM treatment was initiated after January 2013.

Age at onset of epilepsy was <1–61 years, and duration <1–77 years (median 19 years). Most patients (94%, n = 214) used LCM in polytherapy with 1–4 other AEDs, while 13 patients (6%) used monotherapy. The refractoriness of their epilepsy is reflected by the use of a median number of 6 (range 1–17, median 6) AEDs prior to LCM.

Pharmacokinetic Variability

TDM-data from the 344 patients showed pronounced pharmacokinetic variability as demonstrated by the wide distribution of serum concentration and dose relationships (Fig. 1a; Table 1). There was a linear correlation between dose and serum concentration (Fig. 1a). The variability in C/D-ratios was less in patients where complementary updated data from the medical records were available (Table 1). No gender differences in doses and serum concentrations were found, as calculated from the total TDM-data (Table 1). There were 22 children and adolescents (≤18 years), 284 adults (18–65 years) and 33 elderly (>65 years). The C/D-ratio in the elderly was increased by 28% as compared to adults, pointing to a corresponding decrease in clearance ($p < 0.05$) (Table 2). There was no difference between younger patients and adults. Concomitant use of enzyme inducing AEDs gave a 23% decrease in the C/D-ratio as compared to the neutral group/monotherapy, which is an expression of increased clearance ($p < 0.05$). Comedication with valproate or oxcarbazepine/ eslicarbazepine acetate did not alter the C/D-ratios (Table 2).

Table 1 Demographic and TDM findings in patients using lacosamide

	All patients from the TDM database (n = 344)	Subgroup of patients with additional clinical evaluation (n = 227)
Gender, n (%)		
Women	179 (52%)	120 (53%)
Men	165 (48%)	107 (47%)
Age, years, median (range)	39 (4–86)	36 (4–78)
Dose (mg)		
Mean (SD)	299 (135)	326 (114)
Median (range)	300 (50–1500)	350 (25–700)
Serum concentration (µmol/L)		
Mean (SD)	18.6 (10)	22.0 (9.9)
Median (range)	16.0 (4.0–69)	19.7 (8.1–56.2)
C/D-ratio (µmol/L/mg)		
Mean (SD)	0.07 (0.06)	0.07 (0.02)
Median (range)	0.06 (0.02–0.82)	0.06 (0.03–0.16)

TDM therapeutic drug monitoring, *C/D* concentration/dose

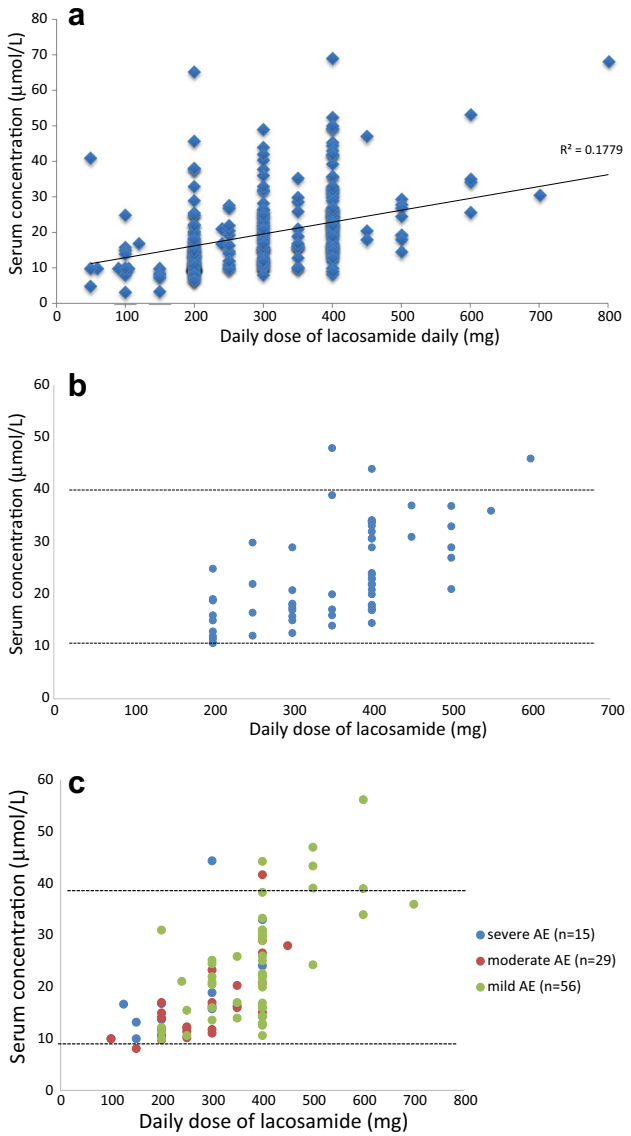

Fig. 1 **a** Distribution of doses and serum concentrations of lacosamide based on therapeutic drug monitoring data in Norway (n = 344). There was a linear correlation between dose and serum concentration ($r^2 = 0.1779$) ($p < 0.05$). **b** Doses and serum concentrations in patients with good clinical efficacy (>50% seizure reduction) (n = 63). In two cases, values were reported as <10 µmol/L to the clinican (and not a precise value) and thus are not shown. The suggested reference range of 10–40 µmol/L is shown as *horizontal lines*. **c** Distribution of doses and serum concentrations (measured as precise values >10 µmol/L as reported to the clinicians) in patients with mild, moderate or severe adverse effects (AE) from lacosamide (n = 94)

Efficacy and Tolerability

Efficacy and tolerability were assessed in 227 patients, of whom 57 had >50% seizure reduction and eight became seizure free (29% responders). Unchanged seizure control was seen in 30%. Regarding tolerability, 100 patients (44%) reported adverse effects. Those who experienced adverse effects used significantly lower doses than those who did not (Table 3). The most common adverse effects were: CNS-related (sedation, cognition, psychiatric, dizziness) (n = 94), gastrointestinal (n = 20), headache (n = 7) and skin reactions (n = 3). Seventy patients (31%) discontinued LCM. The reasons were adverse effects 16 (7%), no effect 25 (11%), combination adverse effects and lack of efficacy 23 (10%) and other 6 (3%). No serious adverse effects leading to hospitalization were reported. Of the 65 responders (>50% seizure reduction), 35 (54%) did not report adverse effects, whereas 23 (15%) reported one or more adverse effects, and two of these reported severe adverse effects leading to discontinuation (dizziness/tiredness/reduced cognition/nausea).

Pharmacokinetic Variability in Relation to Efficacy and Tolerability

Table 3 shows details regarding the relations between doses, concentrations, efficacy and tolerability. Figure 1b shows that 60 out of 65 patients experiencing efficacy from LCM had serum concentrations within the range of 10–40 µmol/L (i.e. 2.5–10 mg/L). In 23 patients, the measured serum concentration was below 10 µmol/L, 10 of these patients had no effect from LCM, and 14 reported adverse effects. Figure 1c shows serum concentration and dose in relation to severity of adverse effects.

We explored the total use of LCM in Norway during the period 2013–15 by use of the Norwegian Prescription Database for comparison to the extent of users covered by the TDM service. The average number of patients in the period 2013–15 was 500. The gender distribution (women/men) was equal with a steady increase every year: 2009: 60/62, 2013: 231 /214, 2015: 279/276. The total use of LCM in defined daily doses (DDD/1000 inhabitants/day = 300 mg) during 2009–15 increased nine-fold from 0.01 to 0.09 DDDs/1000 inhabitants/day. The total number of patients, however, increased 5.5-fold, from 122 to 555 in the same period.

Discussion

Pharmacokinetic Variability

The pharmacokinetic variability of LCM was wide, as also previously demonstrated [6–8, 19]. However, by use of ascertained clinical information from medical records, some of the variability could be corrected for. The results regarding the relationship between dose/concentration and comedication are also in line with previous studies showing linear dose-concentration relationship and about 30% reduced serum concentrations with strong enzyme

Table 2 Impact of gender, age and comedication on the pharmacokinetics of lacosamide

Factors contributing to variability	Numbers (n)	Therapeutic drug monitoring data Mean values (min–max range)
Gender	344	Dose and concentration
Women	179	Dose: 286 (50–1500) mg/day Conc. 18.2 (3.3–50) µmol/L
Men	165	Dose: 312 (50–900) mg/day Conc. 19.0 (3.5–69) µmol/L
Age	344	C/D-ratio
Children and adolescents (≤18 yrs)	22	0.07 (0.04–0.19) µmol/L/mg
Adults (18–65 yrs)	284	0.07 (0.02–0.33) µmol/L/mg
Elderly (>65 yrs)	33	0.09* (0.03–0.19) µmol/L/mg
Comedication	206/227**	C/D-ratio
Neutral AEDs/monotherapy	103	0.07 (0.02–0.16) µmol/L/mg
Enzyme inducers	26	0.05 (0.02–0.10) µmol/L/mg***
Valproate	47	0.07 (0.03–0.13) µmol/L/mg
Oxcarbazepine/Eslicarbazepine	30	0.07 (0.02–0.11) µmol/L/mg

Conc. concentration, conc./dose = C/D µmol/L/mg

*$p < 0.05$ compared to adults. **Only patients with clinical evaluations were regarded to provide precise information on current comedication. Patients using AEDs from multiple categories were excluded (n = 21). ***$p < 0.001$ compared to other groups, where enzyme inducers included carbamazepine (n = 19), phenobarbital (n = 4) and phenytoin (n = 3)

Table 3 Efficacy and adverse effects in relation to dose (mg) and serum concentration (µmol/L) of lacosamide (n = 227)

	Numbers (n)	Therapeutic drug monitoring data
Efficacy		
Good (>50% seizure reduction)	8/57 (29%)	Dose: 347 (SD = 101) Conc: 23.8 (SD = 9.2)
Modest	93 (41%)	Dose: 345 (SD = 116) Conc: 22.8 (SD = 10.3)
None	69 (30%)	Dose: 278 (SD = 107)* Conc: 18.6 (SD = 8.7)
Adverse effects		
None	127 (56%)	Dose: 350 (SD = 117) Conc: 23.3 (SD = 9.7)
One or more	100 (44%)	
Mild	56 (56%)	Dose: 327 (SD = 110) Conc: 22.3 (SD = 10)
Moderate	29 (29%)	Dose: 269** (SD = 91) Conc: 15.99 (SD = 7.7)
Severe	15 (15%)	Dose: 245** (SD = 97) Conc: 20.8 (SD = 9.6)

Conc. concentration

*$p < 0.001$ compared to effect group; **$p < 0.001$ compared to no adverse effects

inducers [7,8]. Moreover, a possible inhibitory effect of CYP2C19 caused by valproate or oxcarbazepine/eslicarbazepine acetate did not influence LCM pharmacokinetics, in contrast to the latter two drugs' effect on clobazam pharmacokinetics [18]. This may be explained by the fact that only a relatively small part of LCM is metabolized through CYP2C19, while the rest is excreted unchanged or eliminated by other pathways [5, 10]. A decreased clearance of 28% was found in the elderly (>65 years). As a consequence, a lower target dose of approximately 30% may be advisable in the elderly compared to other patients, and likewise a 30% higher dose should be considered in those who use strong enzyme inducers.

Efficacy and Tolerability

From the clinical evaluation of 227 patients, nearly 30% had >50% seizure reduction, demonstrating a somewhat poorer effect compared to another long-term study [20]. Adverse effects were reported in 45%. The tolerability profile in the present survey was similar to other clinical studies [6, 21]. CNS-related and gastrointestinal adverse effects were most commonly reported. Noteworthy, adverse reactions were associated with significantly lower doses, conceivably due to polytherapy, pharmacodynamic interactions or early discontinuation in vulnerable patients. However, meta-analyses have shown that occurrence of adverse reactions increase with dosage and that withdrawals often are caused by unwanted effects (e.g. dizziness, vertigo, ataxia, nausea, vomiting) [21, 22], most likely due to high peak concentrations [23]. In contrast to many of the other new AEDs, psychiatric and behavioral adverse reactions do not generally appear to limit the use of LCM.

Pharmacokinetic Variability in Relation to Efficacy and Tolerability

A prerequisite for the implementation of TDM is that the serum concentration measurements reflect the actual concentration of a drug in the brain. Based on serum and CSF samples, it has been concluded that concentration measurements of LCM in serum is a good indicator of its concentration in the brain [24]. Previously, 40–80 μmol/L (10–20 mg/L) has been suggested as a reference range, but these values were partly derived from non-drug-fasting blood samples [16, 19]. In the present study, complementary clinical evaluation of efficacy and tolerability of patients using LCM showed that nearly all with good efficacy had serum concentrations within the range of 10–40 μmol/L (i.e. 2.5–10 mg/L). This finding shows that it is likely that LCM will reveal its potential clinical efficacy within this range. We therefore suggest this as a reference range, given a standard procedure of taking drug-fasting samples in the morning. Accordingly, treatment should preferably be guided by TDM in concert with close monitoring of efficacy and tolerability. In patients without efficacy, LCM should be discontinued to avoid undue long-term polytherapy.

The increase in the total use of LCM in Norway indicates use of higher doses per patient over time (9-fold increase in use versus 5.5-fold increase in the number of users). We measured serum concentrations in 344 patients during the study period; this number reflects the widespread use of TDM in Norway when considering the total number of subjects receiving LCM (NorPD data).

Methodological Considerations

TDM-databases may be used to identify individual and group-related differences and reasons for pharmacokinetic variability. However, studies in natural and retrospective settings always have important limitations. A range of potential confounders are difficult to control for using TDM-data. Contributing factors to variability may include occasional samples requested before steady-state conditions and imprecise reporting of dosage on the request form. However, supplementary information from the medical records allowed more accurate and updated clinical information to be included in the present study. Efforts were made to use only steady-state serum concentrations according to available clinical information. Adherence was controlled for in hospital in-patients, but out-patient data are based on the given information of the time of the last drug intake. The pharmacokinetic variability demonstrated can hardly be predicted or explained by single factors other than comedication with inducers or old age. There is a selection bias regarding the patients included for clinical evaluation, since they were identified from the TDM-database with onset from January 2013. Some of these patients already started with LCM back in 2009, but still used it in 2013 and onwards. Those who discontinued before 2013 could not be included in the study. NorPD gives detailed information on all prescriptions from all pharmacies in Norway and is suitable to study the true utilization of AEDs [14, 15].

Conclusions

The present study demonstrates the use of TDM and pharmacokinetic variability of LCM. Clinical information was available for a large number of patients to evaluate efficacy and tolerability. Overall population data regarding the use of LCM in Norway were included to place the TDM service into a comprehensive and national context. Serum concentrations were influenced by enzyme inducers and ageing in opposite directions, indicating the usefulness of TDM. In this study the average efficacy of LCM was moderate as add-on treatment in patients with refractory epilepsy, and the tolerability was favorable in the majority of patients. The study suggests a TDM serum reference range of 10–40 μmol/L (2.5–10 mg/L) for drug fasting samples in the morning, where efficacy is likely to be obtained. Surveillance of a new drug by use of multiple sources in concert, such as TDM, clinical and pharmacoepidemiological data, contributes to pharmacovigilance on the patient and population levels by documentation of pharmacokinetic variability, efficacy, tolerability and utilization.

Author Contributions The contribution of the authors of this manuscript has been as follows: TS and CJL planned and designed the study, wrote the first draft of the manuscript and have been responsible for revisions. TS was responsible for clinical evaluation of patients from the National Center for Epilepsy and Innlandet Hospital Trust, and clinical data handling. EB has performed the clinical evaluation of patients from St. Olav's University Hospital and affiliated clinics in Mid Norway and contributed to the data handling. AB contributed with data from the Norwegian Prescription Database and statistical analyses. MLB and SIJ contributed with data from the TDM-database at the National Center for Epilepsy. All authors have contributed to writing and revising the manuscript, and have approved the final manuscript.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest or any financial disclosures regarding this manuscript.

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