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Pharmacokinetic variability and clinical use of lacosamide in children and adolescents in Denmark and Norway

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Conflict of Interests

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Abstract

Background: The indication for the antiepileptic drug (AED) lacosamide (LCM) was recently extended to include children from the age of four. Real-life data on the use and serum concentrations of LCM in children and adolescents are limited. The purpose of this study was to investigate the use of LCM in this patient group in relation to age, co-medication, dose, serum concentrations and duration of treatment, and to examine pharmacokinetic variability.

Methods: Children and adolescents (<18 years) who had serum concentrations of LCM measured from January 2012 to June 2018 were retrospectively identified from the therapeutic drug monitoring (TDM) databases at two national epilepsy centers in Norway and Denmark. Clinical data were collected from request forms and medical records.

Results: Data from 124 patients were included, 61 girls/63 boys. Weight was available for 76 patients. Median age was 15 years (range 2-17 years), dose of LCM 300 mg/day (76-600 mg/day) and serum concentration 18 µmol/L (5-138 µmol/L) [4.5 mg/L (1.3-34.5 mg/L)]. Pharmacokinetic variability was demonstrated as the concentration/(dose/kg) ratio ranged from 1.3 to 9.4 (µmol/L)/(mg/kg) and was affected by age. Polytherapy with 1-3 other AEDs

was noted in 107 patients (86%). Treatment was continued beyond 1 year in 71% (n=45) of the 63 patients where such information was available, and all of these 45 patients had serum concentrations within the defined reference range. The 1-year retention rate was higher in patients not concomitantly using other sodium channel blocking drugs (82% vs 56%).

Conclusion: The study demonstrates pharmacokinetic variability in and between age groups, which indicates usefulness of TDM. More than two thirds of patients continued treatment beyond one year, suggesting reasonable effectiveness.

Keywords: Antiepileptic drugs (AED), lacosamide (LCM), therapeutic drug monitoring (TDM), children, pharmacokinetic variability

Introduction

Epilepsy is a common neurological disease in children, with antiepileptic drugs (AEDs) being the primary treatment option. Children taking AEDs require particularly close follow-up, as changes in physiology and development affects pharmacokinetic and pharmacodynamic processes. Thus, effect and tolerability can vary significantly between patients and within patients over time. All AEDs have pharmacokinetic variability, and the variability at any age can be considerable, due to factors such as drug interactions, genetic variability and co-morbidities.[1-4] In recent years, a number of new AEDs have become available, and many are used in children.

Lacosamide (LCM) is indicated as monotherapy and adjunctive therapy for the treatment of focal onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy.[5] After initial approval by the European Medicines Agency as add-on in patients 16 years or older in 2008, the indication was extended to include monotherapy in late 2016, and children >4 years in 2017.[6] LCM exerts its effect by

selectively enhancing the slow inactivation of voltage-gated sodium channels, in contrast to most other sodium channel-blocking AEDs that affect fast inactivation.[7,8]

The National Center for Epilepsy (SSE), Oslo University Hospital, Norway and the Danish Epilepsy Center, Dianalund, Denmark provide care for patients suffering from difficult-to-treat epilepsies. A number of these patients are children, some with rare epilepsy syndromes. The laboratories at these two hospitals analyze serum concentrations of antiepileptic drugs (AEDs) in blood samples from inpatients, as well as patients in other hospitals, institutions and general practice around the country. The reference range for serum concentrations of LCM used in Norway is 10-40 µmol/L (3-10 mg/L),[9] and a recently study has confirmed that efficacy is likely to be obtained within this range in adults.[10] A similar reference range of 9-35 µmol/L is used in Denmark.[11]

As clinical trials are performed on carefully selected populations and follow the patients for a limited period of time, it is important to document real life use of drugs after marketing.[12,13] Such data regarding the use of LCM in children and adolescents are limited. The purpose of this study was to investigate the use of LCM in children and adolescents in relation to age, co-medication, dose, serum concentrations and duration of treatment, and to examine real life pharmacokinetic variability in this population.

Material and Methods

STUDY MATERIAL

Children and adolescents (<18 years) who had serum concentrations of LCM measured from January 2012 to June 2018 were retrospectively identified from the therapeutic drug monitoring (TDM) databases at the National Center for Epilepsy (SSE), Oslo University Hospital Oslo, Norway and the Danish Epilepsy Center, Filadelfia, Denmark. Inclusion

criteria were at least one serum concentration measurement and available information on dose. Measurements below the measuring range were excluded. There is a strong tradition in Scandinavia to use TDM as part of management of patients with epilepsy, and the most common reason for requesting serum concentration measurements are routine follow-up, dosage adjustments, unsatisfactory seizure control and adverse effects. In both Norway and Denmark, standard procedure is to perform TDM on samples drawn drug fasting in the morning at assumed steady-state, and both laboratories provide information to requesting physicians about this. If it was noted on the request form that the sample was not taken under such conditions, it was excluded from the study. Data on gender, weight, and concomitantly used drugs were collected. Additional clinical data from medical records were available for some of the patients. To avoid introducing bias from multiple samples from individual patients, the most recent measurement with complete data was used when more than one result was available.

The study was approved by the local and regional ethics committees.

The number of children/adolescents being prescribed LCM in the period was retrieved from national prescription databases,[14,15] which contain comparable information.[16] Data on population were retrieved from national agencies for statistics.[17,18]

DRUG ANALYSIS

The analyses were routine measurements by validated methods at the Section for Clinical Pharmacology, The National Center for Epilepsy, Oslo University Hospital and The Danish Epilepsy Center, Filadelfia, as measured by HPLC-UV and UHPLC-MS/MS. Until 2018, a HPLC-UV method was in use in Norway, with a measuring range of 10-250 µmol/L based on Greenway et al.[19] Analyses were performed on an Ultimate 3000 HPLC, Dionex, with a 125x3 mm, 3 µm Hypersil BDS C-18 column. In 2018, an UHPLC-MS/MS method was

introduced. These analyses were performed on a Prelude MD HPLC/Endura MD mass spectrometer, using the Antiepileptic Drugs ClinMass TDM Platform Kit System (MS9000, MS9200) from Recipe (Munich, Germany).[20] The lower limit of the measuring range reduced to 3 µmol/L. A complete validation was performed, with no bias towards higher or lower results with the new methodology. At the Danish Epilepsy Center, LCM was analyzed using an in-house LC-MS/MS method applying a Waters Acquity UPLC in connection with a TQ mass detector. Separation was accomplished on a C18 BEH column (Ethylene Bridge Hybrid, C18 1.7 µm 2.1 x 100 mm), and quantified at a measuring range of 2-100 µmol/L, using an in-house calibrator. In both laboratories the methods are validated and subject to monthly, international proficiency testing.

CALCULATIONS

Serum concentrations, doses, concentration/dose (C/D) ratios and C/(D/kg) ratios were calculated as means with standard deviation (SD) or medians with minimum-maximum range to express variability.

The conversion factor for LCM from µmol/L to mg/L is 0.25 (i.e., 1 µmol/L = 0.25 mg/L), as the molecular weight of LCM is 250 g/mol. Conversely, the conversion factor from mg/L to µmol/L is 3.99.

When examining the effect of comedication on C/D and C/(D/kg) ratios, patients were grouped according to concomitantly used AEDs: A) enzyme-inducing AEDs (carbamazepine, phenytoin and/or phenobarbital),[10,21] B) valproate and C) reference group, including all patients not included in group A or B.

When comparing data from patients using additional sodium channel blocking AEDs or not, the following were considered sodium channel blockers: lamotrigine, carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, zonisamide and rufinamide.[22,23]

When examining the effect of age on pharmacokinetics, the patients were divided into three groups: <6, 6-12 and 13-17 years of age.

STATISTICAL ANALYSES

For statistical analyses IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA) was used. For small sample sizes without normal distribution, comparisons were performed by the non-parametric Mann-Whitney rank sum test or the Kruskal-Wallis test in case of multiple comparisons, with pairwise comparisons with post hoc pairwise Mann-Whitney rank sum test and Bonferroni correction. For normally distributed data or large samples (>30), Students' two-sided t-test with unequal variance was used to calculate significant pair-wise differences and ANOVA with post hoc Tukey was used for multiple comparisons.

When comparing categorical variables, the Pearson Chi-square test was used, alternatively the Fisher's exact test (2-sided) when <80% of the cells in the table had expected frequency >5.

P-values of <0.05 were considered statistically significant for all analyses.

Results

DEMOGRAPHIC DATA

Data from 124 patients, 61 girls and 63 boys, were included in the study; 71 from Norway and 53 from Denmark. Patient characteristics are summarized in table 1. Information on clinical indication for the use of LCM was available in 81 cases; most patients were noted to have focal or multifocal epilepsies. Other indications are listed in Table 1. LCM was used in monotherapy in 17 patients, while the other patients used 1-3 concomitant AEDs (Table 1).

SERUM CONCENTRATIONS AND PHARMACOKINETIC VARIABILITY

Doses and corresponding serum concentration measurements are shown in Figure 1A and B.

117 patients (94%) had serum concentrations between 9-40 µmol/L (2-10 mg/L), i.e. within the recommended reference range for one or both countries. The serum concentration was below 25 µmol/L (6 mg/L) (the mid-value of the reference range) in 87 patients. The C/D ratio varied almost 8-fold between patients (0.03-0.23 µmol/L/mg), whereas the C/(D/kg) ratio varied 7-fold [1.3-9.4 (µmol/L)/(mg/kg), n=76)]. There were no significant differences in age distribution, doses, serum concentrations or C/(D/kg) ratios between the patients from Norway and Denmark.

There was a statistically significant difference in the ratio between age groups, with the C/(D/kg)-ratio being higher in the oldest age group (13-17 years, n=44) compared both to the middle (6-12 years, n=29) and the youngest age group (< 6 years, n=3) (Figure 2). There was no statistically significant difference in C/(D/kg)-ratio between girls (n=38) and boys (n=38).

Patients weighing <50 kg (n=31) were prescribed higher doses per kg (6.4 mg/kg) than those weighing 50 kg or more (n=45) (4.8 mg/kg) (p=0.005). In patients weighing < 50 kg C/(D/kg) ratio varied 4.5-fold, and in patients weighing 50 kg or more, 4.1-fold.

CONCOMITANT MEDICATION

LCM was used in combination with 20 different AEDs, and the most commonly used concomitant drugs were clobazam (n=28), levetiracetam (n=28), valproate (n=26), lamotrigine (n=16) and topiramate (n=14). The number of patients using other AEDs is shown in Figure 3.

Complete data (including weight) was only available for 3 patients using enzyme-inducing AEDs, and no statistically significant difference in C/(D/kg) compared to the reference group (n=55) was demonstrated. There was no statistically significant difference in C/(D/kg) ratios between patients using valproate (n=18) and the reference group (n=55).

DURATION OF TREATMENT

Data on start and discontinuation of therapy was available for 63 patients. In 27 of these patients, treatment was still ongoing at the time of review, and all of these had used LCM for more than 1 year. 18 patients had discontinued the drug after less than 1 year, resulting in a one-year retention rate of 71% (45 of 63 patients). Of the 36 patients who had discontinued the drug at the time of assessment, median duration of use was 365 days (range 30-1247 days).

The one-year retention rate in patients concomitantly using other sodium channel blocking AEDs was 56% (14 of 25 patients), in contrast to 82% (31 of 38 patients) among those not using such drugs (p=0.028).

There was no statistically significant difference in serum concentrations between patients using and not using other sodium channel blocking AEDs.

Patients who discontinued treatment within the first year had lower serum concentrations than those who continued treatment past the first year (p=0.037) (Figure 1C). Most of the patients (14 of 18) who discontinued treatment had serum concentration in the lower part (< 20 µmol/L (<5 mg/L)) of the reference range. Furthermore, three patients had serum concentrations outside both reference ranges [i.e. >40 or <9 µmol/L (>10 or <2 mg/L)], one above and two below. None of the 45 patients in the group that continued treatment for more than one year had a serum concentration outside this range.

PRESCRIPTIONS OF LCM IN CHILDREN AND ADOLESCENCE IN NORWAY AND DENMARK

According to nationwide databases covering the whole population in both countries, 47-84 Norwegian and 75-94 Danish outpatients younger than 20 years of age were prescribed LCM per year between 2012 and 2017 (Danish data only available until 2016).[14,15] The number of inhabitants < 20 years in the two countries is similar, 1,262,730 in Norway and 1,310,918 in Denmark in January 2017.[17,18]

The majority of patients using LCM were 15-19 years old (Figure 4), which is also reflected in the age distribution in the current study population.

Discussion

This study describes the use of LCM in a large sample of children and adolescents in two Scandinavian countries. Pharmacokinetic variability was demonstrated by variability in C/(D/kg)-ratios and was affected by age. The doses and resulting serum concentrations used are low or moderate for many of the patients, and the drug is used in combination with numerous other AEDs. More than two thirds of patients continued treatment beyond one year, and retention rates was higher in those not using other sodium channel blocking AEDs compared to those who did.

SERUM CONCENTRATIONS AND PHARMACOKINETIC VARIABILITY

The observed pharmacokinetic variability in children and adolescents was 7-fold between patients, which is less than previously found across all age groups, including adults and elderly.[10,21] A possible explanation is that a number of diseases causing altered organ function occur only in older age groups. There may also be a degree of selection bias; many of the

younger patients had their therapy initiated before regulatory approval, and clinicians may be more conservative with off-label use in patients with significant comorbidities.

The observed lower C/(D/kg) ratio in younger compared to older children and adolescents is in line with previous findings.[21] It is plausible that it reflects an increased clearance of LCM, considering the age-related changes in physiology through childhood.[1,24]

We did not find a significant difference in C/(D/kg)-ratio between males and females, in line with previous findings.[10,21,25]

In contrast to other studies, no significant effect of enzyme inducing AEDs on the pharmacokinetics of LCM was observed, probably due to the small number of patients in this group. Valproate did not affect the C/(D/kg) ratio of LCM, in line with the other studies.[10,21,25,26]

DURATION OF TREATMENT

In post marketing studies, measurement of retention rates or time to withdrawal is considered to provide relevant clinical information, as it is a measure of effectiveness, a composite of both efficacy and tolerability.[27] We found that 71% of patients continued LCM for more than one year, comparable to 65% observed by Ruegger et al.[28] A study of LCM in patients <21 years of age found that the probability of remaining on LCM without addition of another therapy was 45% at 12 months.[29] Neither of these studies included serum concentration measurements of LCM.

In our study all patients who continued treatment beyond one year had serum concentrations within the combined reference ranges for both countries [9-40 µmol/L (2-10 mg/L)]. This is in line with results from adults showing that most patients with good clinical effect had serum concentrations within the reference range.[10]

We noted that most of the patients who discontinued LCM before 1 year had serum concentrations below or in the lower end of the reference range, and overall their serum concentrations were lower than in those who continued treatment past one year. The present study does not include data on reason for discontinuation, which did not allow consideration of whether insufficient drug exposure led to discontinuation due to unsatisfactory effect, or whether these patients suffer from adverse effects at low serum concentrations, not permitting the dose to be increased.

Studies on adults have suggested that tolerability of LCM is affected by concomitant use of sodium channel blocking drugs,[30-33] but results regarding children are conflicting.[28,29] Most studies on the subject only include "traditional sodium channel blockers"; oxcarbazepine, carbamazepine, phenytoin and lamotrigine. Based on mechanisms of action, we considered it reasonable to also include rufinamide, eslicarbazepine and zonisamide.[22,23] We demonstrated a significant correlation with concomitant use of one or more of these seven drugs and discontinuing LCM treatment within one year, suggesting decreased tolerability with such combinations.

PRESCRIPTIONS OF LCM IN CHILDREN AND ADOLESCENCE IN NORWAY AND DENMARK

There has been an increased preference towards using newer AEDs in children and adolescents during the last decade, based on both clinical and population-based evaluations in Norway.[34,35] The finding that most patients included in our study are in the older age groups is in line with data from the national prescription databases. This is not surprising, considering that until recently the drug was approved only for patients 16 years or older. The presented data from the Norwegian prescription database show that more patients aged 5-14 years were prescribed LCM in 2017 compared to previous years. As the drug received EU approval for pediatric use in September 2017 this number could be expected to increase

further in 2018. The number of children and adolescents (<20 years of age) who were prescribed LCM was somewhat higher in Denmark than in Norway, especially early in the studied period, which could be due to differences in treatment tradition or strategy in the two countries.

METHODOLOGICAL CONSIDERATIONS

Our study examines a large (n=124) group of children and adolescents and combines data from serum concentration measurements with clinical information and prescription trends. Some important limitations need to be considered. The established practice for TDM in Norway and Denmark is a standardized sampling time, drug fasting before the morning dose at steady-state, but it cannot be assured that this is complied with at all times. Poor adherence cannot be controlled for in a retrospective and naturalistic setting, and clinical data was not available for all patients. Even though there is a strong tradition for utilizing TDM in epilepsy treatment in both Norway and Denmark, some patients on LCM therapy may not have had serum concentrations measured. Discontinuation before measurement may result in overestimation of retention rates.

Conclusions

This study from two national epilepsy centers in Scandinavia provides a detailed description of the experience using LCM in children and adolescents by combining TDM, clinical and prescription data. Pharmacokinetic variability in and between age groups is demonstrated, indicating the usefulness of TDM. More than two thirds of patients continued treatment beyond one year suggesting reasonable effectiveness, and all of these patients had serum concentrations within the reference range. One-year retention rates were even higher among patients not concomitantly using other sodium channel blocking AEDs.

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Figure legends

Figure 1 Doses and serum concentrations of lacosamide in children and adolescence (< 18 years of age) based on therapeutic drug monitoring data in Norway and Denmark

A) Doses (mg) and serum concentrations (µmol/L) of lacosamide (n=124). One patient using 600 mg lacosamide per day, with a serum concentration of 138 µmol/L is not included in the figure.

B) Doses (mg/kg) and serum concentrations (µmol/L) of lacosamide in patients where weight was available (n=76).

C) Daily doses and serum concentrations of lacosamide in patients who did (crosses, n=45) or did not (dots, n=18) continue therapy for more than 12 months for patients where information on duration of treatment was available.

The combined reference range in Norway (10-40 µmol/L) and Denmark (9-39 µmol/L) of 9-40 µmol/L is indicated with dotted lines. The conversion factor for lacosamide from µmol/L to mg/L is 0.25 (i.e., 1 µmol/L = 0.25 mg/L)

Figure 2 – C/(D/kg) ratio in different age groups.

The differences between the oldest and the middle and between the oldest and the youngest age groups are statistically significant after Bonferroni correction. (*p=0.003 **p=0.006)

Figure 3 Concomitantly used antiepileptic drugs.

Number of patients using the indicated drug in combination with lacosamide. Some patients use multiple drugs.

Figure 4 – Number of patients <20 years of age being prescribed lacosamide in Norway and Denmark

The number of patients in different age groups being prescribed lacosamide in Norway and Denmark. For the Norwegian data results are given as <5 when less than five patients in a group is prescribed the drug. For illustration purposes this value has been set to 2.

Table 1 Demographic and TDM findings in children and adolescence using lacosamide, n=124

Gender, n (%)	
Boys	63 (51)
Girls	61 (49)
Age, years, median (range)	15 (2-17)
Dose, mg	
Mean (SD)	283 (114)
Median (range)	300 (50-600)
Dose, mg/kg (n=76) *	
Mean (SD)	5.5 (2.2)
Median (range)	5.1 (2.4-14.8)
Serum concentration, µmol/L**	
Mean (SD)	21.3 (13.6)
Median (range)	18 (5-138)
C/D-ratio, µmol/L/mg	
Mean (SD)	0.079 (0.033)
Median (range)	0.073 (0.030-0.230)
C/(D/kg)-ratio, (µmol/L)/(mg/kg), (n=76) *	
Mean (SD)	3.99 (1.66)
Median (range)	3.86 (1.26-9.39)
Clinical indication (n=81) *, n**	
Focal or multifocal epilepsies	71
Generalized epilepsies	2
Lennox Gastaut Syndrome	5
Epileptic encephalopathy, unknown etiology	1
Autosomal dominant nocturnal frontal lobe epilepsy	1
Undetermined epilepsy syndrome	1
Concomitant AEDs in use, n (%)	
Monotherapy	17 (14)
1 additional AED	58 (47)
2 additional AEDs	40 (32)
3 additional AEDs	9 (7)

TDM: therapeutic drug monitoring, C/D: concentration/dose, AED: antiepileptic drug
*Number of included patients where weight was available
**Mean serum concentration was 5.3 mg/L and median 4.5 mg/L. The conversion factor for lacosamide from µmol/L to mg/L is 0.25 (i.e., 1 µmol/L = 0.25 mg/L)
***Number of included patients where clinical indication was noted

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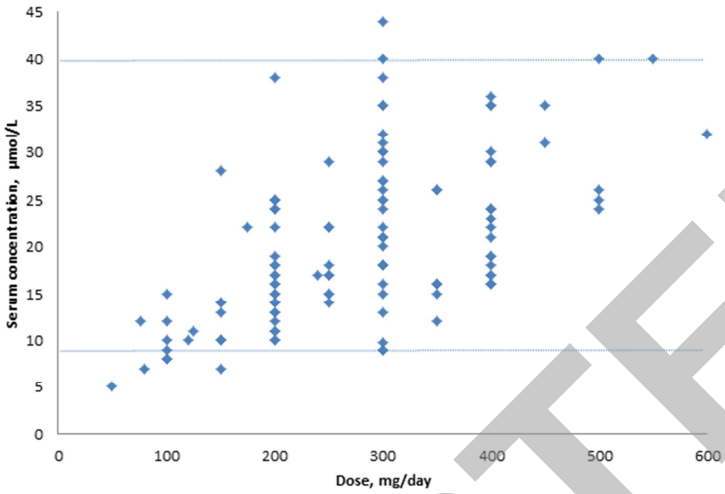

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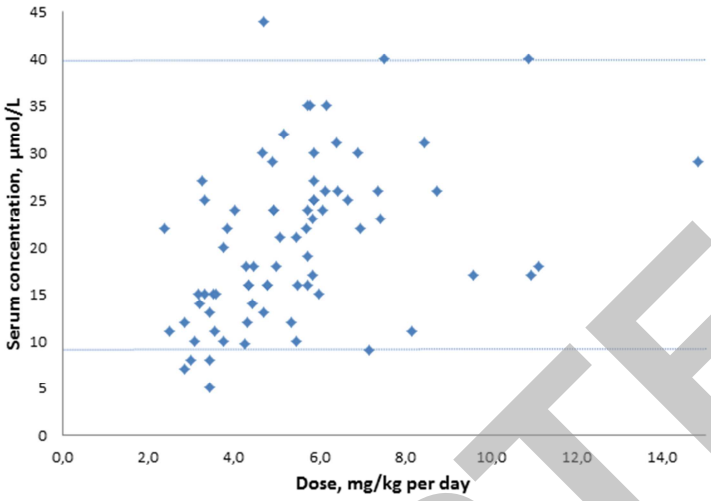

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