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RESEARCH ARTICLE

Effects of *CYP2C19* genetic polymorphisms on the pharmacokinetics of lacosamide in Korean patients with epilepsy

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Abstract

Objective: Many pharmacokinetic studies of lacosamide (LCM) have been reported, but no large-scale clinical study has been conducted on genetic polymorphisms that affect the metabolism of LCM. Therefore, we designed a pharmacogenetic study of LCM to explore the effect of genetic polymorphisms on serum LCM concentration. We evaluated the pharmacodynamic characteristics of LCM, including clinical efficacy and toxicity.

Methods: Adult patients with epilepsy who received LCM at Seoul National University Hospital were enrolled. Blood samples were obtained from 115 patients taking LCM for more than 1 month with unchanged doses and were used to analyze the serum LCM concentration, the concentration/dose (C/D) ratio and the single nucleotide polymorphisms (SNPs) of the cytochrome P450 (*CYP*)2C9 and *CYP2C19* genes. In addition, clinical information—including efficacy, toxicity, and concomitant drugs—was collected.

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Results: The serum LCM concentration showed a linear correlation with the daily dose ($r = .66$, $p < .001$). In genetic analysis, 43 patients (38.7%) were extensive metabolizers (EMs), 51 (45.9%) were intermediate metabolizers (IMs), and 17 (15.3%) were poor metabolizers (PMs). In the group comparison, mean serum concentrations and the C/D ratio showed significant differences between the three groups ($p = .01$ and $p < .001$, respectively). The C/D ratios of IM (27.78) and PM (35.6) were 13% and 39% higher than those of EM (25.58), respectively. In the pharmacodynamic subgroup analysis, patients in the ineffective LCM group had significantly lower serum concentrations (6.39 ± 3.25 vs. 8.44 ± 3.68 μg/ml, $p = .024$), whereas patients with adverse events had higher serum concentrations than those without adverse events (11.03 ± 4.32 vs. 7.4 ± 3.1 μg/ml, $p < .001$). Based on this, we suggest a reference range for LCM in the Korean population (6–9 μg/ml).

Significance: Genetic polymorphisms of the *CYP2C19* gene affect the serum LCM concentration. Because efficacy and toxicity are apparently related to serum LCM levels, the genetic phenotype of *CYP2C19* should be considered when prescribing LCM for patients with epilepsy.

KEYWORDS

anticonvulsants, epilepsy, lacosamide, pharmacogenetics, pharmacokinetics

1 | INTRODUCTION

Lacosamide (LCM: *R*-2-acetamido-*N*-benzyl-3-methoxypropionamide) is a third-generation antiseizure medication (ASM) approved for focal seizures since 2009. In contrast to other ASMs targeting fast-acting sodium channels, LCM selectively enhances the slow inactivation of voltage-gated sodium channels, consequently resulting in stabilization of hyperexcitable neuronal membranes.[1] Initially LCM was shown to have a therapeutic effect in focal-onset epilepsy as an adjuvant therapy.[2] In addition, LCM can now be used to treat primary generalized tonic–clonic seizures or generalized epilepsy.[3]

Several pharmacokinetic characteristics of LCM have been studied. Although ~40% of LCM is eliminated through renal excretion as an unchanged active drug, the other 60% of the drug dose is known to be metabolized through several cytochrome P450 (CYP) enzymes (CYP2C19, CYP2C9, and CYP3A4) or CYP-independent mechanisms.[4] More than half of the metabolites are *O*-desmethyl-lacosamide, and the other minor metabolites include *p*-hydroxy-lacosamide and desacetyl-lacosamide.[5] These metabolites have no pharmacological activities.[6]

More clinical therapeutic drug monitoring (TDM) studies have revealed additional pharmacokinetic features of LCM. The serum concentration of LCM was dose dependent and age independent. Concomitant enzyme-inducing ASMs (EI-ASMs) reduced the serum concentration of LCM.[7–9] In addition, previous pharmacodynamics studies have reported that the dose or plasma concentration of LCM was related to drug efficacy or side effects.[10] However, no large clinical research study on the pharmacogenetics of LCM has been conducted.

Many pharmacokinetics and drug-drug interaction studies have researched various ASMs. To obtain more

Key points

- Serum concentration of lacosamide was affected by genetic polymorphisms of cytochrome P450 (*CYP*)*2C19* gene.
- Poor metabolizer phenotype of *CYP2C19* gene showed significantly higher serum concentration.
- Serum concentration of lacosamide showed definite linear dose-dependent result.
- In pharmacodynamic study, clinical efficacy and toxicity were correlated with serum concentration of lacosamide.
- When prescribing lacosamide to patients, the *CYP2C19* genotype should be considered because it may affect clinical efficacy and toxicity.

precise personalized medical treatment, a prescription that considers drug metabolism according to each genotype is necessary. Therefore, many pharmacogenetics studies on the relationship between various ASMs and genetic variants have already been conducted.[11] However, although a considerable amount of LCM undergoes CYP hepatic metabolism, the relationship between *CYP* genotypes and LCM serum concentrations is still unclear.

The purpose of this study was to evaluate the effect of genetic polymorphisms of CYP enzymes on LCM concentrations. We designed a prospective pharmacokinetic study of LCM with genetic analysis in Korean patients with epilepsy. In addition, pharmacodynamics related to efficacy and toxicity were evaluated in the patients.

2 | METHODS

2.1 | Study design and population

This was a prospective study conducted at a single institution (Seoul National University Hospital). This study included adult patients with epilepsy who were taking LCM. The study aimed to enroll 100 patients in 3 years, from January 2018 to January 2021. The inclusion criteria were as follows: (1) focal or generalized epilepsy lasting over 2 years, (2) age between 17 and 85, (3) taking LCM for over 4 weeks or more, and (4) agreement with genetic analysis. The exclusion criteria included liver failure (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] level more than threefold above the upper limit of normal), renal failure (creatinine clearance <60 ml/min), or pregnancy. Patients with severe medical conditions or ongoing disease and a history of psychogenic nonepileptic seizures were also excluded. All patients received LCM twice a day. The dosage of LCM was determined in each patient personally by experienced epileptologists (SKL, KC). The dosage regimens of LCM were not changed for at least 1 month prior to blood sampling. Blood sampling was conducted in the outpatient clinic 1–4 h after the patient took the morning dose. Blood for genetic testing was also collected from participants who agreed with it.

Clinical data, including age, sex, prescribed dose, concomitant ASMs, seizure frequency, specific diagnosis of epilepsy, electroencephalography (EEG) findings, and magnetic resonance imaging (MRI) findings, were collected. Efficacy and toxicity were also evaluated by the prescribing physicians (SKL, KC). Efficacy and toxicity were evaluated on the same day as blood sample collection.

2.2 | Analysis of drug concentrations

The serum concentration of LCM was determined using high-performance liquid chromatography (HPLC) (1200 series, Agilent Technologies) coupled with tandem mass spectrometry (MS/MS) (Xevo TQ, Waters Corp.) using validated methods. To determine the concentration of LCM, 50 µl of serum was mixed with 150µ L of internal standard (lacosamide-d3). The mixture was centrifuged at 18 473 *g* and 4°C for 10 min, and 5 µl of the supernatant was injected into the LC–MS/MS system. Chromatographic separation was conducted on a UHP ASB C18 column (1.9 µm, 100×2.1 mm) (Agela Technologies), and the column temperature was maintained at 35°C. The mobile phase consisted of 100% water with 0.1% formic acid and 100% acetonitrile with 0.1% formic acid, and the separations were conducted at a flow rate of 0.2 ml/min. The MS/MS was operated in positive electrospray ionization. The LCM and internal standard were detected by the multiple reaction monitoring mode, and the precursor-to-product ion pairs at the mass-to-charge ratios were 251.1 to 108.04 and 254.15 to 108.04 for the LCM and internal standard, respectively. The calibration range of LCM was linear over the range of 5 µg/L to 5000 µg/L, and the limit of quantification was 0.5 µg/L.

2.3 | Analysis of single nucleotide polymorphisms (SNP) in human *CYP2C9* and *CYP2C19* genes

For the genotyping of *CYP2C9* and *CYP2C19*, DNA was extracted from peripheral whole blood samples using the Maxwell CSC Blood DNA Kit and Maxwell CSC Instrument (Promega), and TaqMan allelic discrimination assays were performed on a real-time polymerase chain reaction (RT-PCR) system (Applied Biosystems). Ten microliters of PCR mixture was prepared with 5 µl of 2X TaqMan Genotyping Master Mix, 0.5 µl of 20X Drug Metabolism Genotyping Assay Mix, 3.5 µl of DNase-free water, and 1 µl of DNA. The genotyping for *CYP2C9**3 (rs1057910, assay ID: C__27104892_10), *CYP2C19**2 (rs4244285, assay ID: C__25986767_70), and *CYP2C19**3 (rs4986893, assay ID: C__27861809_10) was performed with validated TaqMan genotyping assays. PCR was carried out as follows: initial denaturation at 95°C for 10 min, 40 cycles of denaturation at 92°C for 15 s, and annealing/extension at 60°C for 1 min. The allelic discrimination results were determined using 7500 Real-Time PCR System software version 2.0.6 (Applied Biosystems).

Based on the *CYP2C9* genotype, the patients were classified as extensive metabolizers (EMs) (*1/*1) or intermediate metabolizers (IMs) (*1/*3). Based on the *CYP2C19*

genotype, the patients were classified into three phenotype groups. An EM is an individual carrying two normal function (*1) alleles. An IM is an individual carrying one normal function allele (*1) and one no-function allele (*2 or*3). A poor metabolizer (PM) is an individual carrying two no-function alleles (*2 or *3).

2.4 | Efficacy and toxicity evaluation

Efficacy was evaluated by dividing the patients into three subgroups. The first group included patients whose seizure frequency at the time of blood collection decreased by more than 50% compared to the previous visit. The second group included patients whose seizure frequency did not decrease by more than 50% but remained in a seizure-free state or whose seizure frequency was tolerable. The third group included patients in whom LCM was ineffective. Because seizure control was not sufficient, physicians increased the doses of LCM or other ASMs for patients in this group after blood sampling. This third group was classified as the ineffective group.

Toxicity and possible adverse events of LCM were also evaluated by the prescribing physician. If an adverse event known previously as a possible side effect of LCM occurred after the prescription of LCM, it was judged as an adverse event associated with LCM. When the prescribing doctor stopped the drug or reduced the prescribed dose of LCM due to side effects, it was classified as a case of severe adverse events.

2.5 | Data analysis and statistics

The concentration/dose (C/D) ratio was calculated by dividing the blood concentration by the prescribed drug dose. The correlation analysis of serum concentration and prescribed LCM dose was performed using Pearson correlation coefficients. Normality test was conducted with Shapiro–Wilk test. One-way analysis of variance (ANOVA) and chi-square tests were used to assess significant differences in genotype group comparisons. Bonferroni correction for post hoc analysis was conducted in one-way ANOVA. The Student's t test was used to compare the serum concentration and C/D ratio in subgroup analysis. Multivariate linear regression analysis was conducted to identify the effect of genetic phenotype to the C/D ratio after controlling for confounding factors. Multivariate logistic regression analysis was used to evaluate the predictive factors of efficacy and adverse events after taking LCM. The exposure-efficacy or exposure-toxicity relationship were investigated by logistic regression analysis using LCS serum concentration and binary outcomes of efficacy and toxicity. The level of significance was set at $p < .05$. Statistical procedures were performed with R (version 3.5.3).

2.6 | Standard protocol approvals, registrations, and patient consents

This study was approved by the Seoul National University Hospital Institutional Review Board. Written informed consent was obtained from all enrolled patients.

3 | RESULTS

3.1 | Patient characteristics

Measurement of serum LCM concentration and genetic analysis were completed for a total of 115 patients with epilepsy. Among them, four patients with outlier values were excluded, which could be errors in blood concentration tests. These outlier values were two maximums and two minimums. These excluded four patients met the criteria for z score >3 and <−2 of serum concentration. Therefore, a total of 111 patients were included in this study. Specific data is available in the Supplementary Table 1.

The specific demographics of the 111 patients are described in Table 1. Of 111 patients, 62 were male and 49 were female. The median age was 41 years (range 17–84 years). The mean serum concentration was 8.12 ± 3.65 μg/L. The median prescribed daily dose of LCM was 300 mg (range 100–600 mg). The mean C/D ratio was 27.5 ± 9.3. In the 111 patients, the serum concentration showed a linear correlation with the daily dose taken ($r = .66$, $p < .001$) (Figure 1A). The serum concentration and C/D ratio were independent of age and sex. Test of normality was satisfied with Shapiro–Wilk test in the serum concentration and the C/D ratio.

Twenty-eight patients were taking LCM as monotherapy, whereas the other 73 patients were taking concomitant ASMs with LCM. Among them, 13 patients were taking concomitant EI-ASMs such as carbamazepine, phenytoin, or phenobarbital. Most of the patients were diagnosed with focal epilepsy (103 patients).

A total of 22 patients had adverse events while taking LCM. Dizziness was the most frequently reported adverse event (15 patients), followed by tremor (4 patients). Other than that, various other minor side effects were reported, including headache, ataxia, dysarthria, diplopia, somnolence, and chest pain. A total of 18 patients were classified into the ineffective group.

3.2 | Results of SNP analysis of the *CYP2C9* and *CYP2C19* genes in Korean patients

Genetic analysis was performed for both *CYP2C9* and *CYP2C19*. The *CYP2C9* genetic analysis identified four IMs and 107 EMs. The *CYP2C19* genetic analysis identified 43 EMs (38.7%), 51 IMs (45.9%), and 17 PMs (15.3%). The detailed demographics compared to the CYP2C19 phenotype groups are described in Table 2.

With *CYP2C19* genotyping, we calculated the allele frequencies of *CYP2C19* SNPs. The *CYP2C19*1* allele accounted for 61.7% (137/222) of the total, followed by the *CYP2C19*2* allele at 29.9% (53/222) and the *CYP2C19*3* allele at 14.1% (32/222).

3.3 | CYP2C19 phenotypes affect the serum concentration and C/D ratio of lacosamide

We performed group comparisons between the three phenotypes of CYP2C19 metabolism. To eliminate potential bias that could affect the serum concentration of LCM, we excluded 13 patients who were taking concomitant EI-ASMs in this analysis. The median age and sex ratio were all similar among the three CYP2C19 phenotype groups. The PM group showed the highest mean serum concentration (10.97 ± 5.51 μg/ml) of LCM compared to EM and IM phenotype groups (7.95 ± 3.11, 7.88 ± 2.98 μg/ml, respectively). In one-way ANOVA analysis of serum concentration, three phenotype groups showed significant differences ($p = .009$). Post hoc analysis (Bonferroni correction) showed significant difference between PM vs EM ($p = .016$) and PM vs IM ($p = .011$).

The median daily doses of LCM were the same in the three groups (300 mg). The mean daily doses of LCM were slightly higher in the PM group but showed no significant difference among the three phenotype groups. Although the mean daily dose of LCM was similar, we compared the C/D ratio to exclude the effect of dose on serum concentration.

The mean C/D ratio of LCM showed high values in the order of PMs (35.6 ± 11.13), IMs (28.78 ± 8.72), and EMs (25.58 ± 6.89) (Table 2, Figure 1B). In one-way ANOVA, the C/D ratios of the three phenotype groups showed significant differences ($p = .0007$). Post hoc analysis (Bonferroni correction) showed significant difference between PM vs. EM ($p < .001$) and PM vs. IM ($p = .021$). As a result, compared to the EM group, the C/D ratio were 13% higher in the IM group and 39% higher in the PM group. This result indicates that the capacity to metabolize LCM sequentially declines according to the phenotype of CYP2C19, from PM to EM.

The proportion of patients with adverse events was the highest in the PM group (5/16, 31.25%). In addition, the proportion of patients in whom LCM was determined

TABLE 1 Demographics and clinical characteristics of the patients

Patient characteristics	Value
Median age, range	41 (17–84)
Sex	
Male	62 (55.86%)
Female	49 (44.14%)
Mean serum LCM concentration (μg/ml)	8.12 ± 3.65
Mean C/D ratio	27.5 ± 9.3
Daily dose of lacosamide	
100 mg < daily dose ≤200 mg	38 (34.23%)
200 mg < daily dose ≤400 mg	63 (56.76%)
400 mg < daily dose ≤600 mg	10 (9.01%)
Number of concomitant ASMs	
LCM monotherapy	28 (25.23%)
One concomitant ASM	27 (24.32%)
Two concomitant ASMs	21 (18.92%)
Three concomitant ASMs	17 (15.32%)
More than four concomitant ASMs	18 (16.22%)
Type of concomitant ASMs	
LCM monotherapy	28 (25.23%)
LCM + enzyme-inducing ASMs	13 (11.71%)
LCM + other ASMs	60 (54.05%)
Adverse events (total $n = 22$)	
Dizziness	15 (13.51%)
Headache	1 (0.9%)
Tremor	4 (3.6%)
Ataxia	2 (1.8%)
Dysarthria	2 (1.8%)
Diplopia	1 (0.9%)
Somnolence	1 (0.9%
Chest pain	1 (0.9%)
Efficacy	
50% > seizure reduction	8 (7.21%)
Unchanged, tolerable control	85 (76.58%)
Ineffective	18 (16.22%)
Epilepsy type	
Focal epilepsy	103 (92.79%)
Generalized epilepsy	5 (4.5%)
Others/unknown	3 (2.7%)

Note: $n = 111$.

Abbreviations: ASMs, antiseizure medications; LCM, lacosamide.

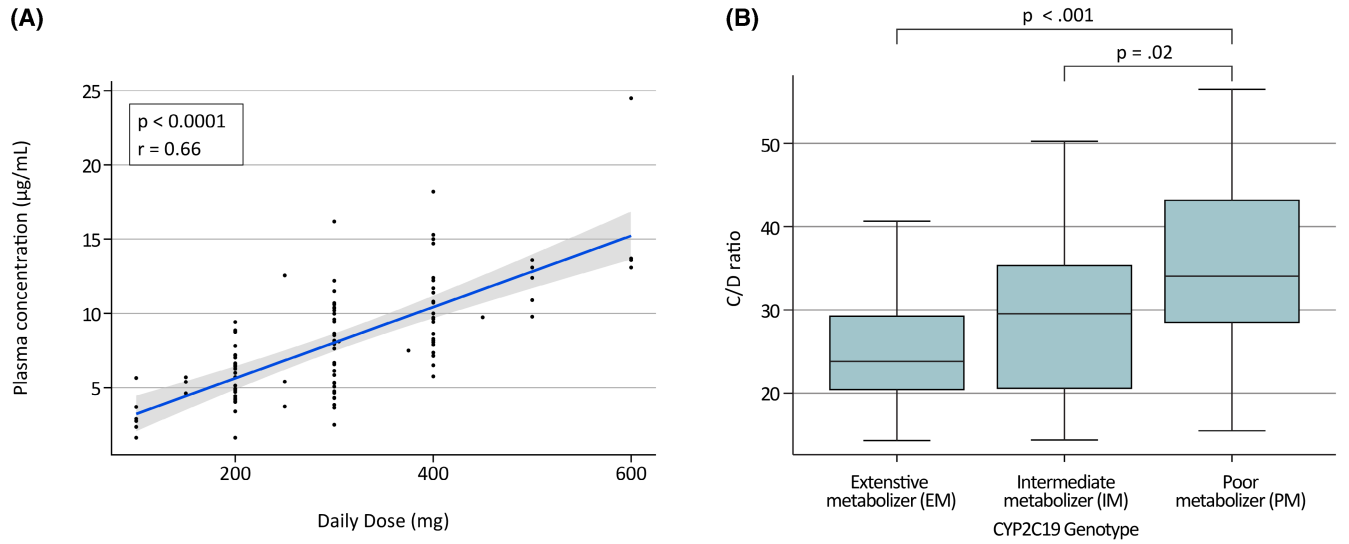

FIGURE 1 (A) Relationship of plasma concentration and daily dose of lacosamide (LCM). The plasma concentration of LCM showed a linear correlation with the daily dose ($r = .66$, $p < .001$). (B) Boxplot of C/D ratios in CYP2C19 phenotype subgroups. The C/D ratio of LCM showed higher values in the order of the PMs, IMs, and EMs ($p < .001$). CYP, cytochrome P450; EMs, extensive metabolizers; IMs, intermediate metabolizers; LCM, lacosamide; PMs, poor metabolizers.

TABLE 2 Demographics and TDM findings in three CYP2C19 phenotype groups

Characteristic	CYP2C19 phenotypes			
	Extensive metabolizer ($n = 38$)	Intermediate metabolizer ($n = 44$)	Poor metabolizer ($n = 16$)	*p* Value
Median age, range	39 (17–68)	43 (20–72)	37.5 (19–84)	NS
Sex (M/F)	20/18 (1.11:1)	25/19 (1.32:1)	8/8 (1:1)	NS
Median LCM dose (mg), range	300 (100–600)	300 (100–600)	300 (100–600)	NS
Mean LCM dose (mg), SD	314.47 (105.85)	289.77 (117.42)	321.88 (147.16)	NS
Mean serum concentration (μg/ml), SD	7.95 (3.11)	7.88 (2.98)	10.97 (5.51)	.009
Mean C/D ratio, SD	25.58 (6.89)	28.78 (8.72)	35.6 (11.13)	<.001
Adverse effect, *n* (%)	9/38 (23.68%)	8/44 (18.18%)	5/16 (31.25%)	NS
Ineffective patients, *n* (%)	7/38 (18.42%)	6/44 (13.64%)	2/16 (12.5%)	NS

Abbreviations: C/D, concentration/dose; LCM, lacosamide; NS, not significant; SD, standard deviation.

to be ineffective was the lowest in the PM group (2/16, 12.5%). However, there were no significant differences between groups in the proportion of patients with adverse events or those in whom LCM was ineffective.

To see the effects of confounding factors including age, sex, and concomitant EI-ASMs, we employed multiple linear regression analysis in the whole patient population (111 patients). After controlling for age, sex, and concomitant EI-ASMs, CYP2C19 phenotypes still showed significant association with mean C/D ratio. Compared to EM, IM (coefficient estimate [CE] = 3.32, $p = .05$) and PM (CE = 9.7, $p < .001$) showed significant higher mean C/D ratio. In the analysis, age and female gender showed positive correlation with meant C/D ratio. There was also a significant interaction between mean C/D ratio and concomitant EI-ASMs (CE = −8.86, $p < .001$). Results of multiple linear regression model are described in Table 4.

3.4 | Lower serum LCM concentration in the ineffective group

As we described in the Section 2 (Methods), the efficacy of LCM was evaluated by dividing the patients into three groups. Eight patients (7.21%) had more than 50% seizure frequency reduction. Eighty-five patients (76.58%) were in a group whose seizure frequency did not decrease more than 50% but remained in a seizure-free state or whose seizure frequency was maintained at a tolerable rate. Combining these two groups, a total of 93 patients were classified as the effective LCM group. In the remaining 18

patients (16.22%), the dose of LCM or other ASMs was increased due to uncontrolled seizures. These patients were classified into the ineffective group.

Compared to the effective group, the mean prescribed LCM dose was slightly lower in the ineffective group (269.44 ± 89.34 vs. 310.71 ± 118.33 mg), without statistical significance ($p = .1$). For the mean serum concentration, the ineffective group showed a significantly lower plasma level of LCM (6.39 ± 3.25 vs. 8.44 ± 3.68 μg/ml, $p = .024$) (Figure 2A). The mean C/D ratio showed no significant difference between the two groups (23.99 ± 11.39 vs. 28.16 ± 8.85, $p = .16$). These results confirm that the efficacy of LCM is associated with the serum concentration. Because the C/D ratio was not significantly different between the groups, the lower serum concentration might be associated with the lower prescribed dose.

3.5 | Higher serum LCM concentration level in the adverse events group

We analyzed the mean LCM dose, serum concentration, and the C/D ratio between the adverse events group ($n = 22$) and the no adverse events group ($n = 89$) (Table 3). The mean serum LCM concentration was significantly higher in the adverse events group (11.03 ± 4.32 vs. 7.4 ± 3.1 μg/ml, $p < .001$) (Figure 2B). The mean prescribed LCM dose was significantly higher in the adverse events group (377.27 ± 126.99 vs. 286.8 ± 103.78 mg, $p = .004$), whereas the mean C/D ratio showed no significant difference (30.37 ± 9.75 vs. 26.85 ± 9.15, $p = .14$). These results indicate that high serum LCM levels are related closely to the occurrence of side effects, and that these high serum concentrations are associated with the prescription of high doses of LCM.

The reported adverse events are summarized in Table 1. Two patients complained of serious adverse events (chest pain, severe dizziness), so the physicians immediately discontinued the LCM for these patients after blood collection. Another two patients were prescribed reduced doses of LCM after blood collection due to adverse events. These four patients were classified into the severe adverse event group. The remaining 18 patients who maintained unchanged medication doses were classified into the minor adverse event group. The mean serum concentrations did not differ significantly between these two groups.

3.6 | Effects of enzymes inducing ASMs on LCM serum concentration

Because LCM is metabolized to a major inactive *O*-desmethyl metabolite by CYP enzymes, the serum concentration of LCM could be influenced by CYP-inducing drugs. We additionally evaluated the effects of concomitant CYP EI-ASMs. Patients who were taking any drugs, including phenytoin, phenobarbital, or carbamazepine, were categorized into the concomitant EI-ASM group. A total of 13 patients were classified into this group and were compared to the other remaining patients (no EI-ASM group, $n = 98$) (Table 3).

Although the mean prescribed LCM dose was similar between groups, the mean serum concentration of LCM was significantly lower in the EI-ASM group (5.9 ± 2.48 vs. 8.41 ± 3.7 μg/ml, $p = .004$). The percentage difference between the two values was 35%. Consequently, the mean C/D ratio in the concomitant EI-ASM group was significantly lower than that in the no EI-ASM group (19.21 ± 6.76 vs. 28.65 ± 9.09, $p < .001$) (Figure 2C). These results confirmed that concomitant EI-ASMs lowered the plasma concentration of LCM. The effect of concomitant use of EI-ASMs to mean C/D ratio was also confirmed in multiple linear regression analysis (Table 4).

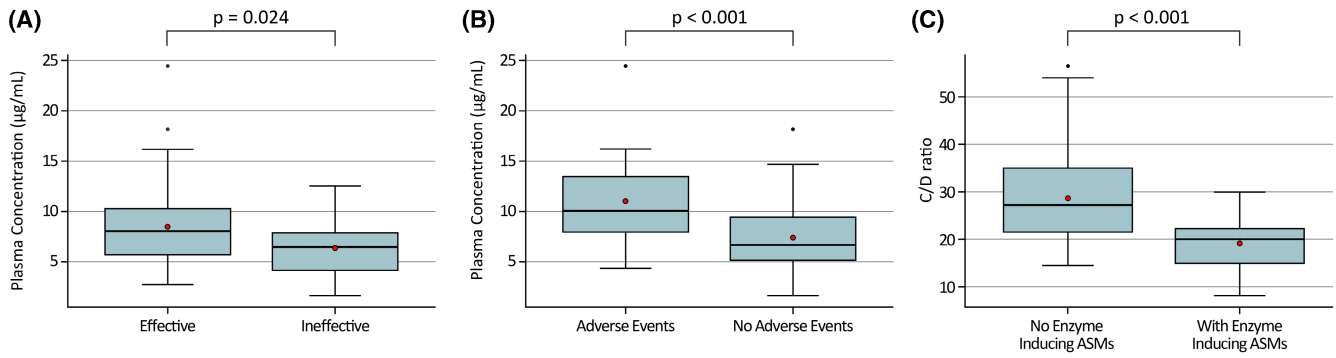

FIGURE 2 Plasma concentration and C/D ratio comparison in subgroup analysis. (A) The mean serum lacosamide (LCM) concentration was significantly lower in the ineffective group ($p = .024$). (B) The mean serum LCM concentration was significantly higher in the adverse events group ($p < .001$). (C) The mean C/D ratio was significantly lower in the concomitant enzyme-inducing antiseizure medication group ($p < .001$).

TABLE 3 Results of the subgroup analysis

Subgroup	Efficacy			Toxicity			Concomitant EI-ASMs		
	Effective (n = 93)	Ineffective (n = 18)	p Value	With AE (n = 22)	Without AE (n = 89)	p Value	No EI-ASMs (n = 98)	With EI-ASMs (n = 13)	p Value
Mean LCM dose (mg)	310.71	269.44	.1	377.27	286.8	.004	304.59	305.77	.96
(SD)	(118.33)	(89.34)		(126.99)	(103.78)		(117.99)	(81.75)	
Range	100–600	100–400		200–600	100–600		100–600	200–450	
Mean serum concentration (μg/ml)	8.44	6.39	.024	11.03	7.4	<.001	8.41	5.9	.004
(SD)	(3.68)	(3.25)		(4.32)	(3.1)		(3.7)	(2.48)	
Range	2.76–24.5	1.63–12.56		4.3–24.5	1.63–18.2		2.36–24.5	1.63–9.74	
Mean C/D ratio	28.16	23.99	.16	30.37	26.85	.14	28.65	19.21	<.001
(SD)	(8.85)	(11.39)		(9.75)	(9.15)		(9.09)	(6.76)	
Range	14.4–56.5	8.16–50.24		17.9–54	8.16–56.5		14.33–56.5	8.16–29.97	

Abbreviations: AE, adverse event; EI-ASMs, enzyme-inducing antiseizure medications; LCM, lacosamide; SD, standard deviation.

3.7 | Multivariate logistic regression analysis: Predictive factors for effective outcomes and adverse events

To evaluate the predictive value of the serum concentration of LCM to efficacy and adverse events, multivariate logistic regression analysis was conducted. In the analysis of efficacy, we adopted EEG and MRI findings as covariates in addition to serum concentration and CYP2C19 phenotypes. This is because generally EEG and MRI findings are good predictors of seizure control and outcome. In the result, serum concentration was still a good predictive factor for effective seizure outcome (odds ratio [OR] = 1.31, p = .013). CYP2C19 phenotypes and concomitant use of EI-ASMs were not predictive factors for effective seizure outcome after taking the LCM. An abnormal MRI finding was strongly correlated with ineffective seizure outcome (OR = 0.15, p = .004) (Table 5).

In the analysis of adverse events, concomitant use of sodium channel blockers (SCBs) was additionally adopted as a covariate because SCBs such as lamotrigine, carbamazepine, and phenytoin were associated with adverse events. In the result, serum concentration was a strong predictive factor for adverse events after taking LCM (OR = 1.36, p < .001). In our analysis, concomitant use of SCBs was not related with adverse events. In addition, CYP2C19 phenotypes were not predictive factors for adverse events (Table 6). These results showed the importance of adequate serum concentration of LCM regardless of CYP2C19 phenotype.

3.8 | Suggesting a reference range for LCM in the Korean population

With the results of the trough plasma concentrations in the subgroup analysis of efficacy and toxicity, we calculated dose–response relationships. The LCS plasma concentration had a significant relationship between exposure (p < .05) or toxicity (p < .001) in the logistic regression analysis. In Figure 3, the left blue curve represents the probability of a clinical effective response to LCM. Approximately 80% of patients showed clinical efficacy above 6 μg/ml [effective dose $(ED)_{80}$]. If the serum concentration exceeded 10 μg/ml, LCM was effective in more than 90% of patients. The right red curve represents the dose–response curve of toxicity. Side effects of LCM may occur with a probability of ~50% at a plasma concentration of ~14 μg/ml. For the probability of adverse events less than 20%, the blood concentration should be less than ~9 μg/ml [toxic dose $(TD)_{20}$].

Considering that four patients were classified into the severe adverse events group (4/22, 18.2%), we set the

TABLE 4 Multiple regression model comparing mean C/D ratio between *CYP2C19* phenotypes after age, sex and EI-ASMs

Variables	Coefficient estimates	Standard error	*p* Value
Intercept	17.5	2.5	<.001
CYP2C19 phenotype			
Extensive metabolizer			
Intermediate metabolizer	3.32	1.61	.05
Poor metabolizer	9.7	2.23	<.001
Age	0.15	0.05	.005
Sex (Female)	4.32	1.5	.005
Concomitant use of EI-ASMs	−8.86	2.32	<.001

Note: $R = .34$ (Adj $R = .3$). $n = 111$.

Abbreviation: EI-ASMs, enzyme-inducing antiseizure medications.

TABLE 5 Multivariate logistic regression model to identify independent predictors of effective seizure outcome after taking lacosamide

Variables	OR	95% CI	*p* Value
Serum concentration (μg/ml)	1.31	1.07–1.65	.013
CYP2C19 phenotype			
Extensive metabolizer	Reference		
Intermediate metabolizer	1.52	0.47–5.14	.48
Poor metabolizer	0.66	0.11–5.34	.65
Concomitant use of EI-ASMs	0.86	0.19–4.77	.85
EEG (Abnormal)	0.96	0.23–3.46	.95
MRI (Abnormal)	0.15	0.03–0.49	.004

Abbreviations: CI, confidence interval; EEG, electroencephalography; EI-ASMs, enzyme-inducing antiseizure medications; MRI, magnetic resonance imaging; OR, odds ratio.

TABLE 6 Multivariate logistic regression model to identify independent predictors of adverse event after taking lacosamide

Variables	OR	95% CI	*p* Value
Serum concentration (μg/ml)	1.36	1.17–1.64	<.001
CYP2C19 phenotype			
Extensive metabolizer	Reference		
Intermediate metabolizer	0.69	0.22–2.14	.52
Poor metabolizer	0.58	0.1–2.69	.51
Concomitant use of SCBs	2.14	0.67–6.73	.19

Abbreviations: CI, confidence interval; OR, odds ratio; SCB, sodium channel blocker.

upper limit of the reference range as the TD_{20}. The lower limit of the reference range was set as the ED_{80}. Based on these results, we propose a serum level of 6–9 μg/ml as an appropriate reference range for LCM in Korean epilepsy patients. In the CYP2C19 phenotype analysis, the EM and IM groups showed mean serum concentrations of LCM of 7.95 and 7.88 μg/ml, respectively, with a median prescribed daily dose of 300 mg. These values are appropriately included in the reference range we suggested. However, the mean serum concentration of PM was 10.97 μg/ml, exceeding the upper limit of the suggested reference range. Based on this result, the dose of LCM for patients who have genetic polymorphisms in the PM group should be reduced from the usual dose.

4 | DISCUSSION

In this study, our data showed that CYP2C19 polymorphisms influence the serum concentration of LCM. Although the mean prescribed dose of LCM was similar between phenotype groups, the mean serum concentration and mean C/D ratio for LCM were significantly higher in CYP2C19 PMs. PMs had an ~39% higher C/D ratio

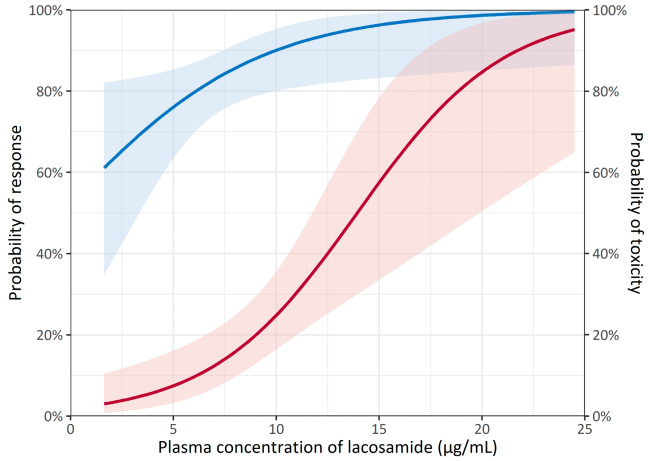

FIGURE 3 Dose–response relationships of lacosamide (LCM). The blue curve represents the probability of a clinical effective response to LCM. The red curve represents the probability of toxicity to LCM.

than EMs and IMs had 13% higher C/D ratio than EMs. To the best of our knowledge, this is the first large-scale pharmacogenetics study showing associations between CYP2C19 polymorphisms and LCM serum concentrations. Furthermore, our data showed a strong correlation between the efficacy/toxicity and serum concentration. With the results of subgroup pharmacodynamics analysis, we suggested a suitable therapeutic window for LCM plasma concentration. In addition, we confirmed a few more pharmacokinetic characteristics of LCM. The serum LCM concentrations showed a strong linear correlation with the oral dosages. Concomitant EI-ASMs significantly reduced the serum concentration of LCM. These results are consistent with previous TDM studies of LCM.[4,8,9,12]

The relationship between the metabolism of LCM and CYP2C19 has not yet been properly studied. In an in vitro study, the concentration of LCM was 15-fold higher than therapeutic levels when CYP2C19 was inhibited.[13] There was only a limited amount of study information provided by the US Food and Drug Administration (FDA). In the 2016 statement from the US FDA, there were no clinically relevant differences between CYP2C19 PMs ($N = 4$) and EMs ($N = 8$). The plasma concentrations in both groups were similar in the results.[14] This previous study had low statistical reliability due to the small number of subjects. The summary of product characteristics (SPCs) from the European Medicines Agency (EMA) also mentions that CYP2C9, CYP2C19, and CYP3A4 are capable of catalyzing the formation of the *O*-desmethyl metabolite in vitro, but there are no data showing a significant difference in vivo.[5] Because our study was conducted on more than 100 patients who satisfied the normal distribution, it has the advantage of statistical reliability. Our results are also consistent with the results of previous in vitro experiments; therefore, we strongly suggest that CYP2C19 metabolism has a significant effect on LCM serum concentrations.

Previous studies have examined the pharmacodynamics of LCM. In 2011, Hillenbrand et al. studied the relationship between the serum concentration and adverse events in the case of LCM add-on therapy.[7] In this study, the authors did not find a clear correlation between the serum concentration and adverse events. In 2017, a larger-scale TDM study was conducted in Norway.[12] In this retrospective study with 344 patients, they showed clear pharmacokinetic variability in relation to efficacy and tolerability. With this result, they suggested a reference range of serum concentrations of 10–40 μmol/L. In our study of Korean patients with epilepsy, we also proved the association between the serum concentration of LCM and efficacy/toxicity. The patient group in which adverse events occurred had significantly higher blood concentrations. These higher concentrations originated from higher prescribed doses of the drug (Table 3). Based on these results, we suggested a narrower range of reference range (6–9 μg/ml). Converting our reference range to μmol/L, it corresponds to 24–36 μmol/L. This fall within the reference range of previous study, and refers to a narrower range. According to the results of our study, CYP2C19 PM patients need to be prescribed a lower dose of LCM to be within the appropriate reference range. Compared to EM patients, it is predicted that it would be appropriate to prescribe a dose that is about 40% lower.

A few more reports of studies have been published that studied LCM serum concentrations and factors that affect them. In the study of Markoula et al.,[9] the serum LCM concentration increased dose-dependently and was age independent. In addition, concomitant EI-ASMs (carbamazepine and phenytoin) significantly decreased serum LCM concentrations. In another cohort study of 75 consecutive patients with epilepsy, carbamazepine, phenobarbital, or phenytoin significantly reduced the plasma concentration of LCM.[8] In our study, it was confirmed that the group taking concomitant EI-ASMs had significantly lower serum LCM levels than the no EI-ASMs group, even though the prescribed doses were similar. These consistent results suggest that LCM is affected by CYP enzyme metabolism.

Serum concentrations of a few old ASMs are known to be affected by CYP2C19 metabolism. For example, phenytoin and phenobarbital were affected by *CYP2C19* polymorphisms.[15,16] Diazepam is another example of an ASM in which *CYP2C19* polymorphisms affect pharmacokinetics.[17] The results of our study indicated that LCM was another ASM affected by *CYP2C19* polymorphisms.

Among the non-ASM drugs, there are many drugs that are affected by *CYP2C19* genotypes. For example, the serum concentrations of proton pump inhibitors (PPIs)[18] voriconazole[19] and clopidogrel[20] are significantly

associated with the *CYP2C19* genotype. With many previous pharmacogenetics studies of these drugs, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has suggested dosing guidelines.[18–20] According to our study, LCM also needs to be dosed with the *CYP2C19* genotype. For future personalized medical care and to create accurate dosing guidelines for this drug, many more pharmacogenetic studies of LCM need to be performed.

CYP2C19 has diverse functional variants. To date, the SNP variants of *CYP2C19* *2, *3, *4, *5, *6, *7, *8, *16, *17, and *26 have been found.[21] These diverse alleles are categorized into a few functional groups. *CYP2C19*2* and **3* were categorized into the no-function group, and *CYP2C19*9* was categorized into the decreased function group. On the other hand, *CYP2C19*17* was categorized into the increased function group. It is also known that various phenotypes are possible by combining various alleles of *CYP2C19*. For example, an individual carrying two increased function alleles (*17/*17) is an ultrarapid metabolizer with CYP2C19.[18] In our study, only the *CYP2C19*2* and **3* alleles were found as SNP variants in a total of 115 enrolled patients.

Specific allele frequencies of CYP2C19 were different between human ethnicities.[22,23] For example, in Asia, the proportions of *CYP2C19*2* and **3* alleles are known to be high, so this should be considered when prescribing drugs such as LCM. However, in central Europe, the *CYP2C19*17* allele is most prevalent.[24] Considering the different allele frequencies between races, further study of pharmacogenetics should be conducted with various ethnicities.

There are a few limitations in our study. First, our study was not conducted with LCM monotherapy. Although the effect of concomitant EI-ASMs was calculated separately, it is also possible that many other prescribed ASMs affected the results. Second, the body distribution of pharmacokinetics calculated by the patient's body weight was not included. Because body weight information was missing in about a half of patients, we excluded this information in this study. However, because blood concentrations showed a linear correlation with the LCM doses irrespective of body distribution, it is unlikely that it affected the results of this study. Third, we did not obtain through drug level even though blood was collected at relatively the same time in the patients. In particular, because the trough level is generally used for the reference range in the concentration researches, the reference range results of this study should be carefully interpreted. Finally, when evaluating toxicity, the prescribing physician judged only whether the adverse events were present and whether it is serious or not. Questionnaire and quantitative analysis on side effects of the drug were not conducted in this study. Based on this study, future studies on the relationship between blood concentration and detailed side effects are also expected.

In conclusion, *CYP2C19* polymorphisms affect the serum concentration of LCM. *CYP2C19* PMs carrying two no-function alleles (*2 or *3) are likely to have higher serum concentrations of LCM. Similar to previous pharmacodynamics studies, the serum concentration of LCM was dose dependent, and clinical efficacy and toxicity were closely associated with serum concentration. When prescribing LCM to patients, the *CYP2C19* genotype should be considered to optimize drug efficacy and minimize the occurrence of adverse events.

AUTHOR CONTRIBUTIONS

S.J.A., K.C., and S.K.L. contributed to study design and conceptualization, data collection, analysis, interpretation of data, and original draft of the manuscript. J.S.O., S.L., and K.S.Y. performed the genetic analysis and interpretation. D.Y.K. performed concentration analysis. H.S., S.H., H.R.S., E.Y.K., H.S.L., W.J.L., J.M., S.T.L., K.H.J., K.I.P., and K.Y.J. contributed to data collection and interpretation. J.M., S.T.L., K.H.J., K.I.P., and K.Y.J. contributed to revise the manuscript for intellectual content. Statistical analysis was made by S.J.A.

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CONFLICT OF INTEREST

The authors S.J.A., J.S.O., D.Y.K., H.S., S.H., H.R.S., E.Y.K., H.S.L., W.J.L., J.M., S.T.L., K.H.J., K.I.P., K.Y.J., S.L., K.S.Y., K.C., and S.K.L. have no conflict of interest relevant to the manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

PATIENT CONSENT

Informed and signed patient and caregiver and guardian statements were obtained to perform genetic analysis for all the participants.

ACCESS TO DATA

S.J.A., K.C., and S.K.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Raw anonymous data are available on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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