Received: 8 August 2018 | Revised: 20 November 2018 | Accepted: 22 November 2018

DOI: 10.1002/npr2.12045

ORIGINAL ARTICLE

WILEY NEUROPSYCHOPHARMACOLOGY REPORTS

Determination of lamotrigine in human plasma using liquid chromatography-tandem mass spectrometry

Shogo Itabashi[1] | Rina Bito[1] | Maika Nishina[1] | Maki Fukumoto[1] | Midori Soda[1] | Mitsunori Doi[1,2] | Shigeyuki Usui[1] | Kiyoyuki Kitaichi[1]

[1]Laboratory of Pharmaceutics, Department of Biomedical Pharmaceutics, Gifu Pharmaceutical University, Gifu, Japan

[2]Department of Pharmacy, Wakayama Medical University Hospital, Wakayama, Japan

Correspondence
Kiyoyuki Kitaichi, Laboratory of Pharmaceutics, Department of Biomedical Pharmaceutics, Gifu Pharmaceutical University, Gifu, Japan.
Email: kitaichi@gifu-pu.ac.jp

Abstract

Aim: Lamotrigine (LTG) is a widely used anti-epileptic drug that is administered to avoid seizures and to maintain seizure-free status. However, several factors reportedly cause individual differences of plasma LTG levels, and the therapeutic target range of LTG varies between individuals. Thus, to optimize effective doses of LTG, we developed a rapid and simple method for determining plasma LTG concentrations.

Methods: Lamotrigine and the internal standard papaverine were extracted from human plasma using solid-phase extraction. After filtration, 5-μL aliquots of final samples were injected into the liquid chromatography-tandem mass spectrometry instrument and LTG and internal standard were separated using a Cadenza CD-C18 column (100 × 2 mm, 3 μm) with 0.1% formic acid in water/acetonitrile (2/1, v/v).

Results: The calibration curve was linear from 0.2 to 5.0 μg/mL, and assessments of recovery, intra- and inter-day precision and accuracy, matrix effects, freeze and thaw stability, and long-term stability demonstrated good reproducibility. Retention times of LTG and internal standard were 1.6 and 2.0 minutes, respectively, and the total run time was 3.5 minutes for each sample.

Conclusion: We developed a rapid and simple method for determining plasma LTG concentrations. The present novel system could be used to inform LTG dose adjustments for individual patients.

KEYWORDS

epilepsy, lamotrigine, liquid chromatography-tandem mass spectrometry, plasma concentration, solid-phase extraction

1 | INTRODUCTION

Lamotrigine (LTG), widely used as an anti-epileptic drug, is administered alone or in combination with other anti-epileptic drugs to prevent partial and general seizures. Since anti-epileptic drugs are required to prevent seizures and to maintain seizure-free status, doses need to be adjusted for each patient. Although plasma concentrations of LTG have been associated with efficacy in the prevention of epileptic seizures,[1] the therapeutic ranges of LTG vary between individuals. So far, it has been reported that several factors influence plasma LTG levels. For example, activities of uridine diphospho-glucuronosyl transferase (UGT) isoenzymes, which predominantly metabolize LTG via N-glucuronidation, affected plasma LTG levels in previous studies,[2,3] and UGT polymorphisms,[4–6]and

Itabashi and Bito equally contributed to this study.

drugs that affect UGT activities, such as valproic acid and phenytoin, likely affect the metabolism of LTG.[5,7,8] Renal replacement therapy also influenced plasma concentrations of LTG,[9,10] because LTG was likely to be removed during hemodialysis.[10] Moreover, switching from branded drugs to generic formulations or from one generic formulation to another reportedly provoked breakthrough seizures and other negative consequences, probably due to changes in intestinal absorption.[11–13] Therefore, to control individual plasma LTG levels through the selection of appropriate dosing regimens, we developed a rapid, simple, and available method to detect plasma concentrations of LTG over a wide range by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

2 | METHODS

2.1 | Chemicals and reagents

Lamotrigine (purity > 98.0%) was purchased from Sigma-Aldrich Co. LLC. (St. Louis, MO, USA). Injection solutions of papaverine hydrochloride (40 mg/mL) were purchased from Nichi-Iko Pharmaceutical Co., Ltd. (Toyama, Japan). Acetonitrile (LC-MS grade) and methanol (LC-MS grade) were purchased from Honeywell (Morristown, NJ, USA) and Kanto Chemical Co., INC. (Tokyo, Japan), respectively. Formic acid was purchased from Sigma-Aldrich Co. LLC. Human plasma was purchased from Cosmo Bio Co., Ltd. (Tokyo, Japan).

2.2 | Liquid chromatography

The LC system comprised a Shimadzu Nexera X2 HPLC (Shimadzu Corporation, Kyoto Japan) equipped with a binary pump (LC-30AD) and an autosampler (SIL-30AC). Chromatography was performed on a Cadenza CD-C18 column (100 × 2 mm, 3 μm, Imtakt Corporation, Kyoto, Japan) maintained at 40°C. The mobile phase comprised 0.1% formic acid in water and acetonitrile (2/1, v/v) and was eluted at a flow rate of 0.2 mL/min. The injection volume was 5 μL.

2.3 | Mass spectrometry

Quantification was achieved by MS/MS detection in positive ion mode for LTG and papaverine that was used as internal standard (IS) using a Shimadzu LCMS-8040 triple quadrupole mass spectrometer equipped with electrospray source for ion production. The MS parameters were optimized with auto-optimized software by infusing standard solutions of LTG and IS (100 ng/mL). Optimal parameters were as follows: nebulizer gas (nitrogen) 3.0 L/min; DL temperature 250°C; heat-block temperature 400°C; drying gas (nitrogen) 15.0 L/min. Q1 Pre vias, collision energy and Q3 pre vias were 29, 26, and 21V for LTG, and 16, 31, and 21V for IS, respectively. The transitions (m/z; precursor ion → product ion) for multiple reaction monitoring were 255.9 → 210.8 for LTG and 340.0 → 324.3 for IS. The dwell time was 100 msec. Data acquisition and integration were controlled using Lab Solutions LCMS software (Shimadzu Corporation).

2.4 | Preparation of working solutions

Lamotrigine and IS were diluted with acetonitrile/water (50/50, v/v) to 100 μg/mL and 4 μg/mL, respectively, and then were stored at −30°C until use as stock solutions. The working solutions of both LTG and IS were prepared from their stock solutions with acetonitrile/water (50/50, v/v) immediately before use. Final concentrations of LTG calibration curves were 0.2-5.0 μg/mL. Regarding IS, the final concentration was 0.8 μg/mL.

2.5 | Preparation of quality control samples

Quality control (QC) samples were prepared for method validation, and final concentrations of low-quality control (LQC), medium-quality control (MQC), and high-quality control (HQC) samples were 0.2, 2.0, and 5.0 μg/mL, respectively.

2.6 | The extraction of LTG

Lamotrigine extraction was performed using the solid-phase extraction (SPE) method. Oasis hydrophilic lipophilic balance (HLB) cartridges (1 cc, 10 mg; Waters) were conditioned using 1.0 mL of methanol followed by 1.0 mL of distilled water. In brief, the extraction of LTG from samples was achieved with three steps; (a) sample preparation for SPE, (b) SPE, and (c) injection into LC-MS/MS (Figure 1). Initially, an aliquot of 50 μL plasma QC sample was mixed with 100 μL of IS and 350 μL of distilled water. For standard calibration, 50 μL of brank human plasma was mixed with 20 μL of LTG, 100 μL of IS and 330 μL of distilled water. Secondly, after mixing well, the mixture was loaded into prewashed the cartridge. After washing with 1.0 mL of distilled water twice, 500 μL of acetonitrile/methanol (9/1, v/v) was applied to the cartridge to obtain eluates. Finally, after diluting the analyte to minimally four times with 0.1% formic acid, 5 μL of filtered samples by Millex®-LG filters (0.2 μm, 4 mm, Merck, Darmstadt, Germany) was injected into the LC-MS/MS system.

2.7 | Recovery

Recovery rates of LTG and IS were determined after preparing samples using blank plasma. LTG and IS were then added to eluted samples and were adjusted to theoretical concentrations. The recovery was calculated by comparing peak areas obtained from extracted spiked QC samples with those of the postextracted spiked samples.

2.8 | Carryover peak

Carryover peak was assessed by checking peaks in LTG and IS peak regions of blank sample (no LTG or IS) injections after HQC (5.0 μg/mL) sample injection. This procedure was repeated three times.

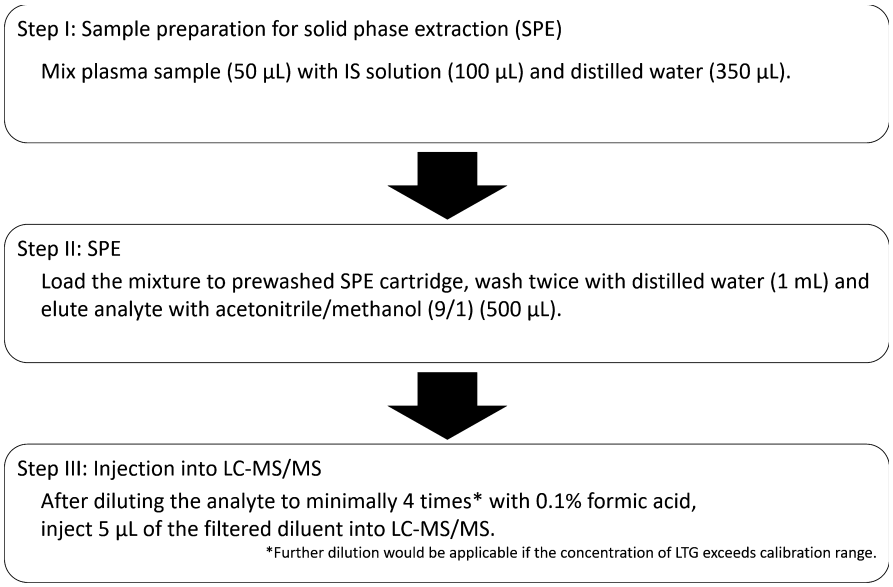

FIGURE 1 Scheme of sample preparation

2.9 | Method validation

The method was fully validated according to the Food Drug Administration guidance for biological method validation.[14]

2.10 | Specificity and selectivity

Specificity and selectivity of the method were evaluated using human plasma at five different lots by investigating potential interferences at peak regions of LTG and IS.

2.11 | Matrix effect

Matrix effects of human plasma constituents were evaluated from the ratio of ionization responses of LTG and IS between human blank plasma samples and diluting solvent. QC samples were prepared with human plasma in four different lots and matrix effects on LTG were determined in LQC, MQC, and HQC samples. Matrix effects on IS were determined at a single concentration of 0.8 μg/mL.

2.12 | Linearity

A six-point calibration curve was constructed by plotting LTG/IS peak area ratios against nominal concentrations of calibration standards in human plasma. Linearity was evaluated using linear regression analyses with the least squares method.

2.13 | Intra- and inter-day accuracy and precision

Intra-assay precision and accuracy were evaluated by repeating analyses of QC plasma samples in five independent runs at three LTG concentrations (LQC, MQC, and HQC) in one day. Inter-assay precision and accuracy were evaluated by analyzing three QC samples on five different days. Accuracy was considered acceptable when the relative error (RE) was within ±15%, and precision was considered acceptable at a relative standard deviation (RSD) of less than 15% except at lower limit of quantification should not deviate by more than 20%.

2.14 | Stability

The stability of LTG was determined in LQC, MQC, and HQC samples. The stability of LTG in injection solvent was evaluated by injecting prepared samples after storage at 15°C in the autosampler for 6 hours from the first cycle injection. Peak area ratios of LTG and IS at the initial cycle were used as standards to determine 6-hour stability at corresponding concentrations. The stability of LTG in human plasma was evaluated at room temperature for 5 hours. The stability of LTG in human plasma following three freeze-thaw cycles was assessed by analyzing QC samples after the third round of thawing. In these experiments, samples were thawed at room temperature for approximately 1 hour and were then frozen and stored at −30°C until the next thaw. Short-term stability of LTG in human plasma was assessed by analyzing QC samples after storage at 4°C for 12 hours. Long-term stability of LTG in human plasma was assessed by analyzing QC samples after storage at −30°C for 3 months. The stability of LTG in diluting solvent was assessed by analyzing LTG working solution after storage at room temperature for 6 hours at LTG concentrations of LQC, MQC, and HQC. Peak area ratios of LTG and IS from these samples were then compared with standard samples, which were analyzed soon after diluting and spiking at corresponding concentrations. In all experiments, the criteria for acceptability of accuracy and precision were as described for intra- and inter-day accuracy and precision experiments.

3 | RESULTS

3.1 | Mass spectroscopy conditions

To optimize electrospray ionization conditions for LTG and IS, we determined Q1 pre bias, collision energy, and Q3 pre bias in positive ion detection mode. Following ionization and collision, the LTG

precursor ion (m/z = 255.9) produced five product ions at m/z 43.0, 89.0, 133.0, 210.8, and 239.2 at retention time (Rt) of 1.6 minutes (Figure 2A). The mass spectra showed the main product ion was the fragment at m/z 43.0, followed by the product ion at m/z 210.8. The product ions at m/z 43.0[15]and 210.8[16–18] were also used to measure LTG reported in previous studies. We then selected the product ion at m/z 210.8 for the measurement LTG due to peak forms and quantitative stability. The mass spectra for IS showed that the fragment at m/z 324.3 was the main product ion (Figure 2B) and the product ion showed quantitative stability (data not shown). Therefore, we selected product ion of the m/z 324.3 for the measurement of IS.

3.2 | Sample preparation and liquid chromatography conditions

In the present experiments, we performed experiments using various ratios of organic (acetonitrile and methanol) and aqueous solvents with buffering effects at various concentrations with and without formic acid. We also compared normal and reverse phase columns. Optimal peaks and electrospray responses for LTG and IS were achieved with 0.1% formic acid in water/acetonitrile (2/1, v/v) using a Cadenza CD-C18 column (100 × 2 mm, 3 μm). Under these conditions, Rts for LTG and IS were 1.6 and 2.0 minutes, respectively, and the total run time was 3.5 minutes. In experiments with various injection volumes of LTG, the linear relationship between LTG contents and IS peaks deteriorated following injections of greater than 1 ng LTG (data not shown). Thus, to ensure that injections contained less than 1 ng of LTG, we diluted 50 μL aliquots of plasma with 500 μL aliquots of elution buffer, diluted 100 μL aliquots of eluted solvent with 300 μL of 0.1% formic acid, and set the injection volume to 5 μL.

Samples were prepared using the SPE method. The Oasis HLB cartridges are reportedly suitable for extraction of various analytes due to the presence of both hydrophilic and hydrophobic groups. We slightly modified the SPE method which was provided by the manufacturer. After sample loading, cartridges were washed twice in 1 mL of distilled water, which reduced protein contents of eluents more effectively than single wash. Moreover, as suggested by the column manufacturer, we also eluted using acetonitrile/methanol (9/1, v/v), which prevented ionization of the analyte. This solvent also improved the shape of the LTG form and decreased the height of a shoulder peak of LTG. Based on these investigation, we finally obtained chromatographic peaks of LTG and IS (Figure 3A,B).

3.3 | Selection of IS

Papaverine was used as IS because it has demonstrated the good recovery of 96.3% without interfering the detection of LTG with a Rt of 2.0 minutes (Figure 3A,B)

3.4 | Recovery

Recovery rates of LTG were determined in three independent runs of LQC, MQC, and HQC and were good at all concentrations (93.8%-98.6%) (data not shown).

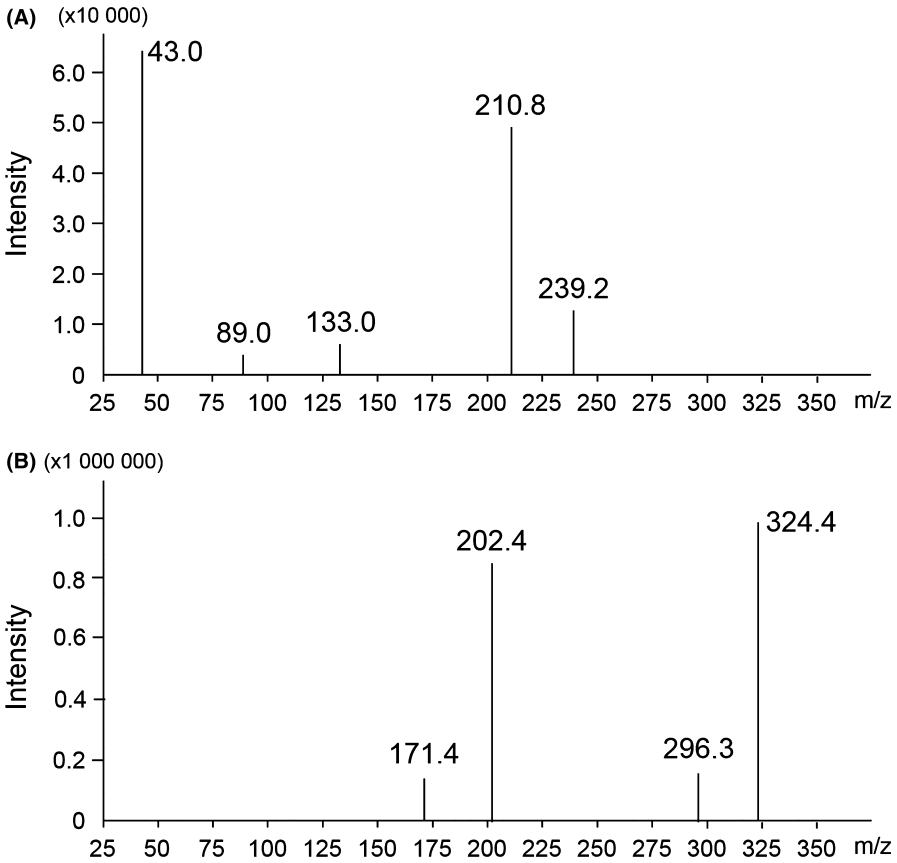

FIGURE 2 Mass spectra of LTG and IS. A, Mass spectra of LTG at Rt of 1.6 min; B, Mass spectra of LTG at Rt of 2.0 min

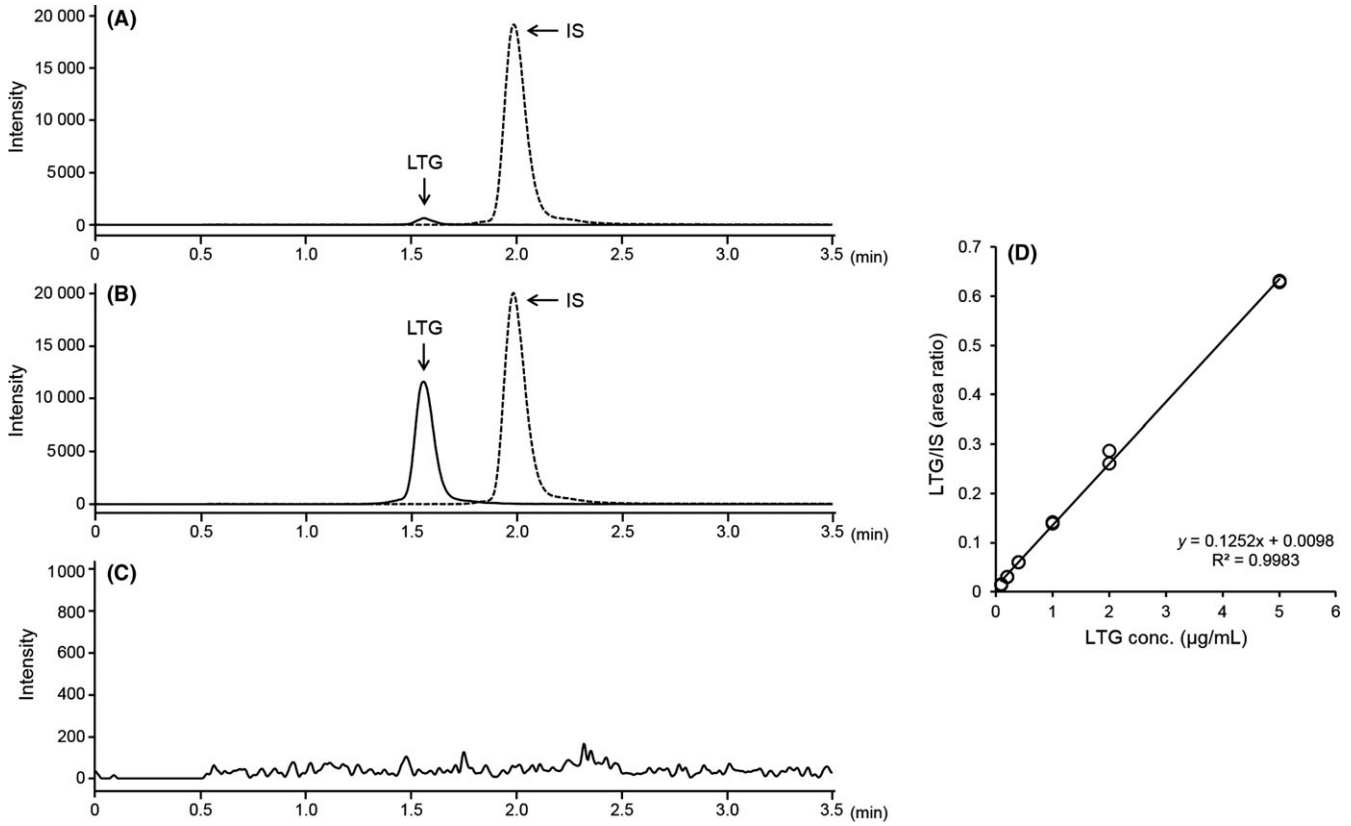

FIGURE 3 Typical chromatograms of LTG and IS in plasma. A, Low-quality control of LTG (0.2 μg/mL, solid lines) and IS (dashed lines); B, High-quality control of LTG (5.0 μg/mL, solid lines) and IS (dashed lines); C, Blank plasma (LTG- and IS-free sample); D, Standard curve

3.5 | Specificity, selectivity, and matrix effects

Regarding the matrix effect, the precision among different lots of human plasma was 11.86% (LQC), 4.05% (MQC), and 3.20% (HQC) and that of IS was 2.05% (0.8 μg/mL) (data not shown). No significant interfering peaks were observed in LTG and IS peak regions (Figure 3C).

3.6 | Linearity

The present plasma calibration curve was generated with six concentrations between 0.2 and 5.0 μg/mL and showed reproducibility across the range, with an average correlation coefficient (r^2; n = 2) of >0.99 (Figure 3D). The lower limit of quantitation was the same as the lowest concentration (0.2 μg/mL), and calculated LTG concentrations were within ±15% of standard concentrations at all calibration points. Finally, the area ratio of the largest noise peak in blank plasma over the LTG peak (0.2 μg/mL) was more than five times, indicating good detection with little interference.

3.7 | Precision and accuracy

Intra- and inter-day accuracy and precision in LTG plasma samples met the criteria in all cases, and RSD of each sample was between 1.1 and 6.8%, showing good reproducibility (Table 1).

3.8 | Stability

Table 2 showed the stability of LTG. LTG was stable for 6 hours at room temperature in diluting solvent. Moreover, LTG in human

TABLE 1 Intra-day and inter-day precision and accuracy of LTG determinations

	Intra-day			Inter-day		
LTG theoretical conc. (μg/mL)	Mean ± SD (μg/mL, n = 5)	RSD (%)	RE (%)	Mean ± SD (μg/mL, n = 5)	RSD (%)	RE (%)
0.2	0.19 ± 0.01	4.8	−3.3	0.17 ± 0.01	6.2	−13.5
0.4	0.42 ± 0.03	6.8	5.8	0.40 ± 0.01	1.9	1.1
2.0	2.25 ± 0.12	5.3	12.6	2.00 ± 0.02	1.2	0.2
5.0	5.35 ± 0.06	1.1	7.0	4.94 ± 0.11	2.2	−1.2

LTG, lamotrigine; RE, accuracy; RSD, precision.

TABLE 2 LTG stability in diluting solvent and plasma

	LTG spiked conc. (μg/mL)								
	0.2			2.0			5.0		
Stability	Mean ± SD (μg/mL)	RSD (%)	RE (%)	Mean ± SD (μg/mL)	RSD (%)	RE (%)	Mean ± SD (μg/mL)	RSD (%)	RE (%)
Diluting solvent									
Bench-top									
6 h at room temperature	0.18 ± 0.01	5.8	−9.2	2.07 ± 0.01	0.6	3.7	4.94 ± 0.05	1.1	−1.1
Plasma									
Freeze and thaw[a]	0.19 ± 0.01	4.5	−2.6	2.15 ± 0.08	3.9	7.5	5.07 ± 0.26	5.1	1.4
Bench-top									
5 h at room temperature	0.20 ± 0.01	3.4	0.5	2.07 ± 0.06	2.7	3.5	5.17 ± 0.10	1.9	3.3
Short-term									
12 h at 4°C	0.23 ± 0.01	3.1	14.4	2.11 ± 0.09	4.5	5.3	5.00 ± 0.04	0.7	−0.0
Long-term									
3 mo at −30°C	0.17 ± 0.01	6.4	−14.5	2.13 ± 0.07	3.2	6.6	5.04 ± 0.11	2.3	0.9
Processed sample									
6 h in autosampler	0.22 ± 0.01	3.0	8.6	2.26 ± 0.04	1.7	13.0	5.26 ± 0.11	2.1	5.2

LTG, lamotrigine; RE, accuracy; RSD, precision.
[a]After three freeze (−30°C)-thaw (room temperature) cycles.

plasma was stable for 5 hours at room temperature, for 12 hours at 4°C, for 3 months at −30°C, and following three freeze-thaw cycles. Moreover, stability of LTG in autosampler met the criteria.

3.9 | Carryover peak

No significant interfering peaks were detected from blank samples after injections of HQC samples (data not shown).

4 | DISCUSSION

In the present study, we established and validated the measurement method of LTG in plasma. Regarding the calibration curve range, we selected the range of 0.2-5.0 μg/mL since drug information of LTG showed that average trough levels of LTG are 2.81-4.12 μg/mL and the minimum trough level is also 0.32 μg/mL.[19] Drug information of LTG also showed the maximum trough level is 13.3 μg/mL.[19] Additionally, the guideline of the Japanese Journal of Therapeutic Drug Monitoring has recommended 2.5-15 μg/mL in plasma for therapeutic range of LTG.[20] So, our range is slightly low. However, if the concentration of LTG is higher than 5.0 μg/mL, further dilution would be applicable. The noncompliance and the removal of LTG by hemodialysis might cause epileptic seizure due to the decrement of LTG below therapeutic range. In that cases, precise valued of the concentration of LTG would be needed to adjust it dosage.

Our method detected with Rts for LTG and IS of 1.6 and 2.0 minutes, respectively, and a total run time of 3.5 minutes. These parameters led to faster determinations than shown in previous reports.[15,17,21]

Lamotrigine has the structure of an aromatic amine and interacts with chromatographic solid phases. Thus, we considered reverse-phase extraction with a hydrophobic solid phase, normal-phase extraction with a hydrophilic solid phase, and ionic and polar separation. Several previous studies have achieved LC separation with C8,[16] C18,[15,17,21] or cyano[22]solid phases. Moreover, in experiments using a normal-phase column with a silica column and aqueous-acetonitrile mobile phases,[23] researchers established systems for determining basic compounds that contained guanidine groups and are structurally similar to LTG.[23] Alternatively, concentrations of LTG and 18 other drugs were determined using pentafluorophenyl reverse-phase column that separates polar and basic compounds by targeting compounds with hydrophobic interactions and hydrogen bond and dipolar interactions.[24] Although LTG could be separated using a normal-phase Unison UK-silica column with a mobile phase containing 0.05% formic acid in methanol/water (50/50, v/v), reverse-phase separation using a C18 column with acetonitrile instead of methanol further improved LTG detection, as shown in numerous previous reports.[17,19,25]

We selected papaverine as IS since easily purchasable papaverine is rarely coadministered with LTG and it had a good recovery in the present method, although previous studies used lamotrigine-$^{13}C_3$-d3 as an IS for LTG determinations.[17,18,26] Moreover, intra- and inter-day precision for IS was within approximately 5% (data not shown). Thus, these results indicate that papaverine is suitable as an IS for the measurements of LTG.

Regarding sample preparation, several studies have demonstrated methods for extracting LTG from plasma using protein precipitation with organic solvents such as methanol and acetonitrile.[15,18,22,26] However, other studies were used SPE method.[16,25,27,28] In general, human plasma constituents frequently inhibit ionization of analytes in LC-MS/MS quantifications.[29–31] Moreover, it has been reported that protein precipitation is unable to sufficiently remove phospholipids which are one of major factor to inhibit the ionization.[31] Thus,

we employed the SPE method using the Oasis HLB cartridge and obtained chromatographic peaks of LTG and IS. The present method did not require drying under nitrogen, providing greater simplicity of methods for preparing samples than those reported previously[25,27,28] and shortened sample preparation times.

Validation experiments showed that LTG is stable in human plasma and that our measurement system is highly quantitative in the range of 0.2-5.0 μg/mL. The experiments for intra- and inter-day validation showed good reproducibility with RSD values at around 5%. Moreover, LTG under each storage conditions also met the criteria.

In conclusion, we developed a rapid and simple method for determining plasma LTG concentrations and show good validation for a relatively wide range (0.2-5.0 μg/mL) of LTG concentrations. Using the present method sample preparation takes approximately 30 minutes and plasma LTG concentrations are detected in a 3.5-minute run time. Thus, the present method could be used clinically for rapid estimates of plasma LTG concentrations within 1 hour of sample collection. This method could be used to inform LTG dose adjustments for individual patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

KK and MS participated in research design. SI, RB, MN, and MF performed experiments and analyzed data with assistance from MD and SU. SI and RB wrote the manuscript, which was revised and approved by all of the authors.

DATA REPOSITORY

We have made our data publicly available in the Supporting Information of our article.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

N/A.

INFORMED CONSENT

N/A.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

ORCID

Midori Soda https://orcid.org/0000-0002-1205-3447

REFERENCES

1. Frosher W, Keller F, Vogt H, Kramer G. Prospective study on concentration-efficacy and concentration-toxicity: correlations with lamotrigine serum levels. Epileptic Disord. 2002;4(1):49–56.
2. Brzakovic BB, Vezmar Kovacevic SD, Vucicevic KM, et al. Impact of age, weight and concomitant treatment on lamotrigine pharmacokinetics. J Clin Pharm Ther. 2012;37(6):693–7.
3. Baldoni AO, Freitas-Lima P, de Santi Ferreira FI, et al. An investigation of the influence of patient-related factors and comedications on lamotrigine clearance in patients with epilepsy. Clin Exp Pharmacol Physiol. 2016;43(7):685–9.
4. Liu L, Zhao L, Wang Q, Qiu F, Wu X, Ma Y. Influence of valproic acid concentration and polymorphism of UGT1A4*3, UGT2B7 -161C > T and UGT2B7*2 on serum concentration of lamotrigine in Chinese epileptic children. Eur J Clin Pharmacol. 2015;71(11):1341–7.
5. Inoue K, Yamamoto Y, Suzuki E, et al. Factors that influence the pharmacokinetics of lamotrigine in Japanese patients with epilepsy. Eur J Clin Pharmacol. 2016;72(5):555–62.
6. Wang Q, Liang M, Dong Y, et al. Effects of UGT1A4 genetic polymorphisms on serum lamotrigine concentrations in Chinese children with epilepsy. Drug Metab Pharmacokinet. 2015;30(3):209–13.
7. Yamamoto Y, Inoue Y, Matsuda K, Takahashi Y, Kagawa Y. Influence of concomitant antiepileptic drugs on plasma lamotrigine concentration in adult Japanese epilepsy patients. Biol Pharm Bull. 2012;35(4):487–93.
8. Yamamoto Y, Takahashi Y, Imai K, et al. Influence of uridine diphosphate glucuronosyltransferase inducers and inhibitors on the plasma lamotrigine concentration in pediatric patients with refractory epilepsy. Drug Metab Pharmacokinet. 2015;30(3):214–20.
9. Kaufman KR. Lamotrigine and hemodialysis in bipolar disorder: case analysis of dosing strategy with literature review. Bipolar Disord. 2010;12(4):446–9.
10. Smetana KS, Cook AM, Bastin ML, Oyler DR. Antiepileptic dosing for critically ill adult patients receiving renal replacement therapy. J Crit Care. 2016;36:116–24.
11. Makus KG, McCormick J. Identification of adverse reactions that can occur on substitution of generic for branded lamotrigine in patients with epilepsy. Clin Ther. 2007;29(2):334–41.
12. Nielsen KA, Dahl M, Tommerup E, Wolf P. Comparative daily profiles with different preparations of lamotrigine: a pilot investigation. Epilepsy Behav. 2008;13(1):127–30.
13. Andermann F, Duh MS, Gosselin A, Paradis PE. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. Epilepsia. 2007;48(3):464–9.
14. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Bioanalytical method validation guidance for industry [Internet]. Rockville: U.S. Food and Drug Administration; 2018 [updated 2018 May]. Available from https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf
15. Yin L, Wang T, Shi M, et al. Simultaneous determination of ten antiepileptic drugs in human plasma by liquid chromatography and tandem mass spectrometry with positive/negative ion-switching electrospray ionization and its application in therapeutic drug monitoring. J Sep Sci. 2016;39(5):964–72.
16. Shah HJ, Subbaiah G, Patel DM, Suhagia BN, Patel CN. Rapid quantification of lamotrigine in human plasma by two LC systems connected with tandem MS. J Chromatogr Sci. 2010;48(5):375–81.

17. Namdev KK, Dwivedi J, Chilkoti DC, Sharma S. A simple, rapid and stability indicating validated method for quantification of lamotrigine in human plasma and dry plasma spot using LC-ESI-MS/MS: Application in clinical study. J Chromatogr B Analyt Technol Biomed Life Sci. 2018;1072:362–9.
18. Wong JM, Jones JW, Jiang W, Polli JE, Kane MA. Quantification of lamotrigine in patient plasma using a fast liquid chromatography-tandem mass spectrometry method with backflush technology. Ther Drug Monit. 2015;37(2):188–97.
19. GlaxoSmithKline K.K. Medicine interview form of Lamictal [Internet]. Tokyo: GlaxoSmithKline K.K. [updated September 2018]. Available from: https://gskpro.com/content/dam/global/hcpportal/ja_JP/products-info/lamictal/lamictal-if.pdfo
20. Tanigawara Y, Sendo T, Imamura T, et al. Standardize guideline for TDM of antiepileptic drug 2017. Jpn J Ther Drug Monit. 2017;304 (2):67–95.
21. de Souza ID, Domingues DS, Queiroz MEC. Hybrid silica monolith for microextraction by packed sorbent to determine drugs from plasma samples by liquid chromatography-tandem mass spectrometry. Talanta. 2015;1(140):166–75.
22. Hotha KK, Kumar SS, Bharathi DV, Venkateswarulu V. Rapid and sensitive LC-MS/MS method for quantification of lamotrigine in human plasma: application to a human pharmacokinetic study. Biomed Chromatogr. 2012;26(4):491–6.
23. Cheng CL, Chou CH, Hu OY. Determination of lamotrigine in small volumes of plasma by high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci. 2005;817(2):199–206.
24. He X, Kozak M. Simultaneous quantitation of 19 drugs in human plasma and serum by LC-MS/MS [Internet]. San Jose, CA: Thermo Fisher Scientific [accessed 2018 April]. Available from: https://assets.thermofisher.com/TFS-Assets/CMD/Application-Notes/AN-571-LC-MS-Drugs-Human-Plasma-AN63671-EN.pdf
25. Carrier DJ, Eckers C, Wolff JC. "In-source" fragmentation of an isobaric impurity of lamotrigine for its measurement by liquid chromatography tandem mass spectrometry after pre-concentration using solid phase extraction. J Pharm Biomed Anal. 2008;47(4–5):731–7.
26. Kuhn J, Knabbe C. Fully validated method for rapid and simultaneous measurement of six antiepileptic drugs in serum and plasma using ultra-performance liquid chromatography-electrospray ionization tandem mass spectrometry. Talanta. 2013;15(110):71–80.
27. Zufia L, Aldaz A, Ibanez N, Viteri C. LC method for the therapeutic drug monitoring of lamotrigine: evaluation of the assay performance and validation of its application in the routine area. J Pharm Biomed Anal. 2009;49(2):547–53.
28. Tai SS, Yeh CY, Phinney KW. Development and validation of a reference measurement procedure for certification of phenytoin, phenobarbital, lamotrigine, and topiramate in human serum using isotope-dilution liquid chromatography/tandem mass spectrometry. Anal Bioanal Chem. 2011;401(6):1915–22.
29. Waters Corporation. Topics in Solid-Phase Extraction Part 1. Ion suppression in LC/MS analysis: a review strategies for its elimination by well-designed, multidimensional solid-phase extraction (SPE) protocols and methods for its quantitative assessment [Internet]. Milford: Waters Corporation [accessed 2018 April]. Available from: https://www.waters.com/webassets/cms/library/docs/720001273en.pdf.
30. Malodia K, Sharma R, Gupta V, Kumar S, Singh Y. Strategies & considerations for bio analytical method development and validation using LCMS/MS: a review. Pharm Res. 2011;6(1):12–20.
31. Adaway JE, Keevil BG. Therapeutic drug monitoring and LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2012;883–884:33–49.

SUPPORTING INFORMATION

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

How to cite this article: Itabashi S, Bito R, Nishina M, et al. Determination of lamotrigine in human plasma using liquid chromatography-tandem mass spectrometry. *Neuropsychopharmacol Rep*. 2019;39:48–55. https://doi.org/10.1002/npr2.12045