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Pharmacokinetics, Brain Distribution, and Plasma Protein Binding of the Antiepileptic Drug Lacosamide in Rats

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The study aimed to characterize the pharmacokinetics of lacosamide, a new antiepileptic drug, in rats after intravenous and oral administration at doses of 1, 3, 10, and 30 mg/kg. Moreover, brain distribution and plasma protein binding were estimated. After intravenous injection, terminal half-life, systemic clearance, and steady state volumes of distribution remained unaltered as a function of dose with values in the range 3.01-3.53 h, 221-241 mL/h/kg and 702-732 mL/kg, respectively. Following oral administration, absolute oral bioavailability was not dose dependent and was at 93.3-106%. However, the time to peak concentration and the dose-normalized peak concentration for 30 mg/kg were significantly different with those for other doses. The extent of urinary excretion of lacosamide was 17.1% and 16.5% for intravenous and oral doses, respectively, whereas fecal excretion was negligible. The brain to plasma ratio of lacosamide was consistent regardless of post-dosing time and the brain to plasma partition coefficient was 0.553. Further, the plasma protein binding of lacosamide was concentration independent with free fraction at 95.9%. Lacosamide showed linear pharmacokinetics at an intravenous dose of 1-30 mg/kg and an oral dose of 1-10 mg/kg but non-linear pharmacokinetics at a 30 mg/kg oral dose.

Key words: Lacosamide, Pharmacokinetics, Bioavailability, Plasma protein binding, Brain distribution

INTRODUCTION

Epilepsy is a common chronic neurological disorder characterized by seizures and affects about 50 million people worldwide (Blume et al., 2001). Although approximately 70% of patients become seizure-free using a single antiepileptic drug, the remaining 30% may develop a chronic form of epilepsy that is usually refractory to all available pharmacological treatments (Schmidt, 2002). Lacosamide (Vimpat; UCB Pharma) is a new antiepileptic drug that was licensed in Europe in 2008 and in the United States in 2009 for the adjunctive treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older (Cross and Curran, 2009; Halász et al., 2009). Lacosamide is a functionalized amino acid that acts by selectively enhancing the slow inactivation of voltage-gated sodium channels, resulting in the stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing without exhibiting effects on fast inactivation (Beyreuther et al., 2007; Errington et al., 2008). However, lacosamide does not affect AMPA, kainate, NMDA, $GABA_A$, $GABA_B$, or a variety of dopaminergic, serotonergic, adrenergic, muscarinic, or cannabinoid receptors. Moreover, it does not block potassium or calcium currents (Errington et al., 2006).

Some clinical studies about human pharmacokinetics of lacosamide have been reported in recent years. Lacosamide is completely absorbed after oral administration, with negligible first-pass effects and with a high absolute bioavailability of ~100% (Hovinga, 2003). The maximum lacosamide plasma concentrations occur approximately 1 to 4 h post-dose after oral dosing, while the elimination half-life is ~13 h (Horstmann et al., 2002). Moreover, the volume of distribution is approximately 0.6 L/kg, and the plasma protein binding is

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less than 15% (Kropeit et al., 2005; Beydoun et al., 2009). Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation (Doty et al., 2007; Beydoun et al., 2009). However, in terms of experimental animals, there is very limited information about the animal pharmacokinetics of lacosamide (Beyreuther et al., 2007). In particular, epilepsy is attractive CNS indication, because of predictive rodent animal model, standardized clinical trials with established end points. The pharmacokinetics of experimental animals, especially rat, is generally used as reference data on antiepileptic drug discovery and basic data on analyzing efficacy and toxicity. Thus, the purpose of this study was to report the pharmacokinetics of lacosamide after intravenous and oral administration of this drug to rats and to determine the brain tissue-to-plasma partition coefficient and the plasma protein binding in rats.

MATERIALS AND METHODS

Chemicals

Lacosamide and LCD001 (lacosamide analog, internal standard) were obtained from Changwon National University (Changwon, Korea; Fig. 1). Acetonitrile and methanol (HPLC grade) were purchased from Burdick & Jackson Inc. The other chemicals were of HPLC grade or of the highest quality available. Rat plasma containing sodium heparin as anticoagulant was prepared in our laboratory.

Animals

Male Sprague-Dawley (SD) rats (age, 8 weeks; body weight, 230-260 g) were purchased from Orient Bio Inc. and used in all *in vivo* studies. Animals were kept in plastic cages with free access to a standard rat diet (PMI Nutrition International) and water. The animals were maintained at a temperature of 20-26°C with a 12-h light/dark cycle and a relative humidity of 40-60%. Before the test, the animals were fasted prior to dosing by withholding food but not water overnight. After dosing, food was withheld for an additional 4 h. All animal experiments were approved by the Institutional Animal Care and Use Committee of SK Life Science (Daejeon, Korea).

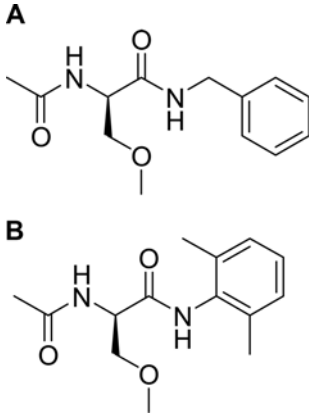

Fig. 1. Chemical structures of (**A**) lacosamide and (**B**) LCD001 (internal standard)

Animal experiments

Intravenous and oral administration of lacosamide to rats

Lacosamide dissolved in a vehicle (10% DMSO, 27% polyethylene glycol 400, and 63% saline; dosing solution of 250 μL per 250 g body weight) was given either as a single intravenous bolus dose via the tail vein or as an oral gavage dose at 1, 3, 10, and 30 mg/kg in the rats (n = 3). Blood samples (200 μL) were collected from the jugular vein using a rat restrainer (NAIGAI-CFK-1S; NMS) at 0.05 (IV only), 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after dosing. Blood samples were immediately centrifuged at 3,000 × g for 5 min, and the harvested plasma samples were stored at 70°C until analysis.

Determination of urinary and fecal excretion

Male SD rats (n = 4) were intravenously and orally administered at a dose of 10 mg/kg, and were placed in metabolic cages. Urine and feces were collected for 24 h after the administration. The metabolic cage was rinsed with about 10 mL distilled water, and the rinsed solutions were combined with the pooled urine samples collected for 24 h. The obtained samples were weighed and stored at 70°C until analysis. The amount of drug excreted in urine or feces (A_e) and the fraction of dose excreted unchanged in urine or feces (f_e) were calculated as:

$$A_e = C_{obs,\ \text{urine or feces}} \times V_{\text{urine or feces}}$$
$$f_e = A_e / Dose$$

The urinary and fecal clearances of lacosamide were calculated as:

$$CL_{\text{urine or feces}} = A_{e,\ \text{urine or feces}} / AUC$$

Estimation of brain-to-plasma concentration ratio

Male SD rats (n = 3) were orally administered lacosamide at a dose of 10 mg/kg (10% DMSO, 27% polyethylene glycol 400, and 63% saline; dosing solution of 250 μL per 250 g body weight). The animals were sacrificed at 0.5, 1, 2, 4, 8, or 24 h after the administration, and blood and brain samples were collected.

Brain samples were rinsed with cold saline, and the wet-weights were determined. The brain samples were then placed in the same volume (w/v) of saline and homogenized using a 150T Ultrasonic homogenizer (Fisher Scientific). The plasma samples and brain homogenates were stored at 70°C until analysis.

Estimation of the fraction of lacosamide bound to plasma protein

A protein-binding study was carried out to determine the fraction of unbound lacosamide in rat plasma. Binding of the test article was assessed by equilibrium dialysis using RED® filter devices (Thermo). All assessments were made in triplicate. After 200 μL samples of plasma containing 0.2, 2, and 20 μg/mL lacosamide were placed into a sample chamber, 350 μL of phosphate buffer (pH 7.4) was added to the buffer chamber. The device containing the samples was incubated at 37°C for 4 h in a shaking water bath. After incubation, lacosamide in the plasma and buffer was assayed.

Analytical procedure for the determination of lacosamide

The lacosamide levels in biological matrix were determined by a specific high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) developed from our laboratory (Kim et al., 2011). An aliquot (100 μL) of internal standard solution (i.e., LCD001; 1 μg/mL in acetonitrile) and 350 μL of acetonitrile were added to an aliquot (50 μL) of biological sample (plasma or brain homogenate or diluted urine or methanol extract from feces). The mixture was vigorously mixed for 10 min and then centrifuged at 10,000 × g for 10 min at 4°C to induce the precipitation of proteins. The supernatant was collected, and an aliquot (50 μL) was transferred to a well plate. After dilution with 150 μL of distilled water, an aliquot (5 μL) was directly injected into the HPLC/MS/MS system.

The HPLC/MS/MS system consisted of an Agilent 1200 HPLC system (Agilent Technologies) and an API 4000 tandem quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX). The separation of lacosamide and IS from endogenous substances was achieved using a reversed phase column [Gemini® C18 column; 50 mm length × 2.0 mm internal diameter, 5.0 μm (Phenomenex)] with 0.1% formic acid and acetonitrile. The mobile phase was delivered using a gradient-elution program: 0.1% formic acid (A): acetonitrile (B) = 95:5 (v/v) from 0 to 0.5 min, A:B = 20:80 from 1.5 to 2.5 min, and A:B = 95:5 from 3.0 to 4.5 min. The flow rate was 0.3 mL/min. The temperatures for the column and auto-sampler tray were maintained at 25°C and 4°C, respectively. The analytical run time was 4.5 min. The eluent was introduced directly into the tandem quadrupole mass spectrometer through the turbo ion-spray source with typical settings as follows: curtain gas, 25 psi; nebulizer gas, 40 psi; turbo gas, 40 psi; ion-spray voltage, 5500 V; temperature, 500°C in positive mode. The molecular ions of lacosamide and LCM001 were fragmented at a collision energy of 61 and 66 V by collision-activated dissociation with nitrogen gas. Multiple-reaction-monitoring (MRM) mode was employed for the quantification. Detection of the ions was performed by monitoring the transitions of m/z 251.2 to 108.2 for lacosamide and m/z 265.2 to 74.1 for LCD001. Peak areas for all components were automatically integrated using Analyst® software version 1.41 (Applied Biosystems/MDS SCIEX). The detection limit for lacosamide in rat plasma, brain, urine and feces was 0.3 ng/mL. The coefficients of variation of the assay (within- and between-day) were generally low (below 11.7%).

Pharmacokinetic analysis

The area under the plasma concentration-time curve (AUC) and the area under the first moment curve (AUMC) were calculated by the linear trapezoidal method extrapolated to time infinity. The terminal half-life ($t_{1/2}$) was calculated to be 0.693/λ, where λ represents the slope of the log-linear portion of the concentration time profile. The systemic clearance (CL), mean residence time (MRT), and the volume of the distribution at steady state (V_{ss}) were calculated as dose/AUC, AUMC/AUC, and CL·MRT, respectively. The extent of absolute oral bioavailability (BA) was estimated by dividing the AUC after oral administration by the AUC after intravenous administration of the respective dose. The peak concentration (C_{max}) and the time to reach C_{max} (T_{max}) were directly read from individual plasma concentration-time profiles. The brain-to-plasma partition coefficient (K_p) for lacosamide was calculated by dividing the mean AUC_{brain} by the mean AUC_{plasma} after the administration. For obtaining the above pharmacokinetic parameters, all plasma and tissue concentration-time profiles were analyzed by a non-compartmental method with nonlinear least squares regression using Winnonlin® software version 4.2 (Pharsight).

Statistical analysis

All data were expressed as the mean ± S.D. Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Tukey's test. For the determination of statistically significant correlation, tests of zero correlation were used. In both analyses, $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Fig. 2 shows the plasma concentration-time profiles for lacosamide after an intravenous administration of 1, 3, 10, and 30 mg/kg doses in rats. The plasma concentration-time curves declined in a polyexponential fashion for all doses studied. The pharmacokinetic parameters of lacosamide were estimated as shown in Table I. After intravenous injection of lacosamide at dose of 1, 3, 10, and 30 mg/kg, the average $t_{1/2}$, CL, and V_{ss} were in the range 3.01-3.53 h, 221-241 mL/h/kg and 702-732 mL/kg, respectively. There were no significant differences in these parameters as a function of the administered doses. The AUC was increased linearly as the dose was increased. Taken together, the pharmacokinetics of lacosamide were linear over the intravenous dose range studied. The V_{ss} values in rats were close to the volume of total body water (about 668 mL/kg in rats) (Davies and Morris, 1993), suggesting that lacosamide is not extensively distributed to body tissues.

The plasma concentration-time profiles obtained after oral administration of 1, 3, 10, and 30 mg/kg to rats are shown in Fig. 3. After oral administration, the systemic absorption of lacosamide was fast, and the T_{max} reached within 1 h post-dosing at all doses except 30 mg/kg (Table II). Although the T_{max} at 30 mg/kg dose was 3.33 h, the concentration of lacosamide reached plateau from 0.5 h to 4 h post-dosing, indicating saturated absorption profile. After reaching the respective C_{max}, the plasma concentration of lacosamide declined in a polyexponential fashion for all doses studied (Fig. 3). The dose-normalized AUCs and BA of lacosamide were not significantly different among the three doses (1, 3, and 10 mg/kg) (Table II). These data indicate that pharmacokinetic parameters of lacosamide were independent of the oral doses ranged from 1 to 10 mg/kg and that orally administered lacosamide was almost completely absorbed in rats.

Following an intravenous dose of lacosamide in rats, 17.1 ± 4.5% and 1.06 ± 0.16% of the dose was excreted in urine and in feces, respectively, as unchanged drug. The fractions of the dose excreted unchanged in urine and feces after oral administration are 16.6 ± 5.5%

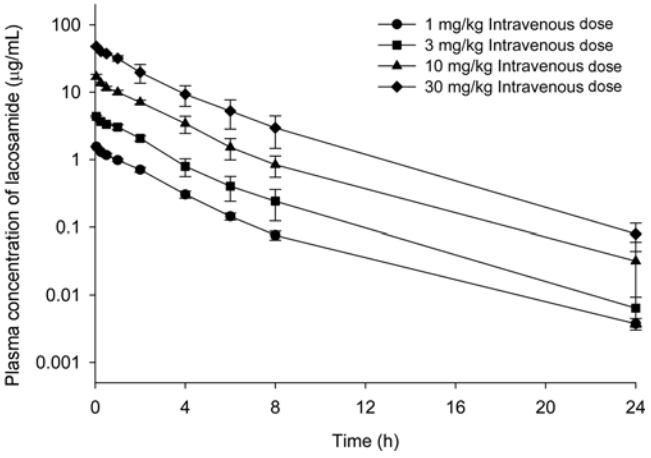

Fig. 2. Plasma concentration-time profiles for lacosamide in rats after intravenous administration. Each data point represents the concentration of lacosamide after intravenous administration of doses ranging from 1-30 mg/kg. Each point represents the mean ± S.D. of triplicate runs.

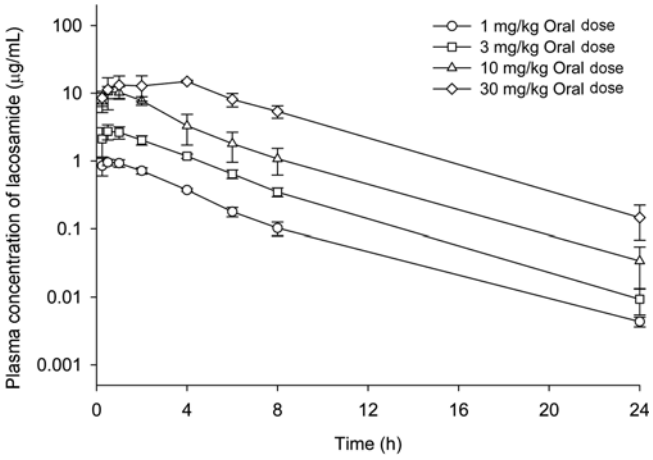

Fig. 3. Plasma concentration-time profiles for lacosamide in rats after oral administration. Each data point represents the concentration of lacosamide after oral administration of doses ranging from 1-30 mg/kg. Each point represents the mean ± S.D. of triplicate runs.

Table I. Pharmacokinetic parameters of lacosamide after intravenous administration[a]

Parameters	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Body weight (kg)	0.229 ± 0.011	0.248 ± 0.014	0.261 ± 0.005	0.248 ± 0.007
$t_{1/2}$ (h)	3.53 ± 0.32	3.02 ± 0.26	3.25 ± 0.80	3.01 ± 0.21
AUC (μg·h/mL)[b]	4.39 ± 0.30	12.8 ± 2.3	45.9 ± 7.0	140 ± 34
CL (mL/h/kg)	229 ± 15	241 ± 43	221 ± 32	223 ± 45
V_{ss} (mL/kg)	732 ± 42	723 ± 16	702 ± 59	709 ± 78
MRT (h)	3.20 ± 0.07	3.06 ± 0.49	3.21 ± 0.39	3.25 ± 0.47

[a]The data represent the mean ± S.D. from triplicate experimental runs; [b]Dose-normalized (based on 1 mg/kg) AUC was compared by statistical analysis.

Table II. Pharmacokinetic parameters of lacosamide after oral administration[a]

Parameters	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Body weight (kg)	0.232 ± 0.006	0.247 ± 0.005	0.256 ± 0.008	0.251 ± 0.003
$t_{1/2}$ (h)	3.42 ± 0.02	2.98 ± 0.25	3.17 ± 0.34	3.09 ± 0.49
T_{max} (h)	0.563 ± 0.315	0.667 ± 0.289	0.667 ± 0.289	3.33 ± 1.15*
AUC (μg·h/mL)[b]	4.42 ± 0.22	13.5 ± 1.8	47.1 ± 8.2	131 ± 14
C_{max} (μg/mL)[b]	0.975 ± 0.128	2.82 ± 0.61	10.4 ± 2.1	16.1 ± 2.1*
MRT (h)	3.85 ± 0.40	4.00 ± 0.16	3.59 ± 0.72	5.29 ± 0.43*
BA (%)	101 ± 5	106 ± 14	102 ± 18	93.3 ± 10.1

[a]The data represent the mean ± S.D. from triplicate experimental runs; [b]Dose-normalized (based on 1 mg/kg) AUC and C_{max} were compared by statistical analysis.
*30 mg/kg was significantly different ($p < 0.05$) from 1, 3, and 10 mg/kg.

and 0.955 ± 0.348%, respectively. The elimination profiles of lacosamide as unchanged drug between oral or intravenous dose were not different. The renal and fecal clearances of lacosamide were 37.8 ± 9.9 mL/h/kg and 2.35 ± 0.35 mL/h/kg, respectively (Table III). The fecal clearance was lower than the systemic clearance of lacosamide (2.35 mL/h/kg *vs* 221 mL/h/kg), indicating the fecal excretion of lacosamide appears negligible. Considering the plasma protein binding and CL_r of lacosamide, the estimated CL_r values for the free (unbound in plasma proteins) fraction of lacosamide was 36.3 mL/h/kg; the value was slower than the reported glomerular filtration rate in rats (314.4 mL/h/kg; Davies and Morris, 1993). The above data suggested that approximately 90% lacosamide is reabsorbed in the renal tubules after glomerular filtration and the calculated reabsorbed ratio in rats was similar with that in human (13.3 mL/h/kg *vs* 107 mL/h/kg; Davies and Morris, 1993; Kropeit et al., 2004; Beydoun et al., 2009). Although it seems that lacosamide was almost completely eliminated within 24 h in rats, the amounts of lacosamide excreted unchanged in urine and feces were less than 20% of administered dose. In a preliminary study of metabolic stability using liver microsome, lacosamide was highly stable in rat and human liver microsome (data was not published). Considering negligible hepatic first pass and high metabolic stability in liver microsome, lacosamide may be mainly eliminated by extrahepatic biotransformation as well as renal excretion in rats; it appears that further investigation is necessary to explain the biotransformation of lacosamide.

Table III. The extent of urinary and fecal excretion of lacosamide after intravenous and oral administration of 10 mg/kg dose in rats[a]

Parameters	Intravenous	Oral
Body weight (kg)	0.253 ± 0.006	0.260 ± 0.005
Urine		
$A_{e,\ urine}$ (μg)[b]	430.55 ± 109.47	430.38 ± 137.05
$f_{e,\ urine}$ (%)[c]	17.05 ± 4.49	16.61 ± 5.50
CL_r (mL/h/kg)[d]	37.8 ± 9.9	-
Feces		
$A_{e,\ feces}$ (μg)[e]	26.82 ± 3.56	24.91 ± 9.52
$f_{e,\ feces}$ (%)[f]	1.06 ± 0.16	0.95 ± 0.35
CL_f (L/h/kg)[g]	2.35 ± 0.35	-

[a]The data represent the mean ± S.D. from triplicate experimental runs; [b,e]Amount of lacosmaide excreted unchanged in urine or feces; [c,f]Fraction of dose excreted unchanged in urine or feces; [d,g]Renal or fecal clearance

The ratio of the AUC of lacosamide in a tissue to that in the plasma (K_p) was evaluated for the rat brain after an oral administration of 10 mg/kg. The brain-to-plasma concentration ratio was consistent and ranged from 0.464 to 0.644 regardless of post-dosing time (Fig. 4). The K_p value on oral administration was determined to be 0.553. After 4 h incubation of rat plasma

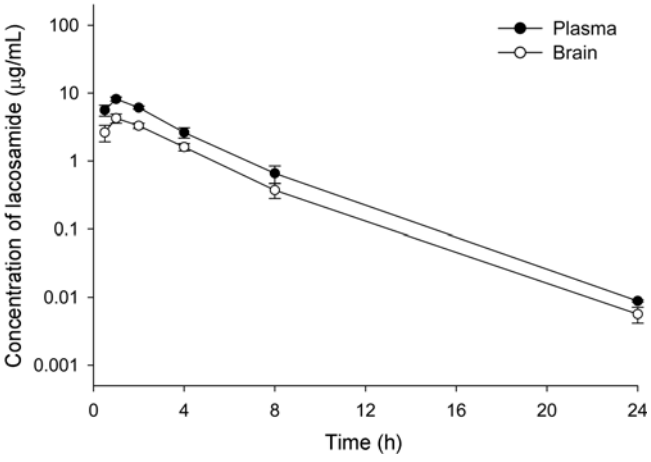

Fig. 4. Plasma and brain concentration-time profiles of lacosamide in rats after oral administration. Filled circles and unfilled circles represent the concentration in the plasma and the brain after oral administration of doses of 10 mg/kg, respectively. Each point represents the mean ± S.D. of triplicate runs.

containing 0.2, 2, and 20 μg/mL of lacosamide in an equilibrium device, the final plasma concentration of lacosamide was 0.0684, 0.684, and 6.85 μg/mL, respectively. Lacosamide was low bound to rat plasma protein in a concentration-independent manner, and the free fraction amounted to 95.1 ± 0.2%, 96.7 ± 1.2%, and 95.9 ± 1.1% for 0.0684, 0.684, and 6.85 μg/mL, respectively.

In summary, dose-independent pharmacokinetics was observed for lacosamide in rats after intravenous and oral administration in the dose ranges of 1-30 and 1-10 mg/kg, respectively. However, non-linear kinetics was observed for the oral dose of 30 mg/kg; this appeared to result from absorption saturation. For all doses tested, lacosamide was completely absorbed after oral administration, with negligible first-pass effect and a high absolute bioavailability of approximately 100%. The findings of this report may be helpful for the analysis of results obtained in other preclinical studies.

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