Original Article

The Plasma Concentration Profiles and Pharmacokinetics of Levetiracetam among Thai Adult Patients Undergoing Intermittent Hemodialysis

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Background: Levetiracetam is a second-generation antiepileptic drug that is primarily eliminated in urine via glomerular filtration and requires dose adjustment in patients with renal insufficiency. However, there are still a lack of evidence on pharmacokinetics including dialysis clearance of levetiracetam among patients undergoing intermittent hemodialysis.

Objective: To assess the plasma concentrations and pharmacokinetic parameters of levetiracetam in patients undergoing intermittent hemodialysis.

Materials and Methods: A pharmacokinetic study was conducted on six Thai adult patients receiving intermittent hemodialysis. The patients received levetiracetam 1,000 to 1,500 mg administered by intravenous injection once daily. Blood samples were obtained prior to hemodialysis, during the hemodialysis session, and post-hemodialysis to investigate levetiracetam pharmacokinetic parameters in each phase of treatments.

Results: Five of six patients had residual urine volume of more than 50 mL/day. The Pharmacokinetic parameters derived from the present study were as followed, the median dialysis clearance was 9.07 L/hour (IQR 7.13, 12.17), the median elimination rate constant (K_e) was 0.30 $hour^{-1}$ (IQR 0.24, 0.56), and the median elimination half-life ($t_{½}$) during hemodialysis session was 2.34 hours (IQR 1.25, 2.91). The present study found the median percentage of levetiracetam plasma concentration reduction after four hours of hemodialysis was 76.89% (IQR 69.02, 85.43). Overall, plasma concentration of levetiracetam was decreased during intermittent hemodialysis sessions.

Conclusion: The findings of the present study support the use of LEV dosing of 1,000 to 1,500 mg/day and a supplemental dose after each hemodialysis session should be considered. Levetiracetam dose reduction in patients undergoing intermittent hemodialysis will lead to subtherapeutic plasma concentrations. Levetiracetam plasma concentration should be monitored in patients receiving intermittent hemodialysis.

Keywords: Levetiracetam; Hemodialysis; Pharmacokinetics; Antiepileptic drug

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Levetiracetam (LEV) is one of the second-generation antiepileptic used to treat status epilepticus, focal or generalized myoclonic and tonic-clonic seizures[1]. A systematic review and network meta-analysis of Lattanzi et al[2] published in 2019 showed that LEV was one of the antiepileptic drugs that had the highest probability of ranking best for achieving seizure freedom in the elderly with new-onset epilepsy. The therapeutic range of LEV is 12 to 46 µg/mL for LEV plasma trough concentration measurements. LEV is widely used in patients with seizures and epilepsy because it is broad-spectrum and has good efficacy. Moreover, LEV undergoes enzymatic hydrolysis as non-cytochrome P450, to an inactive metabolite. For this reason, it has lower possibility of drug-drug interactions compared to any other antiepileptic drugs[3]. For pharmacokinetic

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properties in general population, LEV bound to plasma protein less than 10% and has volume of distribution (V_d) of 0.5 to 0.7 L/kg. LEV concentration in plasma was increased in proportion to the dosage with no evidence of accumulation during multiple administration. Steady state plasma concentrations of LEV are achieved within 24 to 48 hours and about 66% of LEV is renally eliminated via glomerular filtration as unchanged drug. As a result, LEV requires dose reduction in patients with renal insufficiency. However, patients with end-stage renal disease who require hemodialysis treatment, LEV dose reduction may lead to subtherapeutic plasma concentrations and treatment failure because of LEV removal via hemodialysis. Regarding to drug dialyzability, LEV has a molecular weight of 170.21 Dalton, which is classified as a small drug molecule or molecular that weight less than 500 Dalton. It also has a very low plasma protein binding at less than 10%, low V_d at less than 1.0 L/kg, and a high degree of water solubility. These characteristics of LEV are consistent with known characteristics of a drug that can be eliminated via hemodialysis[4,5]. Previous studies found that about 40% to 50% of LEV was removed via four hours of hemodialysis session. The removal was increased up to 73% in critically ill patients[3,6,7]. Whereas, the amount of LEV removal via hemodialysis depends on types of dialyzer membranes, blood flow rate (BFR), and dialysate flow rate (DFR) used during the procedures[8]. At present, there is a lack of evidence on pharmacokinetics including renal and dialysis clearance of LEV among Thai renal patients receiving intermittent hemodialysis (IHD). Therefore, the aim of the present study was to assess the plasma concentrations and pharmacokinetic parameters of LEV in patients undergoing IHD, focusing on the assessment of pharmacokinetic parameters during IHD session.

Materials and Methods

The present study was an open-label, pharmacokinetic study conducted at Phramongkutklao Hospital, a military teaching hospital in Bangkok, Thailand, between November 2018 and October 2019. The study protocol and the statement of informed consent were approved by the Institutional Review Board, Royal Thai Army Medical Department, Study identification number Q026h/61. Prior to participate in the present study, written informed consents were obtained from all individual participants or their legally authorized representatives. The study was registered at the ClinicalTrials.gov (registration number: NCT04511676).

Participants

Adult patients aged at least 18 years old undergoing epilepsy treatment with intravenous LEV injection for not less than two consecutive days and receiving IHD were included in the present study. The pregnant and lactating patients, the patients who had IHD less than three hours, and the patients undergoing sustained low efficiency dialysis (SLED) were excluded. Patient demographics and dialysis data were obtained from the paper-based dialysis records and electronic medical records of Phramongkutklao Hospital.

Intermittent hemodialysis procedure

All patients included in the present study underwent IHD with a polyethersulfone hollow-fiber dialyzer (ELISIO-13H PP, Nipro Medical Corp., Osaka, Japan) with a surface area of 1.3 m^2 and the ultrafiltration coefficient (KUF) of 64 mL/hour/mmHg with urea mass transfer-area coefficient (KoA) of 1,190 mL/minute. A dialysis prescription of BFR, DFR, and duration of hemodialysis sessions were determined by a nephrologist. Various kinds of dialysis vascular access were used among patients such as double-lumen catheter, permanent central venous catheter, arteriovenous fistula (AVF), and arteriovenous graft (AVG).

Levetiracetam dosing regimen and administration

All patients received 1,000 to 1,500 mg of LEV injection once daily for not less than two consecutive days before IHD. LEV was administered intravenously as a 15-minute infusion. The physician prescribed the dosages of LEV injection. The patients might also receive other antiepileptic drugs concomitantly with LEV depending on their clinical symptoms.

Blood samplings and levetiracetam plasma concentration measurements

Five blood samples were obtained from a peripheral vein of each patient on their dialysis day. Venous blood samplings were performed at various times, before the initiation of hemodialysis sessions (T_0) then at 1, 2, 3, and 4 hours after the initiation of hemodialysis sessions (T_1, T_2, T_3, and T_4), respectively. All blood samples were centrifuged at 1,500 g for 15 minutes then plasma samples were transferred to cryogenic tubes and stored at –80°C until LEV plasma concentration measurements were performed. LEV plasma concentration was

measured by the method of high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. The protocol of LEV plasma concentration measurement and HPLC-UV method in the present study were performed according to Engelbrecht et al[9]. Plasma samples were deproteinized by methanol spiked with gabapentin as an internal standard. HPLC was carried out with a COSMOSIL $5C_{18}$-MS-II column at 4.6 mm ID × 250 mm, at a flow rate of 1.0 mL/minute. Mobile phase consisted of potassium dihydrogen phosphate-acetonitrile 50 mmol/L at a pH of 5.5. The UV detector was set at 205 nm. Relative standard deviation values for both the inter-day and intra-day precision and accuracy were less than 5% for the concentration range. The lower limit of detection (LLOD) of the assay was set as 2.0 µg/mL and the lower limit of quantification was 1.0 µg/mL.

Pharmacokinetic analysis

A non-compartmental analysis using Phoenix WinNonlin software version 8.3 (Certara USA, Inc., Princeton, NJ) was performed to derive the pharmacokinetic parameters of LEV including the volume of distribution (V_d), the elimination rate constant (K_e), the half-life (t½), and the dialysis clearance (CLdial) of LEV.

For non-anuric patients with residual urine volume of more than 50 mL/day, the residual renal function (RRF) was measured by a calculation of residual renal clearance (CL_{res}) using the mean of endogenous creatinine clearance (24-hour CrCL) and urea clearance (CL_{urea}) from the 24-hour urine collection as the following equation (Eqn 1)[10,11].

$$CL_{res} = \frac{(\text{24-hour CrCL}) + (\text{24-hour } C_{urea})}{2} \quad \text{(Eqn 1)}$$

As for the 24-hour CrCL and the 24-hour CL_{urea}, they were calculated by equation 2.1 and equation 2.2, respectively.

$$CrCL = \frac{U_{cr} \times V}{S_{cr}} \quad \text{(Eqn 2.1)}$$

$$CL_{urea} = \frac{U_{urea} \times V}{BUN} \quad \text{(Eqn 2.2)}$$

Where U_{cr} was the concentration of urine creatinine in mg/dL, U_{urea} was the concentration of urine urea in mg/dL, V was the volume of urine excreted as mL/minute, S_{cr} was the concentration of serum creatinine in mg/dL, and BUN was the concentration of blood urea nitrogen in mg/dL.

Statistical analysis

Patient demographics, dialysis data and clinical variables were analyzed by descriptive statistics and were presented as medians and interquartile ranges. The analysis was carried out using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA).

Adverse event and adverse drug reaction monitoring

The adverse events due to subtherapeutic plasma concentrations or toxicities of LEV, such as seizure, fatigue, and sedation, were monitored and diagnosed by LEV plasma concentration, clinical symptoms, or electroencephalography (EEG). Adverse drug reactions of LEV such as fatigue, asthenia, somnolence, and dizziness were monitored during hemodialysis sessions and throughout the study.

Results

Six patients were enrolled in the present study including two males and four females, with a median age of 62.5 years and a range of 40 to 84 years. The patients had a median body weight of 60.3 kg with a range of 50 to 67 kg. There were one anuric patient and five patients had residual urine volume more than 50 mL/day, which were three oliguric and two non-oliguric patients. All patients received a prescription for four hours of hemodialysis. Two patients were on chronic hemodialysis and four patients were on acute hemodialysis. Blood flow rate (BFR) ranged from 250 to 300 mL/minute and dialysate flow rate (DFR) was set as 500 mL/minute for all patients. Five of six patients completed the four hours of hemodialysis. One patient only received three hours of hemodialysis due to thrombus formation in the extracorporeal circuit. The demographic and dialysis data of each patient are shown in Table 1.

The LEV plasma concentrations were measured and pharmacokinetics of LEV during the IHD sessions were evaluated. The results showed that the median volume of distribution (V_d) was 0.54 L/kg (IQR 0.39, 0.74). The median LEV plasma concentration prior to the start of hemodialysis sessions ($C_{pre\text{-}HD}$) was 42.80 µg/mL (IQR 31.41, 84.60), and the median LEV plasma concentration at the end of hemodialysis sessions ($C_{post\text{-}HD}$) was 9.07 µg/mL (IQR 6.15, 12.33). The median percentage of LEV plasma concentration reduction after the four hours of hemodialysis was 76.89% (IQR 69.02, 85.43). As for the pharmacokinetic parameters during IHD sessions, the results showed that the median hemodialysis clearance was 9.07 L/hour (IQR 7.13,

Table 1. Demographics and dialysis data of patients receiving levetiracetam and intermittent hemodialysis (n=6)

Patient no.	Sex	Age (years)	BW (kg)	Residual urine (mL/day)	CL_{res} (mL/minute)	LEV dose (mg)	Concomitant antiepileptic drug	Types of HD	BFR (mL/minute)	DFR (mL/minute)
1	F	66	58.6	0	0	1,000	Phenytoin	Chronic	250	500
2	M	67	67.0	2,380	4.80	1,000	No	Acute	250	500
3	F	40	56.5	300	N/A*	1,000	No	Acute	250	500
4	F	58	65.0	300	N/A*	1,000	No	Acute	250	500
5	M	84	62.0	200	N/A*	1,000	No	Acute	300	500
6	F	59	50.0	1,000	2.44	1,500	No	Chronic	250	500

F=female; M=male; BW=body weight; CL_{res}=residual renal clearance; LEV=levetiracetam; HD=hemodialysis; BFR=blood flow rate; DFR=dialysis flow rate; N/A=not available

* Not available because of incomplete patient data

Table 2. Plasma concentrations and pharmacokinetic parameters of levetiracetam during intermittent hemodialysis sessions (n=6)

Patient no.	Parameters							
	V_d (L)	V_d (L/kg)	K_e (h-1)	t½ (h)	CL_{dial} (L/h)	$C_{pre\text{-}HD}$ (µg/mL)	$C_{post\text{-}HD}$ (µg/mL)	Reduction of LEV plasma concentration (%)
1	26.08	0.45	0.32	2.19	8.24	40.41	10.77	73.35
2	51.17	0.76	0.24	2.91	12.17	22.27	7.37	66.91
3	34.80	0.62	0.56	1.25	19.37	31.41	6.15	80.42
4	25.64	0.39	0.28	2.49	7.13	45.19	14.00	69.02
5	45.88	0.74	0.12	5.99	5.31	84.60	12.33	85.43
6	11.62	0.23	0.85	0.81	9.90	108.49	3.69	96.60
Median (IQR)	30.44 (25.64, 45.88)	0.54 (0.39, 0.74)	0.30 (0.24, 0.56)	2.34 (1.25, 2.91)	9.07 (7.13, 12.17)	42.80 (31.41, 84.60)	9.07 (6.15, 12.33)	76.89 (69.02, 85.43)

V_d=volume of distribution; K_e=elimination rate constant; t½=elimination half-life; CL_{NR}=non-renal clearance; CL_{res}=residual renal clearance; CL_{dial}=dialysis clearance (CL_{NR} + CL_{res} + CL_{dial}); $C_{pre\text{-}HD}$=plasma concentration prior to the start of hemodialysis session; $C_{post\text{-}HD}$=plasma concentration at the end of hemodialysis session; LEV=levetiracetam; IQR=interquartile range

12.17). The median elimination rate constant (K_e) was 0.30 $hour^{-1}$ (IQR 0.24, 0.56) and the median dialysis elimination half-life (t½) was 2.34 hours (IQR 1.25, 2.91). All patients had neither seizure episodes nor adverse drug reactions during hemodialysis sessions and throughout the study. The plasma concentrations and pharmacokinetic parameters of LEV during IHD sessions are shown in Table 2. Observed LEV plasma concentration versus time profiles of six patients during intermittent hemodialysis are shown in Figure 1.

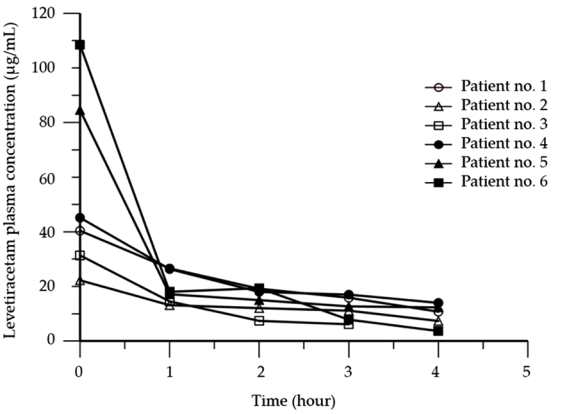

Figure 1. Levetiracetam plasma concentration versus time profiles of six patients during intermittent hemodialysis. The origin of a graph represents levetiracetam plasma concentrations before the initiation of hemodialysis sessions (T_0). Five of six patients were completed 4-hour hemodialysis. One patient (patient no. 3) received 3 hour-hemodialysis. Levetiracetam plasma concentrations of each patient tended to decrease during intermittent hemodialysis.

Discussion

LEV is eliminated primarily via the kidney. Dose reduction may be needed among patients with renal impairment. However, the previous studies found that about 50% of LEV was removed via a four-hour hemodialysis session. Therefore, LEV dose in end-stage renal disease patients undergoing hemodialysis was 500 to 1,000 mg daily, then followed by 50%

of initial dose as the supplemental dose after each hemodialysis session[6,7,12]. A previous study of Yamamoto et al(13) conducted in six Japanese patients that underwent four-hour hemodialysis sessions with a BFR of 180 to 220 mL/minute, a DFR of 500 mL/minute, and a high flux membrane, polysulfone (PSF) with a surface area of 1.2 to 1.8 m^2. The results showed 69% of LEV was removed during the four hours of hemodialysis, while the present study measured LEV plasma concentrations during a hemodialysis session and found that the reduction of LEV plasma concentration after the four hours of hemodialysis was as high as 76.89%. The BFR in the present study was 250 to 300 mL/minute, which was higher than the BFR of 180 to 220 mL/minute that was used in the study of Yamamoto et al[13]. Some patients in the present study still had residual urine output of about 300 to 2,380 mL/day, which might be related to an increase in renal clearance of LEV, especially among the patients that underwent acute hemodialysis because of uremia, electrolyte imbalance, or acute kidney injury. The initial dose of LEV given to the patients in the present study was 1,000 to 1,500 mg/day, which was higher than the general recommendation[6,7] that led to the higher LEV plasma concentration of 42.80 µg/mL at the beginning of dialysis session compared with the previous studies[13-15]. Similarly, the median post-dialysis LEV plasma concentration of the present study was 9.07 µg/mL, which was also greater than the previous studies[13-16]. However, it was still less than a recommended therapeutic range of 12 to 46 µg/mL[6,7,12]. Although, there was not any episodes of seizure during dialysis session in the present study, the LEV dose reduction to less than 1,000 mg/day in patients undergoing IHD should not be used because it could lead to subtherapeutic plasma concentrations during and after dialysis session, which might not be enough for seizure control in patient with unstable epilepsy. Therefore, the present study findings support the use of LEV dosing not less than 1,000 mg/day in patients with renal failure treated with IHD.

As for the results of pharmacokinetic parameters, the authors found that the elimination half-life of LEV during the four-hour hemodialysis session was 2.34 hours, which was equal to the elimination half-life of 2.3 hours in the previous study of Yamamoto et al[13]. However, it was greater than the elimination half-life of 1.0 hour in the case report of Wieruszewski et al[15], which the hemodialysis prescription included thrice weekly, three-hour dialysis sessions with BFR and DFR of 400 and 600 mL/minute, respectively, with a high-flux polyarylethersulfone/polyvinylpyrrolidone membrane dialyzer with a 1.4 m^2 surface area. The IHD procedure of the present study used a high-flux membrane, polyethersulfone, hollow-fiber dialyzer with a surface area of 1.3 m^2, and the ultrafiltration coefficient (KUF) of 64 mL/hour/mmHg. The BFR and DFR were 250 to 300 mL/minute and 500 mL/minute respectively, while there were differences of dialysis equipment and dialysis prescription in other studies. It is obvious that the different dialysis equipment, such as the types of dialysis membrane, a surface area of dialyzer, and dialysis prescription as BFR, DFR, and duration of dialysis session are the key factors that are related to the different pharmacokinetics of LEV in patients undergoing IHD.

The present study has limitations. The first is the small number of participants. However, nowadays there are still lack of evidence on dialysis clearance of LEV among Thai patients receiving IHD, thus the findings of the present study may offer useful information for this patient population. The other limitation is that only LEV plasma concentrations before, during, and after IHD session were measured. The authors did not directly measure LEV concentrations in dialysate samples. Therefore, an actual percentage of LEV removal via IHD could not be obtained. However, the pharmacokinetic analysis was performed to reveal dialysis clearance of LEV by a non-compartmental analysis using Phoenix WinNonlin software version 8.3 (Certara USA, Inc., Princeton, NJ). For non-anuric patients with RRF, urine LEV concentrations were important for the detection of LEV excreted via residual urine and it might not appropriate to use RRF to assume residual renal clearance of LEV. This is also one of the study limitations that the authors did not directly measure the urine LEV concentrations. Therefore, the dialysis clearance in the present study represents the summation of non-renal clearance, residual renal clearance, and intra-dialytic clearance of LEV.

Conclusion

In patients receiving IHD, the plasma concentration of LEV was decreased during IHD sessions, primarily owing to the removal of LEV via dialysis procedure. Consequently, LEV dose reduction in patients undergoing IHD may lead to subtherapeutic plasma concentrations. The LEV dosing of 1,000 to 1,500 mg/day then followed by 50% of initial dose as the supplemental dose after each hemodialysis session should be considered. LEV plasma concentration, episodes of seizure and adverse drug reactions should be monitored in the patients receiving IHD.

What is already known on this topic?

Levetiracetam is a well-known antiepileptic drug that is primarily eliminated via the kidneys and requires dose adjustment in patients with renal insufficiency. The plasma concentration profiles of levetiracetam in patients undergoing intermittent hemodialysis have been reported in case reports and the previous studies. However, there is still a lack of evidence on pharmacokinetic parameters including dialysis clearance of levetiracetam during the intermittent hemodialysis session. Moreover, the different dialysis equipment and dialysis prescription are related to the different pharmacokinetics of levetiracetam in each patient.

What this study adds?

The present study is the first pharmacokinetic study of levetiracetam among Thai renal patients receiving intermittent hemodialysis, focusing on the assessment of pharmacokinetic parameters during hemodialysis session, including dialysis clearance, elimination half-life, elimination rate constant, and the percentage decrease of levetiracetam plasma concentration. The findings of the present study support the use of LEV dosing of 1,000 to 1,500 mg/day and a supplemental dose after each hemodialysis session should be considered. Levetiracetam dose less than 1,000 mg in patients undergoing intermittent hemodialysis will lead to subtherapeutic plasma concentrations.

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Conflicts of interest

The authors declare no conflict of interest.

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