Pharmacokinetics of Levetiracetam in Thai Epilepsy Patients Undergoing Intermittent Hemodialysis

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Abstract

Background: Levetiracetam (LEV) is primarily eliminated by kidney. In patients with kidney failure on hemodialysis (HD), LEV level reduces significantly.

Objectives: We aimed to conduct a pharmacokinetics study and to determine appropriate supplemental dosage for our Thai epilepsy population undergoing intermittent hemodialysis.

Methods: This was a single center prospective investigational cohort study; recruiting adult epilepsy patients with clinically indicated for intermittent hemodialysis. Intravenous LEV maintenance dose was given before hemodialysis. Serum LEV levels were monitored at 8 points over pre-dialysis, dialysis and post-dialysis periods. The supplement LEV dose (half of the maintenance dose) was administered at 1 hour after hemodialysis.

Results: Total of 12 patients, mean age was 64 year old (SD 18), range 24-86, and male was 4 (33.3%). Maintenance LEV dosage was 1,000-1,500 mg/day. All the patients had serum LEV within therapeutic range (12-46 µg/mL) at C_{trough} level, C_{peak} level and just before starting hemodialysis. During intrahemodialysis period, the LEV levels were declined gradually over the time. At the end of hemodialysis, 5 patients (41.7%) had sub-therapeutic LEV levels. There was no predictor related to sub-therapeutic LEV level. After injections of supplemental LEV dose, serum LEV level of all the patients reached therapeutic level.

Conclusion: Intermittent hemodialysis dramatically eliminates levetiracetam. Supplemental dose as 50% of the maintenance dosage is recommended for maintaining levetiracetam therapeutic level.

Keywords: Levetiracetam, Renal replacement Therapy, Pharmacokinetic, Hemodialysis, Supplement dose

Introduction

Levetiracetam (LEV) is a widely use second generation of antiepileptic drug approved by the Food and Drug Administration (FDA) for treatment of partial-onset seizures, myoclonic seizures in patients with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures.[1] Levetiracetam has 100% bioavailability, is not bound to plasma proteins and has a volume of distribution of 0.5-0.7 L/kg. It is not metabolized by liver. Approximately 34% of LEV is excreted by kidney and 66% of an administered dose is recorded as an unchanged form in urine.[2,3] Therefore, in chronic kidney disease or end-stage renal disease, levetiracetam dosage should be reduced and administered as once daily. Currently, therapeutic range of levetiracetam is 12-46 μg/mL.[4]

According to levetiracetam properties, it has been relevantly eliminated by hemodialysis, being about 50-60% removal during a 4-hour hemodialysis session.[5,6] A supplemental dose of 250-500 mg (or approximately 50% of the maintenance dosage) after the 4-hour intermittent hemodialysis is recommended[7]. However, information about LEV pharmacokinetics in patients undergoing hemodialysis is scarce. Moreover, there is no available data among Thai population. We therefore conducted this research.

Objectives

1. To evaluate pharmacokinetics of levetiracetam in Thai epilepsy patients undergoing intermittent hemodialysis by monitoring serum levetiracetam level.

2. To determine whether 50% supplemental dosage prescribed after hemodialysis is adequate.

Materials and Methods

Study design:

This study is a prospective investigational cohort study, at a hemodialysis unit, medical wards and intensive care units at Phramongkutklao Army Hospital, Bangkok, Thailand. The study period was from November 1st, 2018 to October 31st, 2019.

Patients:

Sample size calculation

This study's sample size was calculated by: $N = [(Z_{1\alpha} - Z_{2\beta})^2 SD^2]/E^2$, $Z_{1\alpha} = 1.96$, $Z_{2\beta} = 0.842$, SD = 2, based on data from Yamamoto J, et al[6], E (maximum error) = 0.65. Calculated sample size for our study was 12.

Inclusion criteria were:

1) Adults (age ≥ 18 years) diagnosed with epilepsies on once daily LEV at stable dosage

2) Either acute renal failure or end-stage renal disease diagnosed by nephrologists or intensivists, on intermittent hemodialysis, approximate duration of 3-4 hours/session

Exclusion criteria were:

1) Pregnancy or lactation

2) Unstable vital signs

3) Hemodialysis by Sustained Low Efficiency Dialysis (SLED) method (continuous renal replacement therapy)

Levetiracetam administration:

Although levetiracetam has 100% bioavailability, all the patients in this study received intravenous form with an identical dosage as their enteric maintenance dose in order to be confounded by different absorption variability. Maintenance dose of intravenous LEV was administered as once daily in the morning before hemodialysis, as a frequency recommendation for chronic kidney disease. The

supplement LEV dose (half of the maintenance dose) was administered at 1 hour after hemodialysis. The maintenance dosage of LEV varied individually, depending on their previous conditions.

Hemodialysis technique:

All patients received a 3-4 hour dialysis session utilizing ELISIO-13H PP (1.3 m^2), Synthetic Hemodialyzer filters (effective surface area = 1.3 m^2, KUF = 64 mL/hour/mmHg, KoA = 1,190 mL/min) and Fresenius Medical Care 4008 B 2 Hemodialyzers. Dialysis flow rate and blood flow rate were under judgment of nephrologists.

Measurement of serum levetiracetam levels (Figure 1):

Serum LEV levels were monitored at 8 points over pre-dialysis, dialysis and post-dialysis periods.

Point No.1: before LEV injection, (#1) [trough level or C_{trough}]

Point No.2: 1-hour after LEV injection, (#2) [peak level or C_{peak}]

Point No.3: before starting hemodialysis (#3)

Point No.4, 5, 6, 7: intrahemodialysis at 1st-hour (#4), 2nd-hour (#5), 3rd-hour (#6) and at the end of session (#7)

Point No.8: 1-hour after supplemental LEV dose (#8)

Serum LEV levels were measured by High Performance Liquid Chromatography (HPLC)-UV analysis method. The method was developed from methods described in literature Engelbrecht L, et al. (2017)[8]. The sample preparation and HPLC machine were analyzed at Faculty of Pharmacy, Silpakorn University.

Outcome measure

The serum LEV levels were analyzed.

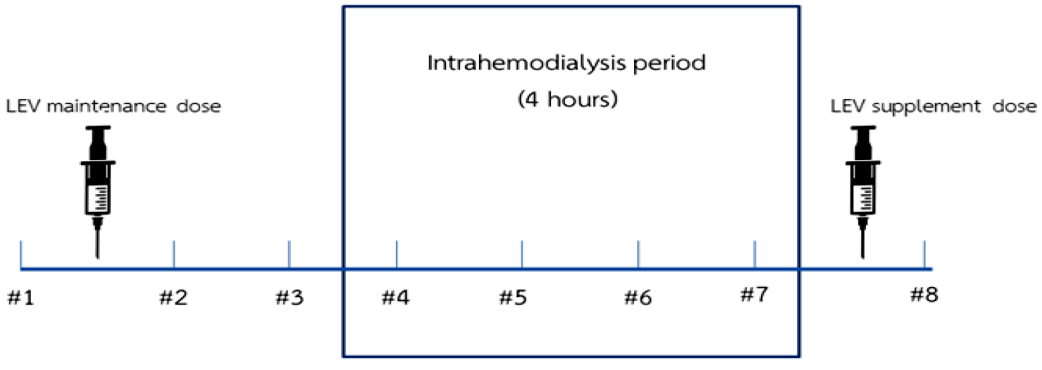

Figure 1 Flow chart of serum levetiracetam (LEV) measurement, #1-8: Point number 1-8 for LEV serum level monitoring

Ethical consideration

This study was approved by Institutional Review Board of Royal Thai Army Medical Department (Q026h/61). The patients read information sheet and signed on the consent form.

Statistical analyses

Descriptive data were shown as mean and standard deviation (SD) while categorical data were shown as frequency and percent. Predictors for lower therapeutic LEV level at the end of hemodialysis were analyzed by Chi-square test and independent

sample t-test. Statistical significance was defined as p-value < 0.05. Statistical analysis was performed by SPSS version 23.0 (License).

Results

Total of 12 patients, mean age was 64 year old (SD 18), range 24-86, and male was 4 (33.3%). Three of 12 patients (25 %) were diagnosed with acute renal failure requiring acute intermittent hemodialysis, while 9 of 12 (75%) were diagnosed with end-stage renal disease on regular chronic intermittent hemodialysis. Average hemodialysis flow rate was 525 mL/hour and average blood flow rate was 270 mL/hour. Among 12 patients, 10 (83.3%) received maintenance LEV dose as 1,000 mg/day, therefore the supplement dosage of 500 mg after hemodialysis were administered. While 2 of 12 patients (16.7%) received maintenance LEV dose as 1,500 mg/day which the supplemental dose after hemodialysis was 750 mg. Four of 12 patients (33.3%) were prescribed concomitant antiepileptic agents along with levetiracetam (valproate in 1 patient and phenytoin in 3 patients). Other demographic data and baseline characteristics were described in Table 1.

Table 1 Baseline Characteristics (n = 12)

Demographic data	Mean ± SD / Number (%)
Age (years)	64.0 ± 18
Male : Female	4 : 8
Body weight (Kg)	56.4 ± 9.1
Height (cm)	1.60 ± 0.1
Body mass index (Kg/m^2)	21.6 ± 1.5
Acute renal failure	3 (25 %)
End stage renal disease	9 (75 %)
Phenytoin concomitant use	3 (25%)
Valproate concomitant use	1 (8.3%)
Hemodialysis flow rate (mL/hour)	525.0 ± 86.6
Blood flow rate (mL/hour)	270.0 ± 25.7
Blood urea nitrogen (mg/dL)	64.5 ± 28.7
Creatinine (mg/dL)	5.4 ± 2.3
Albumin (g/dL)	3.1 ± 0.4
LEV maintenance dose (mg/day)	1,083.3 ± 194.6

All the patients had serum LEV within therapeutic range (12-46 µg/mL) at C_{trough} level (#1), C_{peak} level (#2) and just before starting hemodialysis (#3). During intrahemodialysis period, the LEV levels at point No.4, 5, 6 and 7 (#4, #5, #6, and #7) were declined gradually over the time. At the end of hemodialysis (#7), 5 patients (41.7%) had sub-therapeutic LEV levels (<12 µg/mL). There was no predictor related to sub-therapeutic LEV level at point number 7. After injections of supplemental LEV dose (50% of the maintenance dosage), serum LEV level of all the patients reached therapeutic level. The detailed LEV levels were illustrated in Figure 2, Table 2, and Table 3. During study, there was no clinical breakthrough seizure.

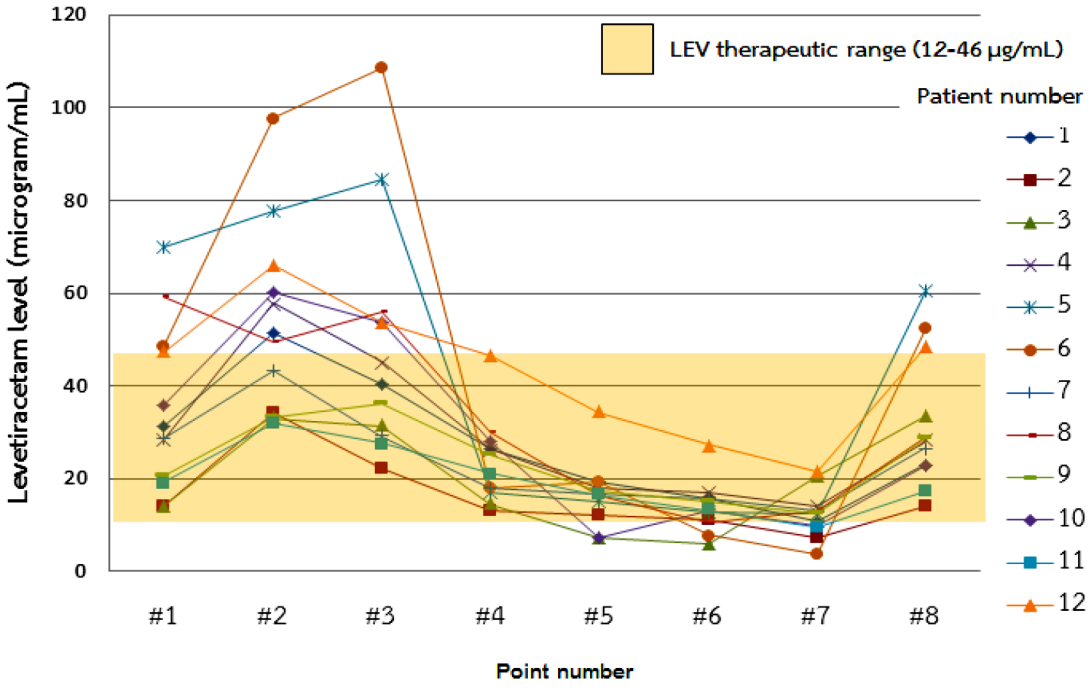

Figure 2 Individual serum levetiracetam (LEV) levels during pre-hemodialysis, intrahemodialysis, and post-supplement LEV dose

Table 2 Levetiracetam (LEV) level at different points

Point number	LEV level (µg/mL) Mean ± SD
#1: Trough level (C_{trough})	34.8 ± 18.1
#2: 1-hour after LEV IV injection (C_{peak})	53.0 ± 20.4
#3: Before starting hemodialysis	49.1 ± 25.3
#4: 1st hour Intrahemodialysis	23.7 ± 9.1
#5: 2nd hour Intrahemodialysis	16.6 ± 6.9
#6: 3rd hour Intrahemodialysis	13.8 ± 5.4
#7: 4th (last) Intrahemodialysis	12.4 ± 5.0
#8: 1-hour after LEV supplement	32.1 ± 14.4

Table 3 Predictors of subtherapeutic LEV level at the last intrahemodialysis point (point No.7)

Demographic data	LEV level < 12 µg/mL [Mean ± SD / Number (%)]	LEV level ≥ 12 µg/mL [Mean ± SD / Number (%)]	*p*-value
Age (years)	59.8 ± 21.8	67.0 ± 15.8	0.521
Body mass index (Kg/m^2)	21.5 ± 1.3	21.7 ± 1.8	0.857
BUN (mg/dL)	65.3 ± 31.0	64.0 ± 29.4	0.944
Creatinine (mg/dL)	6.1 ± 2.6	4.9 ± 2.1	0.379
Albumin (g/dL)	3.1 ± 0.3	3.1 ± 0.5	0.843
LEVmaintenance dose(mg/day)	1,100.0 ± 223.6	1,071.4 ± 188.9	0.815
LEV C_{trough} level	29.8 ± 13.7	38.3 ± 20.9	0.447

Discussion

Our study was a pharmacokinetic study, monitoring levetiracetam level among Thai epilepsy patients undergoing intermittent hemodialysis. All the patients developed decrement of LEV level during hemodialysis. At the end of the dialysis, 76% of LEV level reduced from C_{peak}, which 58% of the patients eventually reached sub-therapeutic level. Our result was concordant with a previous study conducted in Japan. In Japan, the hemodialysis technique was similar to our country (high flux membrane, 4-hour per session, but lower blood flow rate).[6] The LEV level in Japanese epilepsy patients declined 69% after hemodialysis, therefore the higher dialysis blood flow rate, the higher LEV clearance.

Despite the fact that our study and other studies had low LEV level, especially some patients reached sub-therapeutic level, there was no patient reported clinical breakthrough seizures.[9] This would be because 1) the dialysis timings were short, 2) the usage of immediate supplemental dose after hemodialysis and 3) patients were stable without any other seizure triggers. Our study prescribed supplemental dose as 50% LEV maintenance dosage as manufacturer recommendation.[3,10-11] As a result, the serum level after LEV supplemental dose rose up from 12.4 to 32.1 µg/mL, which were comparable as individual C_{trough} level (34.8 µg/mL), within therapeutic level (12-46 µg/mL). Therefore, this study was clearly demonstrated that 50% of LEV maintenance dose for supplementation was appropriate.

In the world, there were only few studies on levetiracetam pharmacokinetic among patients requiring hemodialysis. Ours was the first in Thai population. However, according to relatively small number of population, conducted in a single center, for the further studies, the authors suggested to increase studied population, recruit more dialysis centers, different LEV formulations and routes of administrations as well as dialysis techniques particularly peritoneal dialysis, continuous renal replacement therapy.

Conclusion

Intermittent hemodialysis dramatically eliminates levetiracetam. Supplemental dose as 50% of the maintenance dosage is recommended for maintaining levetiracetam therapeutic level.

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Conflicts of Interest

None

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