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Research Article

Levetiracetam Population Pharmacokinetic in North Indian Epilepsy Patients

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Abstract

Background: Unlike first line Antiepileptic Drugs (AEDs) specific therapeutic range for Levetiracetam (LEV) has not been defined. The present study was conducted to find the mean serum LEV levels using population pharmacokinetics and to find out the correlation with the demographic and physiological determinants (age, gender, weight and dose) and concomitant antiepileptics drugs in the north Indian population.

Methods: The retrospective, record-based study was done at a super-specialty hospital. The trough sample of LEV was collected and serum was separated within 30 minutes of drawing blood sample. All requisitions for therapeutic drug monitoring were included in the analysis except samples reaching after 30 minutes from the time of sample collection, known poor compliance, irregular treatment, known overdose or toxicity.

Results: Out of 2456 samples, 2115fulfilling criteria were divided into 3 age groups <18 years (819, 38.1%); 18 years - 60 years (1296, 60.3%); >60 years (34, 1.58%). Mean ± SD LVM levels (mg/L) reported were children (12.8 ± 9.85), adults (14.09 ± 11.06) and, elderly (22.3 ± 10.4). The sub-therapeutic levels (<12 mg/L) were found in 24.6% (reported range 12 mg/L-45mg/L). Though 48.7% levels were reported within the therapeutic range, but 49.5% were lower than the overall mean serum level (12 mg/L-46 mg/L). Supra-therapeutic LEV levels were reported in only 35 (1.66%) including 2 adults and 3 elderly with levels in toxic range (>75 mg/L). The LEV level distribution curve showed a positive right-skew with a long tail. No-correlation was found with demographics, physiological variables or concomitant antiepileptics drugs.

Conclusion: Population pharmacokinetics of LEV in north Indian though was within the reported reference range but was on the lower side, with lower than reported range in children and higher levels in elderly group. Prospective population pharmacokinetics and pharmacogenetics studies needed to further elucidate these findings especially for establishing therapeutic range TDM in children and elderly to maintain levels within optimal reference range.

Keywords: Antiepileptic drugs; Levetiracetam; Reference range, Pharmacokinetics; Therapeutic drug monitoring; Population pharmacokinetics

Introduction

Levetiracetam (LEV) is one of the newer, broad-spectrum, and frequently used Antiepileptic Drug (AED) in partial and generalized seizures [1]. It has proven effective in treating multiple seizure types, in both adults and children. Besides, LEV can be valuable for acute seizure management [2] especially in critically ill patients due to its rapid onset of action and minimal side-effect profile compared to older AEDs such as phenytoin, carbamazepine, valproic acid, and phenobarbital [3]. It is available as oral and parenteral formulation and can be given as a bolus. Levetiracetam has a linear pharmacokinetic profile with some cytochrome P450 (CYP) metabolism, nearly total excretion by the kidneys, and a good correlation between creatinine clearance and LEV clearance [4].

Effective LEV levels are not known [4], and LEV reference range has been difficult to establish. A comprehensive review by Jarvie D et al. [1] analysed studies, mostly observational or retrospective to assess correlation of LEV levels with the seizure control and suggested a reference range from 6 mg/L-46 mg/L, but the sample size of these studies was small. A wide therapeutic reference range of 12 mg/L - 46 mg/L has been suggested and level above 75 mg/L are considered potentially toxic [5,6].

There are only a few studies on population LEV pharmacokinetics. One study from China [7], reported 45% samples below reference range (12 mg/L), whereas the other study from Norway reported LEV levels between 5 mg/L-25 mg/L in 80% patient [6]. May et al. [8] studied the influence of age, weight, gender, and comedications on the LEV serum levels in patients with epilepsy and suggested a reference range of 12 mg/L-46 mg/L.

There are only limited studies from India, out of three Indian studies reported, first determined the range of LEV levels at a stabilized dose and correlated it with their clinical response, while the other two studies investigated the difference in LEV levels with co-medication and their clinical response [10-12]. Mathew et al. [10] found significant drug interactions with concomitant AEDs.

At our center, Therapeutic Drug Monitoring (TDM) of LEV is being done for the last 7 years and we observed that LEV levels reported were mostly on the lower normal limit of the recommended reference range and only a few were above the upper normal reference range. Based on this understanding, the study was conducted to find the reference range for LEV levels using population pharmacokinetics in the north Indian population and study its correlation with demographic determinants (age, gender, weight, and dose) and concomitant AED therapy.

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Methodology

The retrospective, record-based study of requisitions was conducted at a super-specialty hospital. The trough sample was collected and serum was separated within 30 minutes of sample collection. All requisitions for TDM from 2015 to 2021 period were included except samples arriving more than 30 minutes of sample collection, known poor compliance as stated by patients, history of irregular treatment, known intentional overdose or toxicity. Also result below <2.0 mg/L (i.e., below the analyzer-specific Lower Limit of Quantitation (LOQ)) were excluded from the study. Figure 1 depicts the flow of the patients considered for the study.

Quantification of serum LEV level analysis was done using the Levetiracetam assay reagents (ARKTM) on CDX 90® mass photometric system of Thermo Fisher. Sensitivity and specificity quality control was maintained by running three-level control sera provided along with the ARKTM kits. The range of assay is 2.0 mg/L to 100 mg/L. A concentration between 12 mg/L-46 mg/L [8] was used as the reference range for the normal level of levetiracetam (CV 5.46%). Serum LEV was categorized into sub-therapeutic, therapeutic, supra-therapeutic, and toxic levels (Table 1). The department participates in external quality assurance programme of Biorad®.

Figure 1: Flow chart of selection of study sample.

Table 1: Serum level categorization.

Categories	Levetiracetam
Sub-therapeutic*	<12 mg/L
Therapeutic	12 mg/L-46 mg/L
Supra-therapeutic	>46 mg/L
Toxic	>75 mg/L

*Levels <2 mg/L excluded from sub-therapeutic category

Statistical Analysis

The data obtained were statistically analysed using Microsoft excel 2016. The categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Quantitative variables were compared using Spearman's regression correlation. A r^2-value of >0.3 and p-value <0.05 was considered statistically significant.

Results

Out of the 2456 requisitions for levetiracetam assays, 2115 fulfilled the eligibility criteria and were stratified into three groups according to their age group (Figure 1 and Table 2). The maximum requisitions were received from outdoor (61.65%), followed by emergency (24.96%) and inpatient (13.38%) department. Relapse/breakthrough seizures (55.84%) and adverse effects (13.62%) were the major reasons for the requests for TDM (Table 3).

A mean drug dose of 1214 mg/day ± 495 mg/day of LEV established the mean blood concentration of 13.5 mg/L ± 10.6 mg/L. However, when stratified into different groups, children & adolescents (mean dose 1050 mg/day ± 458 mg/day established a mean serum level of 12.8 mg/L ± 9.85 mg/L), whereas in adults mean dose 1318 mg/day ± 436 mg/day established a mean serum level 14.09 mg/L ± 11.6 mg/L, and in elderly lower mean dose 1217 mg/day ± 416 mg/day established a higher mean serum level 22.3 mg/L ± 10.4 mg/L.

Overall, 1031(48.7%) levels were reported within the therapeutic range. Sub-therapeutic LEV levels were found in 453 (55.3%) children, 657 (50.69%) adults, and 6 (17.6%) elderly. Supra-therapeutic LEV levels were reported in 11 (1.34%) children, 24 (1.85%) adults, and 4 (11.7%) in the elderly. Toxic levels (>75 mg/L) were reported only in 3 elderly and 2 adults.

Figures 2 and 3 depicts the serum drug level distribution curve of LEV in different age group and showed a positive right-skew with a long tail in children and adults. Most reported LEV levels were reported on the lower side (Mean - 1 SD) of the established therapeutic range with 51.5% children, 55.7% adults, 47.2% elderly below reported laboratory mean (13.5 mg/L ± 10.6 mg/L). The mean LEV levels in children were 12.8 mg/L (range 2-53; 95% CI 0.689), adults 14.09 mg/L (range 0-91; 95% CI 0.611), and in elderly was 22.3 mg/L (range 2-81; 95% CI 0.619). Overall absolute range of LEV levels was 2 mg/L to 91.1 mg/L with mean level of 14.09 mg/L.

No significant correlation of LEV levels was observed with age, weight and dose in children and adults (Figure 4). No significant effect was observed in mean serum LEV levels with inducers (carbamazepine r^2=0.01, phenytoin r^2=0.04) and inhibitor (valproic acid r^2=0.07) antiepileptics drugs (Figure 5).

Figure 2: Serum drug level distribution curve of levetiracetam in children and adults.

Table 2: Demographics of the population included in the Study.

	Children (≤18 years)	Adults (18-60 years)	Elderly (>60 years)	Total
N (%)	819 (38.1%)	1296 (60.3%)	34 (1.58%)	2149
Gender				
Male	483 (22.84%)	707 (33.43%)	18 (0.8%)	1208 (56.2%)
Female	336 (15.89%)	589 (27.85%)	16 (0.7%)	941 (43.74%)
Mean age ± SD	12.8 ± 11.8	29.6 ± 11.4	67.89 ± 5.12	23.1 ± 11.4
Weight (Kg)				
Mean ± SD	41.8 ± 17.7	59.2 ± 17.4	64.09 ± 9.43	52.45 ± 18.6
Range	65 (40-74)	60 (40-76)	61 (40-94)	62.2 (39 -98)
Daily dose (mg/day)				
Mean ± SD	1050 ± 458	1318 ± 436	1217 ± 416	1214 ± 495
Dose Range	1000 (800-1700)	1220 (900-2500)	1250 (1000-2000)	1200 (800-2000)
Patient care area				
OPD	509 (24.07%)	795 (37.59%)	16 (0.001%)	1304(61.65%)
Emergency	201 (9.50%)	327 (15.46%)	5 (0.00%)	528 (24.96%)
IPD	109 (5.15%)	174 (8.23%)	13 (0.00%)	283 (13.38%)
Duration of therapy				
<1 month	126 (5.96%)	213 (9.26%)	2 (0.0%)	341 (15.9 %)
≤ 1- 6 months	170 (8.04%)	234 (11.0%)	2 (0.0%)	406 (19.1%)
≤ 6 months - 1 year	100 (4.73%)	149 (7.04%)	12 (0.0%)	261 (11.7%)
> 1 year	367 (17.3%)	630 (29.7%)	15 (0.0%)	1012 (47.14%)
Duration of therapy not known	70 (3.31%)	56 (2.65%)	3 (0.0%)	129 (5.96%)
Drug levels				
Sub-optimal (0 mg/L-12 mg/L)	453 (55.3%)	657 (50.69%)	6	1049 (49.5%)
Therapeutic (12 mg/L-46 mg/L)	354 (43.2%)	614 (47.3%)	24	1031 (48.7%)
Supra-therapeutic (>46 mg/L)	11 (1.34%)	24 (1.85%)*	4	35 (1.66%)*
Toxic levels (>75 mg/L)	0	2	3	5
Mean ± SD (mg/L)	12.8 ± 9.85	14.09 ± 11.06	22.3 ± 10.4	13.5 ± 10.6
Median (mg/L)	10	10	15.2	10
Range (mg/L)	2-69.5	2-91.1	Feb-93	2-91.1
Level/Dose ratio (mg/kg/L)				
Mean ± SD	0.03 ± 0.02	0.02 ± 0.01	0.03± 0.01	0.02 ± 0.01
Median	0.02	0.01	0.01	

*includes toxic levels

Table 3: Reason for requisition of therapeutic drug monitoring of levetiracetam.

Reason for investigation	Children (≤ 18 years)	Adults (18-60 years)	Elderly (>60 years)	Total N=2149
Relapse/Break through seizures	484 (22.8%)	697 (32.9%)	8 (0.003%)	1189 (55.84%)
Adverse effects	110 (5.2%)	214 (10.0 %)	5 (0.002%)	329 (15.3%)
Overdose/toxicity	64 (3.0%)	122 (5.7%)	4 (0.002%)	190 (8.79%)
No response/Compliance/any other	161 (7.6%)	263 (12.3%)	17 (0.008%)	441 (19.9%)

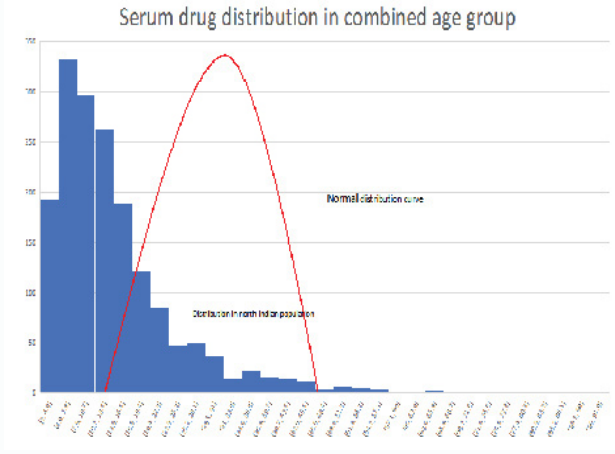

Figure 3: Serum drug level distribution curve of levetiracetam in adults and children combined.

About 1156 (54.6%) requisitions were for no or partial response/ breakthrough seizures, and the overall mean level reported was 12.4 mg/L ± 10.2 mg/L while in 459 (21.7%) requisitions with adverse effects mean LEV levels reported were 12.5 mg/L ± 10.6 mg/L.

Discussion

The present study was conducted to determine the therapeutic LEV range in North Indian epileptic patients and identify demographic and physiological determinants affecting its level. In the present study, Although no significant difference in the mean LEV levels was found in children and adults, but LEV levels were towards lower normal limit i.e., 12.8 mg/L in children compared to adults. However, higher mean levels were reported in elderly, with similar mean dose. Similar findings were reported by Mathew et al., Singh et al., and Gupta et al. [10-12]. As known non-compliance and irregular treatment were excluded from the analysis, lower LEV levels could be due to either fast metabolism or excretion of LEV in the study population.

Iwasaki et al reported peak target range of 20 mg/L-30 mg/L as the optimal range with higher LEV levels associated with greater efficacy [13]. In the present study, we did not find any correlation of LEV levels with the reason for TDM, indicating no correlation of levels with efficacy or tolerability, however, these findings need confirmation in prospective studies.

Figure 4: Correlation between age, weight, and dose and serum levetiracetam level.

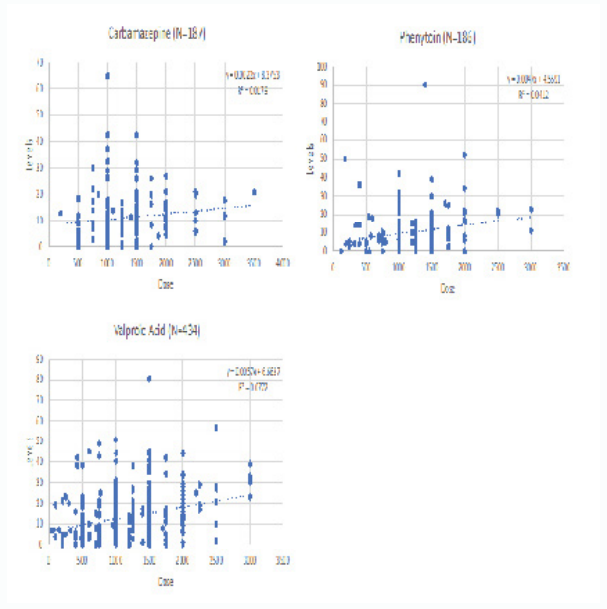

Figure 5: Effect of concomitant drugs on serum levetiracetam level.

Absolute LEV range reported in the present study was wide (2 mg/L to 91.1 mg/L) with nearly half within reference range and a very few in the supra-therapeutic and toxic range. These findings are similar to the findings by Rhee et al. [14] wherein small number of patients in the supra-therapeutic range was reported in neonates.

LEV exhibits a linear relationship between the dose and serum levels, however, several studies suggested that the LEV levels are affected by several parameters such as age, sex, body weight, and concomitant AEDs. In the present study, a non-significant positive correlation between the age and LEV levels was observed as also seen by Mathew et al. and Gupta et al. [10,12]. Elderly reportedly had higher mean LEV levels and some with toxic drug levels. According to May et al older patients need a lower LEV dose per kg body weight compared to children and adults [8]. The elderly since have lower clearance, therefore, require 40% lower LEV dose to achieve therapeutic drug level [6,12]. In elderly renal function should serve as a guide for initiating LEV level monitoring. A small sample size in elderly age group as reported in our study may lack the power to demonstrate the impact of renal function on LEV levels, thus would need elucidation of renal clearance in a larger sample size.

Children & adolescents had lower mean LEV levels compared to adults and elderly, as also reported by other studies [10]. Children need higher LEV weight-based dose to achieve serum concentration similar to those in adults due to higher clearance [15]. Further, we did not find any correlation between LEV levels and weight in children, though non-significant negative correlation was observed in adults. Whereas Pigeolet et al. [9] reported positive effect of body weight on LEV levels. Similar to other studies we did not find any correlation of gender with the LEV levels [6,12,17], however, Pigeolet et al. [9] found higher levels in females. Radtke et al. [17] and Mathew et al. [10] also reported similar findings and concluded that any differences in the pharmacokinetic parameters (if present) are likely to be related to the differences in body weight of both the genders and show no differences when normalized for body weight.

We also explored the effects of other AEDs on LEV pharmacokinetics as LEV is often used as an add-on AED. LEV is not metabolized by hepatic enzymes, but clearance increases when administered with enzyme-inducing AEDs such as phenytoin, carbamazepine, or phenobarbitone [1,10,12,15,16,18,19]. However, we did not find any statistically significant changes in LEV level with concomitant enzyme inducer AEDs or enzyme inhibitor AEDs indicating no requirement for dose adjustment when used with other AEDs. Similar findings are supported by other studies [16,17], but need to be studied in larger sample with a comparative LEV monotherapy group.

Limitations

This is the first study in north Indian population investigating reference range for the Indian population and the results of the present study are compelling due to its large sample size. Although adequate care was taken to select cases, being a record based study there could be an inherent bias due to confounding variables. Correlation with the reason for requisition such as breakthrough seizures or adverse effects was studied but could not establish correlation with clinical response. The effect of other co-variables should also be studied such as fasting; dosage forms/switching of brand, diurnal variation, renal function, and pregnancy.

Conclusion

This population pharmacokinetic study points towards lower mean levetiracetam levels in Indian population and the need for establishing optimal therapeutic range for TDM in children and elderly. This study highlights the need for prospective studies with larger sample size involving children and elderly and pharmacogenetics studies to further elucidate reference range for levetiracetam.

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