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Levetiracetam in genetic generalized epilepsy: A prospective unblinded active-controlled trial

Nasim Tabrizi[a,*], Ashraf Zarvani[a], Parisa Rezaei[a], Hamed Cheraghmakani[a], Reza Alizadeh-Navaei[b]

[a] Neurology department, Mazandaran University of medical sciences, Sari, Iran
[b] Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, Iran

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ABSTRACT

Purpose: To compare the efficacy and tolerability of levetiracetam (LEV) versus valproate (VPA) monotherapy in adults with genetic generalized tonic–clonic seizures alone (GTCS) and juvenile myoclonic epilepsy (JME).

Methods: This study was an open-label, active-controlled trial with a two-parallel-group design. Outcome measures including withdrawal rate and seizure freedom rate at 26th weeks and time to withdrawal, and time to first seizure were compared between LEV and VPA groups. Furthermore, tolerability and development of adverse events (AEs) were investigated and analyzed.

Results: One hundred and three patients enrolled the study. 71.1% of patients in LEV group and 29.3% in VPA group were female. By the end of 26th week, seizure freedom rate and withdrawal rate were 88.9% and 8.9% in LEV group and 86.2% and 10.3% in VPA group with no significant difference. Time to first seizure was longer in VPA group ($p = 0.32$) and time to withdrawal favored LEV ($p = 0.51$). At least one AE was reported in 37.7% of patients in LEV group and 55.1% in VPA group. The most common AEs were psychiatric symptoms and dizziness in those on LEV and weight gain and dyspepsia in VPA group.

Conclusion: LEV has similar efficacy and acceptable safety in comparison to VPA in short-term treatment of patients with genetic GTCS and JME, and it could be considered as an alternative to VPA particularly in women of reproductive age.

1. Introduction

Genetic generalized epilepsy (GGE) is a common subgroup of generalized epilepsies which consists of four epilepsy syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy (JME) and generalized tonic–clonic seizures alone (GTCS) (Scheffer et al., 2017). GGE accounts for 15–20% of patients with epilepsy (Jallon and Latour, 2005) with 70–80% favorable response to treatment (Kay et al., 2013; Mattson, 1992). Necessity of long-term treatment in JME and GTCS, indicates the need for monotherapy by an effective antiepileptic drug (AED) with minimal side effects (Mazurkiewicz-Bełdzińska et al., 2010). Levetiracetam (LEV) is a well-established AED with a unique mechanism of action and potential broad-spectrum efficacy (Abou-Khalil and Schaich, 2005). Rapid absorption, appropriate oral bioavailability, lack of significant pharmacokinetic interaction and low risk of teratogenicity together with acceptable efficacy have made LEV a favorable option for treatment of focal and generalized epilepsies (Yi et al., 2018). Supporting by double-blind, placebo-controlled studies, the drug has been approved by the U.S. food and drug administration (FDA) as adjunctive treatment for GGE in adults (Rosenfeld et al., 2009). But it also has shown promising results as monotherapy in JME and GTCS (Colleran et al., 2017; Montouris and Abou-Khalil, 2009; Stephen et al., 2011).

The importance of the need for monotherapy with LEV is further enhanced by the recent widespread warnings for teratogenesis of valproate (VPA) - the drug of choice in GGE - in women of reproductive age (Chowdhury and Brodie, 2016; Marson et al., 2007; Trinka et al., 2013). However despite the few studies which compared the efficacy and safety of monotherapy with LEV and VPA in JME, comparative studies on GTCS in adults is still lacking. This study aimed to compare the efficacy and safety of LEV with VPA in treatment of genetic GTCS and JME.

* Corresponding author.
E-mail address: nasimtabrizi@gmail.com (N. Tabrizi).

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2. Methods

2.1. Patients

This study was carried out between May 2018 and April 2019. Patients aged ≥16 years with diagnosis of genetic GTCS or JME who were referred to our tertiary University hospital and epilepsy clinic were included. Normal brain magnetic resonance imaging (MRI), lack of focal epileptic discharges with or without generalized spike/polyspike in electroencephalography (EEG) and seizure symptomatology in favor of GTCS or JME were mandatory. Patients were excluded if they previously had hepatic, renal and hematologic disorders, known psychosis, psychogenic non-epileptic seizure, status epilepticus and illegal drug abuse. We also excluded the patients who had been treated with LEV or VPA in the last 6 months and those with poor adherence to medications.

The patients were not randomized because of lack of certain contraceptive methods in many of child bearing age women and the possible teratogenic effects of VPA which put them in high risk of adverse events in case of unplanned pregnancy. Thus, the distribution of gender among two groups was not normal. The decision to choose the medication was made by clinicians.

The study was approved by University ethics committee and performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before participation. The study has been registered in https://clinicaltrials.gov with identifier NCT03940326.

2.2. Study design

This study was an open-label, active-controlled, 26-week trial with a two-parallel-group design. Equivalence for primary outcome and non-inferiority for secondary outcome has been investigated. Patients were treated by LEV (Levebel, Cobel Darou, Iran) or VPA (Depakin, Sanofi-Aventis, France). LEV was started with 500 mg/day (twice daily as equal doses) and the dose was increases by 500 mg/week to a total dose of 2000 mg/day if needed. Starting dose for VPA was 500 mg/day with 500 mg/week increase to the maximum dose of 1500 mg/day in two divided doses based on clinician's decision. Patients, who experienced adverse events (AEs) during titration which could be ameliorated by dose reduction, were reverted to previous acceptable dose. If one episode of seizure occurred, doses were increased to maximum 3000 mg/day for LEV and 2000 mg/day for VPA with the same titration protocol, according to clinician's judgment. Evaluations have scheduled at weeks 4, 12 and 26 after initiation of treatment. In each visit by neurologist, adherence to AED, seizure recurrence and AEs were assessed. AEs were classified into mild, moderate and severe types. Moderate AEs were those which interfere with daily living activities and severe AEs were specified as life threatening events or those which led to hospitalization or persistent disability.

2.3. Outcome measure

The primary outcomes were time to first seizure and seizure freedom rate at 6 months after start of treatment. The secondary outcomes were defined as time to withdrawal and withdrawal rate at 6th month and also severity of adverse events. Withdrawal rate was calculated based on discontinuation of monotherapy with each medication due to AEs, lack of efficacy and need to drug switch or combination therapy.

2.4. Statistical analysis

SPSS version 19 software (SPSS Inc.) was used for statistical analysis. Chi-square test or Fisher's exact test were used to compare categorical variables between groups. Numerical variables were analyzed with student's *t*-test or Mann-Whitney test, according to distribution. Time to first seizure and time to withdrawal were analyzed using the Kaplan–Meier survival curves. For analysis of time to first seizure, patients who did not experience any seizure during the first 26 weeks of treatment were censored at the end of 26 weeks. For analysis of time to withdrawal, patients who discontinue medication before 26 weeks were considered to have the event. Cox's regression model was used to investigate time to withdrawal and time to first seizure. A Hazard ratio (HR) of less than 1 was considered in favor of LEV. P-value of less than 0.05 was considered statistically significant.

The equivalence threshold for primary outcome set at less than 20% difference for seizure freedom rate. In other words, if there was no true difference between two treatment (90% in both groups), then 96 patients were required to be 80% sure that the limits of a two-sided 95% confidence interval would exclude a difference between two group of more than 20%.

3. Results

One hundred and three patients (VPA = 58, LEV = 45) were enrolled. The patients in LEV and VPA groups were similar with respect to demographics and epilepsy characteristics except gender which had not a normal distribution in two arms (Table 1).

The target daily range was 500–3000 mg for LEV and 500–1500 mg for VPA. Eight patients (13.8%) in VPA group and 9 (20%) in LEV group needed to increase medication dosage (p = 0.43).

Treatment withdrawal occurred in 6 patients in VPA group and 4 patients in LEV group. Drug discontinuation was more often due to AEs in LEV group (75% vs. 66.7%) and was more related to seizure recurrence in VPA group (33.3% vs. 25%) without any significant difference (p = 0.66). Seizure freedom rate at 6 months was similar in VPA and LEV groups. Seizures recurred in 10 patients in VPA group (50% myoclonus, 50% GTCS) and 9 patients in LEV group (55.6% myoclonus, 44.4% GTCS). In comparison to VPA group, time to treatment withdrawal was longer in patients treated with LEV (HR 0.63, 95% CI 0.15–2.53). In contrast, time to first seizure favored VPA over LEV (HR 1.06, 95% CI 0.7–1.62) but there was no statistically significant difference in any of these outcome measures. (Table 2, Fig. 1)

Outcome measures were analyzed for patients with GTCS separately. There was no significant difference in outcomes of this group of patients in comparison to all patients and those with JME. However a trend toward longer mean time to withdrawal (221 days in GTCS vs. 170 days in JME, p:0.07) and mean time to first seizure (177 days in GTCS vs. 165 days in JME, p:0.61) was found in patients with GTCs.

Table 1
Baseline characteristics.

Variable	LEV	VPA
Gender; Male/Female	13(28.9)/32(71.1)	41(70.7)/17(29.3)
Marital state; Single/Married	23(51.1)/22(48.9)	35(60.3)/23(39.7)
Age	26.2 ± 8.1	29 ± 9.7
Onset age	22.4 ± 9.1	25.5 ± 10.6
Disease duration (year)	2 [0.2-4.5]	1[0-5]
Risk factors		
Perinatal complication	0(0)	2(3.4)
Developmental delay	1(2.2)	1(1.7)
Febrile seizure	1(2.2)	3(5.2)
Family history of epilepsy; Positive/Negative	27(60)/18(40)	27(47.4)/30(52.6)
Classification of epilepsy		
JME	14(31.1)	10(17.2)
GTCS	31(68.9)	48(82.8)

Data has been shown as n(%), mean ± SD and median[IQR]. Lev: Levetiracetam, VPA: Valproate, GTCS: Generalized tonic–clonic seizures, JME: Juvenile myoclonic epilepsy.

Table 2
Outcome measures at 26th week.

Outcome measure	LEV	VPA	P-value	HR (95% CI)
Time to first seizure; mean ± SE (day)	169 ± 6.1	178 ± 2.2	0.32	1.06 (0.7-1.62)
Time to withdrawal; mean ± SE (day)	220 ± 8.7	172 ± 4.1	0.51	0.63 (0.15-2.53)
Seizure freedom rate n(%)				
All patients	40 (88.9)	50 (86.2)	0.77	
GTCS only	28 (100)	43 (97.7)	0.61	
Withdrawal rate n(%)				
All patients	4 (8.9)	6 (10.3)	0.54	
GTCS only	3 (9.7)	4 (8.3)	0.56	

Lev: Levetiracetam, VPA: Valproate, GTCS: Generalized tonic–clonic seizures.

Safety profile showed no significant difference between two groups. 37.7% of patients in LEV group and 55.1% in VPA group experienced at least one AE. (Table 3) Most of reported AEs were mild and moderate; but severe AEs also occurred. Rise of liver enzymes in two patients treated with VPA, made hospital admission and rapid switch of VPA necessary. (Table 4).

Table 3
Comparison of adverse events.

Adverse events	LEV n(%)	VPA n(%)
Hair loss	0	1(1.7)
Weight gain	0	16(27.6)
Irregularity of menstrual period	0	1(1.7)
Somnolence	3(6.7)	3(5.2)
Tiredness	1(2.2)	2(3.4)
Tremor	0	1(1.7)
Dyspepsia	0	6(10.3)
Dizziness/vertigo	6(13.3)	1(1.7)
Psychiatric symptoms	9(20)	0
Abnormal laboratory data	0	4(6.9)

Lev: Levetiracetam, VPA: Valproate.

Table 4
Severity of adverse events (per patient).

Severity of AEs	LEV n(%)	VPA n(%)	p-value
Mild AEs	14(82.4)	29(90.6)	0.13
Moderate AEs	3(17.6)	1(3.1)	
Severe AEs	0(0)	2(6.2)	

AEs: Adverse events, Lev: Levetiracetam, VPA: Valproate.

4. Discussion

VPA is widely regarded as the AED of choice in treatment of genetic GTCS and JME (Chowdhury and Brodie, 2016). But the high risk of teratogenicity and wide range of AEs have limited its administration in women of reproductive age and directed treatment to promising alternative medications with more tolerable AEs such as LEV and lamotrigine (Berkovic et al., 2007; Cação et al., 2018; Coppola et al., 2017; Crespel et al., 2013; Nevitt et al., 2017; Specchio et al., 2006; Tang et al., 2017). In this study we compared the efficacy and tolerability of LEV and VPA in GGE with focus on patients with GTCS only.

Our results did not show any differences in withdrawal rate and time to withdrawal between groups. However there was a trend toward longer time to withdrawal in patients treated with LEV. The results of a large multicenter comparative study (KOMET) by Trinka et al. (2013) on a mixed population of newly diagnosed patients with focal and generalized epilepsy, have also shown similar time to treatment withdrawal and treatment withdrawal rates between LEV and VPA. Although not significant, they reported longer time to withdrawal in patients with primary generalized seizures who had taken VPA. We could not find any significant differences in seizure freedom rate and time to first seizure between groups but time to first seizure was slightly shorter in those treated with LEV. Studies which compared efficacy of LEV and VPA in JME have shown higher seizure freedom rate for VPA in comparison to other AEDs including LEV (Sala-Padró et al., 2016; Trinka et al., 2013; Zhang et al., 2019). VPA generally provided better seizure control for GTCS in patients with JME, but LEV caused more myoclonic seizure freedom (Sala-Padró et al., 2016). In contrast, there are reports of similar retention rate between LEV and VPA in JME (Silvennoinen et al., 2019) particularly in women younger than 35 years (Chowdhury and Brodie, 2016; Sala-Padró et al., 2016). Findings of these studies are generally affected by combination of GTCS with myoclonic or absence seizures that makes the interpretation of pure efficacy on GTCS difficult. We could not find any randomized controlled study that evaluates the efficacy of LEV in comparison to VPA in adults with GTCS only, to compare our results with.

Previous studies have shown that except psychiatric symptoms and somnolence, the most common AEs that might lead to withdrawal of LEV, AE profile is generally in favor of LEV in comparison to standard older AEDs. This safety and tolerability is more evident in reproductive issues and teratogenicity risk (Chowdhury and Brodie, 2016; Grünewald, 2005; Kowski et al., 2016). In a recent study by Silvennoinen et al. (2019) on efficacy of AEDs in JME, VPA had the most common AEs after topiramate. However, the high efficacy of VPA in GGE often has led to acceptance of considerable numbers of its AEs.

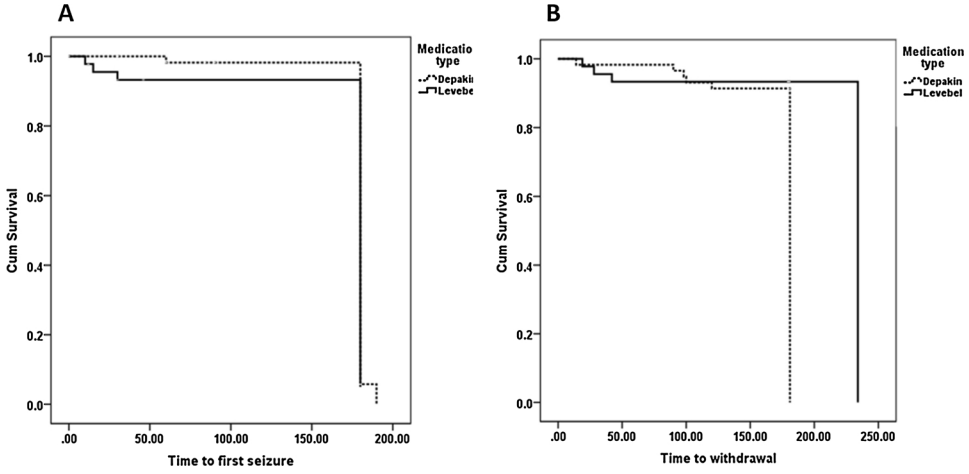

Fig. 1. Kaplan-Meier survival curves for: A. Time to first seizure B. Time to withdrawal.

In current study incidence of AEs was lower in patients on LEV and severe AEs only occurred in those on VPA. But similar to KOMET, treatment withdrawal due to AEs had no significant difference between LEV and VPA groups (Trinka et al., 2013).

This study had some limitations. First of all, the decision to choose the medication (LEV vs. VPA) was made based on clinicians' judgment and we failed to randomized or blind the study. The main reason for this approach was lack of certain contraceptive methods in most of our female patients which made the randomized and blinded administration of VPA, unethical. This problem has also reported in some other comparative studies (Chowdhury and Brodie, 2016) but since there is no evidence of effect of gender on treatment outcome in GGE, we assume that our results have not been affected by this factor. The second limitation is that, current results are based on a 6-month follow up of patients and the results in longer follow up periods might be different. Moreover, we believe that the low number of patients might decrease the power of this study. Thus, randomized double-blind studies with larger sample size and long-term follow up are needed to confirm our results.

5. Conclusion

Overall, in terms of efficacy, our results showed non-inferiority of LEV in comparison to VPA in short-term treatment of adults with GTCS and JME. Although AEs occurred less frequently in LEV group, the difference was not significant and caused no change in withdrawal rate. It seems that regarding safety profile, the main priority of LEV is the lower rate of teratogenicity and it could be considered as an effective, well-tolerated alternative to VPA particularly in women of reproductive age.

Declaration of Competing Interest

None.

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