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Effect of Pyridoxine on the safety of Levetiracetam in a pediatric population with Epilepsy - A Retrospective pharmacovigilance study

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Abstract

Introduction: Epilepsy is one of the most common neurological disorders affecting children. Levetiracetam (LEV) is a widely used anti-epileptic drug (AED) with good pharmacokinetics and a low risk of side effects. Pyridoxine (vitamin B6) is one of the effective additional therapies used to prevent and treat the adverse effects of LEV in children.

Aim of the study: The study's goal was to see how pyridoxine affects the safety of LEV therapy in a pediatric epilepsy population.

Subjects and Methods: A retrospective study on pediatric patients was conducted at Egypt's Fayoum University Hospital. Thirty patients were selected. The age range of patients receiving LEV as monotherapy ranged from 6 months to 11 years. Patients were divided into two groups: those who only received LEV and those who received LVE plus pyridoxine. The causality and severity of adverse drug reactions (ADRs) were evaluated.

Results: ADRs were reported by 71.4% of LEV patients, but only 18.8% of LEV plus pyridoxine patients. These ADRs involved various systems, with 50% involving gastrointestinal symptoms that were significantly p0.006 higher in the LEV group compared to the LEV + Pyridoxine group. In the LEV group, 35.7% had behavioral ADRs that were significantly p0.008 higher. Other neurological side effects were observed. The WHO-UMC criteria for assessing the causality of ADRs revealed that 20% were probable and 23.3% were possible. All of the ADRs were common.

Conclusion: The current study found that pyridoxine can help control some ADRs caused by LEV in children.

Keywords: Pediatric Epilepsy; Pharmacovigilance; Anti-epileptic Drug; Drug safety; Levetiracetam; Pyridoxine

1. Introduction

Pharmacovigilance (PV) has described as the science and activities relating to the detection, assessment, understanding, and prevention of the adverse effects of drugs or any other possible drug-related problems [1]. Pharmacovigilance plays a principal function in ensuring drug safety [2].

Epilepsy is one of the most widespread noninfectious diseases worldwide and one of the most common dangerous neurological disorders [3-9]. The highest rate of epilepsy is in the first year of life and decreases to the adult levels at ten years old [10,11]. The choice of antiepileptic drugs (AEDs) in infants and children depends on the agent's efficacy, safety, effect on learning and behavior, and existing patient comorbidities [3].

Using drugs in the treatment of epilepsy is accompanied by ADRs such as dose-related neurocognitive consequences and idiosyncratic reactions, especially with traditional AEDs such as sodium valproate and with long-term use. The ADRs in patients treated with monotherapy was lower than in patients with polytherapy [12,13].

Levetiracetam (LEV) is used to treat various types of epilepsy. It is licensed as an add-on therapy for juvenile myoclonic epilepsy, primary generalized Tonic-Clonic (grand mal) seizures, and partial-onset seizures in adults and children [3,14,15]. LEV has several appealing properties as a first-line or add-on therapy for epileptic seizures [16,17]. LEV is rapidly and almost completely absorbed orally, reaching plasma peak concentration within one hour of ingestion [18]. Dose adjustment is not required for liver dysfunction patients [19].

Pyridoxine is a portion of the vitamin B group complex, it is fundamental for neurotransmitter synthesis, and its lack causes several neurological disorders [20,21] called pyridoxine-dependent seizures [22]. That genetic situation needs high doses of pyridoxine for lifelong [22-25]. Pyridoxine insufficiency can occur secondary to drug or dietary factors intake and may mimic pyridoxine‑dependent seizures [24]. Pyridoxine might control behavioral ADRs produced by LEV. The mechanism that explains the relationship between LEV and pyridoxine is unknown [21]. Since ADRs differ from one person to another, pharmacovigilance studies were conducted on many people in different countries to monitor these ADRs and how to overcome them. So, the current study aimed to evaluate the effect of pyridoxine on the safety of LEV therapy in a pediatric population with epilepsy at Fayoum Governorate, Egypt.

2. Subjects and methods

2.1. Subjects

That retrospective study was conducted after approval from the Ethical committee, Faculty of Medicine, Fayoum University. Fayoum, Egypt. The study recruited 30 children diagnosed with epilepsy based on clinical evaluation and

electroencephalogram (EEG) findings from June 2015 to June 2018. Children with other commodities, such as an inborn error of metabolism, growth delay, and brain deformation, or treated with other AEDs' were excluded from the study.

2.2. Study design

Participants were divided into two groups:

- Patients treated with LEV only (n=14).
- Patients treated with LEV and pyridoxine combination (n=16).

Data were collected on patient age, sex, dose, duration, seizure type, if taken pyridoxine or not, and different adverse effects in either LEV group or LEV plus pyridoxine.

2.3.Statistical analysis

Analysis was performed by using SPSS 26 (IBM, Armonk, NY, United States). The analysis included a description of the basal characteristics of the study population, regimens differences regarding the distribution of ADRs, common ADRs experienced by patients who received LEV only and LEV with pyridoxine schedule regimens, and characteristics of ADRs by frequency and percentage. Pearson's chi-square test measures the association between two continuous variables. *P-value < 0.05* was set at a point of significance.

3. Results

A total of 30 patients were evaluated from June 2015 till June 2018. All patients were recruited according to the criteria mentioned above. Results of demographic data revealed that 63.3% (n=19) were males, and 36.7% (n=11) were females, with a mean age of 6.7±2.8 years. The results showed that the predominant types of seizure were generalized tonic-clonic seizures at 56.7% (n=17) and tonic seizures at 20% (n=6). Other types involved myoclonic 13.3% (n=4) and focal seizures 10% (n=3), as shown in Table 1. LEV was administered at mean doses of 503.3±198.7 mg IV/PO q12hr, and the mean duration use was 1.7±0.8 year. About 53.3% (n=16) of participants were treated with pyridoxine plus LEV, and 46.7% (n=14) were treated with LEV alone (Table 1).

Table 1: The baseline characteristics of the study participants as regards to different treatments.

Parameters		Frequency
Gender	Male	19 (63.3%)
	Female	11 (36.7%)
Age (years)	6.7±2.8	
Type of seizure	Generalized tonic clonic	17 (56.7%)
	Myoclonic	4 (13.3%)
	Focal convulsions	3 (10%)
	Tonic convulsions	6 (20%)

Pyridoxine	Yes	16 (53.3%)
	No	14 (46.7%)
Mean LEV dose (mg)	503.3±198.7	
LEV duration (year)	1.7±0.8	

In terms of treatment, 46.7% (n=14) received only LEV, while 53.3% (n=16) received LEV plus pyridoxine. The number of ADRs reported was statistically significant (*P=0.003*), with 13 (43.3%) patients reporting 14 different ADRs. ADRs were reported by 71.4% (n=10) of patients who received only LEV and 18.8% (n=3) of patients who received LEV plus pyridoxine (Table 2).

Table 2: ADRs in patients treated with LEV alone vs. LEV plus pyridoxine.

Parameters		**LEV only (n=14)**	**LEV+ pyridoxine (n=16)**	**Total**	***P-value***
Adverse effects	**Yes**	10 (71.4%)	3 (18.8%)	13 (43.3%)	0.003*
	No	4 (28.6%)	13 (81.3%)	17 (56.7%)	

* Significant at (*P<0.05*).

Increased appetite was the most common ADR observed in patients treated with LEV alone (21.4%). 14.3% reported irritability, headache, vomiting, and loss of appetite. 7.1% reported fatigue, screaming, loud laughter, insults, insomnia, long sleep, constipation, abdominal pain, and abdominal distention. ADRs for LEV plus pyridoxine included increased sleep, headache, and increased appetite in 6.3% of patients, as shown in figure1.

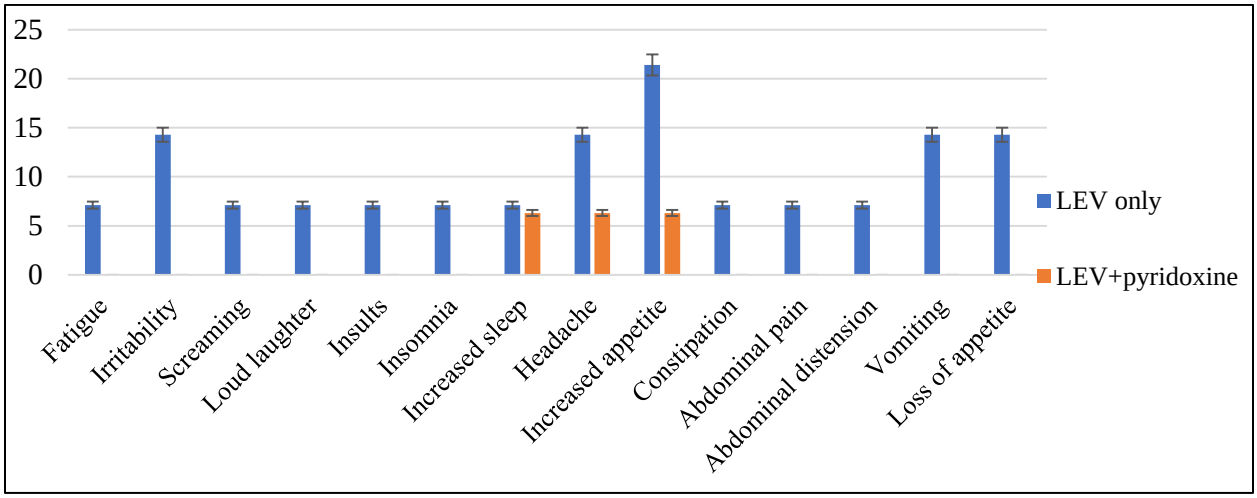

Figure 1: Bar chart of the most reported ADRs in terms of treatments.

According to that study, 50% of patients with gastric intestinal tract (GIT) symptoms belonged to the LEV group, which had a considerably greater incidence of GIT symptoms than the LEV + Pyridoxine group (*P = 0.006*). In comparison to the LEV + Pyridoxine group, 35.7% of patients exhibited behavioral ADRs that were statistically significant (*P = 0.008*) greater. Insomnia, more sleep, headaches, increased appetite, and exhaustion were other neurological side effects that were noted but did not significantly differ (*P = 0.05*) between the two groups. Only in those receiving LEV alone were less common ADRs such yelling, loud laughter, insults, constipation, abdominal pain, and abdominal distension recorded. With LEV with pyridoxine, 6.3% (n = 1) of patients experienced improved sleep, headaches, and increased appetite (Table 3). Regarding Causality assessment by WHO-UMC criteria, six symptoms were probable and seven were possible, while regarding severity, all ADRs were common (Table 4).

Table 3: Different regimens and ADRs in patients treated with LEV alone vs. LEV plus pyridoxine.

System	Symptoms	LEV only (n=14)	LEV+ pyridoxine (n=16)	*P-value* [a]	*P-value* [b]
General	Fatigue	1 (7.1%)	0 (0%)	0.293	0.293
Behavior	Irritability	2 (14.3%)	0 (0%)	0.126	0.008*
	Screaming	1 (7.1%)	0 (0%)	0.293	
	Loud laughter	1 (7.1%)	0 (0%)	0.293	
	Insults	1 (7.1%)	0 (0%)	0.293	
CNS	Insomnia	1 (7.1%)	0 (0%)	0.293	0.288
	Increased sleep	1 (7.1%)	1 (6.3%)	0.925	
	Headache	2 (14.3%)	1 (6.3%)	0.481	
GIT	Increased appetite	3 (21.4%)	1 (6.3%)	0.237	0.006*
	Constipation	1 (7.1%)	0 (0%)	0.293	
	Abdominal pain	1 (7.1%)	0 (0%)	0.293	
	Abdominal distension	1 (7.1%)	0 (0%)	0.293	
	Vomiting	2 (14.3%)	0 (0%)	0.126	
	Loss of appetite	2 (14.3%)	0 (0%)	0.126	

[a] Comparison of the two groups regarding symptoms; [b] Comparison of the two groups regarding systems

* Significant at (*P<0.05*).

Table 4: WHO-UMC criteria assessment of ADRs diagnosed in the study population.

Characteristics of ADRs (n=14)	Frequency
Causality	
Certain	0 (0%)
Probable	6 (20%)
Possible	7 (23.3%)
Unlikely	0 (0%)
Severity	
Common	13 (43.3%)
Severe	0 (0%)

4. Discussion

Pharmacovigilance studies are carried out on a large number of people in various countries to monitor ADRs and how to overcome them. Pharmacovigilance is very important because the information collected from pre-marketing medications with regard to possible ADRs is insufficient. The reasons for imperfect information are limited periods, selective patients, a limited number of patients enrolled, different particular conditions, etc. [26]. After FDA approval, the actual side effect of the drug will be recognized [27].

Epilepsy is a common chronic disease that needs long-term AEDs therapy. Among the definitive goals of epilepsy treatment is the reduction of adverse effects from AEDs [13]. LEV is a widely prescribed drug in the treatment of epilepsy and has been reported to be a broad-spectrum AEDs [17].

This retrospective study was conducted to present a better overview of the variety and frequency of ADRs of LEV in epileptic children. We demonstrated in our study that the record of ADRs was statistically significant (*P=0.003*), as 13 (43.3%) patients reported 14 different ADRs.

Similar to the findings of the present study Verrotti *et al.,* 2015, performed a meta-analysis for a total of 2832 patients and found 5 ADRs associated with LEV treatment: dizziness, somnolence, nasopharyngitis, nervousness/irritability, and asthenia/fatigue [14].

The observed ADRs profile of LEV treatment among pediatric patients in prior studies were mainly nervous manifestations. The most frequent were dizziness, asthenia, behavior difficulties, and somnolence [3]. A previous study reported that ADRs of LEV include irritability, dysphoria, somnolence, drowsiness, and dizziness [28].

Regardless of the frequent ADRs of LEV, such as irritability, dizziness, aggressive behavior, nausea, and gastrointestinal symptoms, some infrequent ADRs have been reported for rhabdomyolysis, reduced sperm quality, and pneumonia [29–31].

In contrast to the findings of our study, Elberry *et al.*, 2012, and his colleagues demonstrated in their retrospective study that no ADRs were associated with LEV except for 1 child who experienced a loss of appetite and a change in behavior and attitude [3]. The data concerning the frequency of LEV-associated ADRs are controversial [32].

The current study found that 50% of patients experienced gastric intestinal tract (GIT) adverse effects, all of whom were in the LEV group, which was significantly higher than the LEV + Pyridoxine group ($P=0.006$). 35.7% of patients experienced behavioral ADRs that were significantly higher in the LEV group ($P<0.008$).

In pediatrics, many reports and similar studies have elucidated the potentially favorable impact of pyridoxine to control behaviors ADRs associated with LEV use. Pyridoxine is readily available, inexpensive, and safe but the exact mechanism to antagonize LEV's adverse effects is not clear [21].

In accordance with the findings of this study, Major *et al.*, 2008, analyzed 42 children who had been treated with LEV plus pyridoxine and observed that a significant improvement in behavior was noticed in 41% of patients. The results of pyridoxine supplementation were noticed in the first week of treatment [33]. Consequently, in the current study, we concluded that pyridoxine could be used safely to control LEV-induced ADRs.

Conclusion

The current study was conducted on a pediatric epilepsy population in Fayoum Governorate to provide a better understanding of pyridoxine's control of LEV-induced behavioral and gastrointestinal ADRs. We concluded that pyridoxine could be used safely to alleviate LEV-induced ADRs, ensuring adequate therapy, and successful seizure control in children. Because of the limited studies regarding the effect of pyridoxine on LEV ADRs and the limited number of patients in our study, more investigations are required on a larger number of participants to provide additional data on the potential effects of pyridoxine on LEV and to discover the underlying mechanism.

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Ethical considerations

The study was approved by the ethical committee of the faculty of medicine at Fayoum University. Ethical approval code for this study is (R 301).

Patient consent

Patient consent was not required for this study.

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Conflicts of Interest: All authors declare no conflict of interest.

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