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Original Article

Amelioration of Levetiracetam-Induced Behavioral Side Effects by Pyridoxine. A Randomized Double Blind Controlled Study

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ABSTRACT

Background: Levetiracetam is a relatively new-generation antiseizure drug approved for the treatment of focal and generalized seizures. Despite its favorable side effect profile and minimal drug-drug interactions, neuropsychiatric side effects are reported in up to 13% of children. A few case series have suggested that supplementation of pyridoxine may mitigate these side effects, but controlled trials are lacking. To address this issue, a randomized interventional study was carried out in a pediatric tertiary hospital to qualify and quantify the potential beneficial effect of pyridoxine in attenuating the neuropsychiatric side effects of levetiracetam in children.

Methods: A total of 105 children with epilepsy who were taking levetiracetam (as a monotherapy or an adjunct) who showed behavioral symptoms coinciding with the start of levetiracetam, were included. Patients randomly and blindly received either a therapeutic (pyridoxine group, 46 of 105, 44%) or a homeopathic dose of pyridoxine (placebo, 59 of 105, 56%). A 30-item behavioral checklist was used to qualify and quantify the behavioral side effects at baseline and at different time points following initiation of treatment.

Results: Both placebo and pyridoxine groups experienced a statistical reduction in behavioral scores when compared with baseline. Our study indicated that although there was a placebo effect, the improvement in neuropsychiatric symptoms was more prominent in children who received therapeutic doses of pyridoxine.

Conclusions: These data provide clinicians with pertinent evidence-based information that suggests that a trial of pyridoxine in patients who experience behavioral side effects due to the use of levetiracetam may avoid unnecessary change of antiseizure medications.

Introduction

Epilepsy is one of the most common neurological entities in the pediatric population, with a prevalence of 3.5 to 5.5 of 1000.[1] Antiseizure drugs remain the mainstay of seizure management, and attainment of complete seizure remission without adverse drug events remains the ultimate goal of epilepsy treatment.[2] However, in reality, finding a good balance between seizure control and drug side effects remains an important challenge in epilepsy management—a challenge that has motivated the search for newer drugs with novel mechanisms of action that are more efficacious and possess a more tolerable side effect profile.

Over the past two decades, there has been an exponential increase in the number of antiseizure drugs available on the market. Among these is levetiracetam, a renally excreted drug that stands out from other antiepileptic drugs due to its unique biochemical structure and its novel mechanism of action (blocks presynaptic release of neurotransmitters via blocking synaptic vesicle 2A).[3] Levetiracetam is efficacious for a variety of seizure types in both

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the pediatric and adult population, and as such has been approved for use both as a monotherapy for focal seizures and as an adjunct therapy for both focal and generalized seizure disorders.[2-6] Furthermore, since its initial release, increasing evidence in the literature has demonstrated its efficacy in the treatment of patients with status epilepticus,[7,8] electrical status epilepticus during sleep,[9] and even in neonatal seizures.[10,11] In addition to its extended therapeutic utility, it offers other advantages compared with other antiepileptic agents including paucity of drug-drug interactions and the fact that blood monitoring is not required.[3]

Nevertheless, levetiracetam can have important side effects, with neuropsychiatric disturbances being the most common adverse effect leading to its discontinuation.[12-15] Up to 13% of pediatric patients on levetiracetam experience neuropsychiatric disturbances ranging from irritability, aggressivity, personality changes, mood lability, anxiety, and depression.[13,14] The majority of these symptoms tend to be mild, although in up to 2% of cases, serious side effects including suicidality have been reported.[12-14] In the majority of patients, neuropsychiatric symptoms occur within the first month after the initiation of levetiracetam, although these symptoms can also develop later and are reversible upon discontinuation of the drug.[15]

Over the past years, anecdotal evidence from case reports and retrospective chart reviews has suggested a beneficial effect for pyridoxine in treating the neuropsychiatric side effects of levetiracetam.[16-18] In a retrospective chart review, Major et al. found that 41% (n = 22 patients) of children who developed behavioral side effects after starting levetiracetam had a significant improvement in their symptoms, after the addition of pyridoxine.[16] In a more recent retrospective chart review carried out in adults, pyridoxine relieved symptoms of agitation and irritability in 66.6% (n = 34) of patients who developed these symptoms after taking levetiracetam.[18] In both studies, the improvement in behavioral symptoms occurred within the first two weeks after the initiation of pyridoxine.[16,18] In a study by Marino et al. that is a case-control prospective study, which was not placebo-controlled, but was randomized, the patients were subdivided into two groups, according to whether they were treated with levetiracetam only or with levetiracetam and supplemental pyridoxine. Their conclusion was that pyridoxine is safe and effective in controlling levetiracetam-induced behavioral side effects in children.[19]

Although these preliminary data open a therapeutic opportunity for patients who develop neuropsychiatric symptoms due to levetiracetam, evidence from randomized placebo-controlled trials remains lacking. As such, the goal of this study was to conduct the first double-blind placebo-controlled trial to determine whether pyridoxine can truly reverse or ameliorate levetiracetam-induced neuropsychiatric symptoms in pediatric patients with epilepsy by providing evidence-based information to physicians that would prove beneficial in the management of their patients.

Methodology

This study was a randomized interventional study carried out at King Fahad Medical City between March 2018 and March 2020. Children with a diagnosis of epilepsy and receiving levetiracetam were enrolled into the study if meeting the inclusion criteria and after written consent was obtained.

Inclusion criteria

1. Children between one and 17 years on levetiracetam either as monotherapy or as adjunct for seizure control.
2. Neuropsychiatric symptoms induced by levetiracetam (noticed only after levetiracetam use, as stated by the parents, or noted by the primary treating neurologist).

Exclusion criteria

1. Children outside the age range (that is less than one year and older than 17 years).
2. Children using other drugs known to have behavioral side effects.
3. Children with behavioral issues before the use of levetiracetam.

Once consented, a baseline standardized behavioral checklist questionnaire was filled with the family of the patient to qualify and quantify their child's behavioral symptoms (Fig). This 30-item questionnaire screened for various neuropsychiatric symptoms including mood changes and mood lability, aggressive/destructive behavior, changes in eating behavior, changes in sleep, self-mutilating behavior, and suicidality. Face validity was established and the survey was reviewed by different parties; consequently confusing or double-barreled questions were excluded. Even so, the questionnaire was not fully validated as other steps of validation were not done. A score was given at the end of each questionnaire, and the change in this score was monitored for each patient at the different time points during the study period (baseline, two weeks, four weeks, and six weeks). To ensure consistency in reporting of symptoms, an attempt was made by the investigators to fill the questionnaire with the same parent/caretaker at each of the time points (preferably by the parent most involved in the patient's daily care).

Once the baseline questionnaire was completed, the patient was randomized to receive either pyridoxine or placebo (see below for details on treatment). To monitor the response to treatment, the family was re-contacted by phone at two, four, and six weeks after initiation of the placebo or pyridoxine, and the behavioral checklist was filled at each time.

Patients, their families, their primary neurologists, as well as the investigators were all unaware of the treatment arm. The clinical pharmacist who dispensed the pyridoxine or the placebo was the only unblinded team member. This individual was involved neither in the data collection nor in the data analysis. Subjects were randomized in a 1:1 ratio by the pharmacist to receive either pyridoxine or placebo using a computer-generated scheme.

Study objectives

Primary

To determine whether pyridoxine can reverse or ameliorate the behavioral side effects caused by levetiracetam in children with epilepsy between the age one and 17 years.

Secondary

1. To determine the time it takes for improvement to be noted in patients who do respond favorably to pyridoxine.
2. To assess the side effects and tolerability of pyridoxine supplementation.

Treatment arms

Patients were randomized into two treatment arms, pyridoxine or placebo. Patients randomized to the pyridoxine group received pyridoxine starting at a dose of 10 mg/kg/day given once a day (minimum of 50 mg and maximum of 200 mg); this was prepared

Evaluation time point: ☐ Baseline ☐ 2 weeks ☐ 4 weeks ☐ 6 weeks

Instructions: Check each item in the list and decide whether it applies to the above child's behavior.

Put (x) on the correct box: 1 Never 2 Sometimes 3 Always

	Behavior	1	2	3
1	Sad – Unhappy			
2	Rapidly shifts between happy and sad			
3	Withdrawn			
4	Screaming			
5	Sensitive (feelings easily get hurt)			
6	Aggressive/Violent			
7	Abusive			
8	Crying often			
9	Can't sit still/ restless			
10	Nervous, tense			
11	Disobedient/Oppositional			
12	Unco-operative			
13	Interrupts/impulsive			
14	Destructive behavior (throws things, destroys things)			
15	Doesn't get along with other children (including siblings)/Fights with other			
16	Does not want to play or have fun			
17	Temper tantrums			
18	Self-mutilatory behavior (bites nails, pulls hair, hurts himself)			
19	Diurnal enuresis			
20	Nocturnal enuresis			
21	Doesn't want to sleep alone or refuses to go to bed			
22	Has trouble falling asleep			
23	Decreased or interrupted sleep			
24	Nightmares			
25	Restless sleep			
26	Doesn't eat well			
27	Eats things that are not edible			
28	Overeating			
29	Expresses wish to end his/her own life			
30	Please indicate any problem the child has that was not listed above:			
Final Score (maximum 90)				

FIGURE. Behavioral checklist questionnaire.

by dissolving 40 mg pyridoxine tablets in water and prescribing the appropriate volume based on the patient's weight. If at the two-week reassessment there was <50% improvement in the behavioral checklist score, the patient was advised to increase the volume by 1.5 times (15 mg/kg/day, maximum of 200 mg).

To avoid the high costs of designing a true placebo to pyridoxine, it was opted to use homeopathic doses of pyridoxine (0.5 mg/kg/day) and to consider those receiving them as the placebo group. The placebo was prescribed at a dose diluted to one-twentieth of what the patient would have received in the pyridoxine group. Neither the treating physician nor the parents knew whether they were receiving the effective (10 to 15 mg/kg/day) or homeopathic dose (0.5 mg/kg/day) of pyridoxine. Similar to the pyridoxine group, the family was instructed to increase the dose by 1.5 times when there

was no response after two weeks. To ensure stability of the compound, all patients were instructed to store the medication at below 25°C.[20]

Rationale for pyridoxine dosing

The optimal dose of pyridoxine needed for reversing the psychiatric side effects of levetiracetam is unknown. In the pediatric study by Major et al.,[16] the average daily dose of pyridoxine was 6 mg/kg/day (range 4 to 10 mg/kg/day and up to 200 mg), whereas in the adult study by Taoufik et al.,[18] the average dose of pyridoxine was 50 mg/day (range 50 to 100 mg/day). In the treatment of pyridoxine-dependent epilepsy, a dose of 50 to 100 mg intravenous or a maintenance dose of 15 to 30 mg/kg/day is usually effective in controlling seizures.[21]

As such, in this pediatric study, a starting dose of 10 mg/kg/day was used and as mentioned earlier, it increased to 15 mg/kg/day if there was less than 50% improvement in the behavioral score at the two weeks' follow-up. The total given dose never exceeded 200 mg.

Monitoring for adverse events

Pyridoxine is a relatively safe vitamin and is only known to cause a painful sensory neuropathy when used at very high doses (>1000 mg/day).[22,23] Although these doses are more than five times the highest dose that was used in this study, patients were monitored for potential side effects at each study time period (two, four, and six weeks). Furthermore, patients were instructed to visit the emergency room directly or to communicate with the research team by phone for any suspected adverse reactions in between the aforementioned time points. No patients withdrew from the study because of reported adverse events.

Study sample size

Using PASS software (parameters of $\alpha = 0.05$, two-sided hypothesis, testing proportions in a repeated measure design), it was calculated that a sample size of 61 per arm is required to achieve 80% power to detect an effect size of 30% (which corresponds to an odds ratio of 1.7) in a design with four repeated measurements. To account for possible dropouts, attempts were made to enroll 134 patients based on expected attrition rate of 10%. However, due to COVID-19 and the difficulties with recruiting patients during the pandemic, the study was terminated prematurely at 105 patients, which was still considered statistically justifiable.

Results

A total of 105 patients were recruited into this randomized control trial. The majority of patients were male (65.62%) and between the age two and 10 years (71 of 105, 68%). Patients were subsequently randomized into the placebo (59.56%) and pyridoxine (46.44%) groups. There was no statistical difference between the two groups with respect to the distribution of patients based on age (mean age of 85.6 ± 45.45 months in the placebo group and 95.24 ± 46.26 months in the pyridoxine group, $P > 0.05$) or weight (mean weight of 25.1 ± 13.1 kg in the placebo group and 27.05 ± 17.2 kg in the pyridoxine group, $P > 0.05$). The average maintenance dose of levetiracetam was statistically higher ($P < 0.05$) in the pyridoxine group (44 ± 17.9 mg/kg/day) when compared with the placebo group (37 ± 20 mg/kg/day). As expected, the dose of pyridoxine was significantly higher ($P = 0.001$) in the pyridoxine group (197.2 mg/day) when compared with the placebo group (18.88 mg/day) (Table 1).

The reduction of neuropsychiatric symptoms in patients in the placebo and pyridoxine groups was monitored using the behavioral symptoms questionnaire (Fig). For each patient, a cumulative score was obtained initially at baseline and subsequently at each time point after the randomization into the two treatment arms (two, four, and six weeks). For each patient, the total score at each time point was compared with the baseline score to determine what changes in behavioral symptoms occurred. At baseline, there was no statistical difference in the mean behavioral scores between the placebo (42.2 ± 10.3) and the pyridoxine group (46.4 ± 11.6). For the placebo group, the reduction in behavioral symptoms was approximately 4%, 5%, and 6% at two, four, and six weeks. In the pyridoxine group, the reduction in behavioral symptoms was approximately 8%, 10%, and 11% at two, four, and six weeks, respectively (Table 2). Although patients in both placebo and pyridoxine groups experienced a statistical reduction ($P < 0.05$) in behavioral scores when compared with baseline, the relative reduction in symptoms was almost double in the pyridoxine group when compared with the placebo group (1.9 at two weeks, 2.0 at four weeks, and 1.8 at six weeks), which was statistically significant with a P value of 0.001 (Table 3).

To determine whether the reduction in behavioral scores persisted, the questionnaire was repeated at six months after study entry. In both groups, the relative reduction in behavioral scores improved at each time point and persisted even up to six months, although this was more notable in the pyridoxine group (8% in the placebo group and 12% in the pyridoxine group) (Table 2).

A one-way ANOVA was used to determine whether the effectiveness of pyridoxine was age dependent and whether it varied

TABLE 1.
Patient Demographics and Drug Doses

Categorical Variables	Overall N = 105	Placebo Group N = 59	Pyridoxine Group N = 46	*P* Value
Gender				
Male	65 (62%)	36 (61%)	29 (63%)	
Female	40 (38%)	23 (39%)	17 (37%)	
Age group				
Average age (months)	89.81 (±45.84)	85.58 (±45.45)	95.24 (±46.26)	0.286
2 years or less	7 (6.7%)	4 (6.8%)	3 (6.5%)	
2 to 6 years	33 (31.4%)	20 (33.9%)	13 (28.3%)	
>6 to 10 years	38 (36.2%)	21 (35.6%)	17 (37%)	
>10 to 17 years	27 (25.7%)	14 (23.7%)	13 (28.3%)	
Weight (kg)	25.94 ± 14.99	25.07 ± 13.15	27.05 ± 17.17	0.505
Levetiracetam dose (mg/kg/day)	40.19 ± 19.34	37.19 ± 20.01	44.04 ± 17.92	0.001*
Pyridoxine dose (mg/day)	96.96 ± 89.41	18.88 ± 9.86	197.2 ± 8.36	0.001*

Values were reported as mean ± S.D.
* $P < 0.05$ denotes statistical significance.

TABLE 2.
Effect of Pyridoxine Supplementation on Levetiracetam-Induced Neuropsychiatric Symptoms at Different Time Points

Treatment	Time Period	Mean Behavioral Score (±S.D.)	% Mean Reduction in Behavioral Score From Baseline	T	df	*P* Value
Placebo group (n = 59)	2 wks	40.34 (±9.83)	4.38	2.33	58	0.023*
	4 wks	39.93 (±9.83)	5.33	3.02	58	0.004*
	6 wks	39.56 (±10.31)	6.23	3.08	58	0.003*
	6 mo	38.86 (±10.58)	7.87	3.64	58	0.001*
Pyridoxine group (n = 46)	2 wks	42.54 (±10.88)	8.26	3.24	45	0.002*
	4 wks	41.50 (±11.15)	10.50	3.97	45	0.001*
	6 wks	41.24 (±11.30)	11.06	3.89	45	0.001*
	6 mo	40.87 (±11.44)	11.86	3.98	45	0.001*

Values are reported as mean ± S.D. and analyzed by paired *t* test.
* $P < 0.05$ denotes statistical significance.

across various age groups. As illustrated in Table 4, there was no statistical difference in pyridoxine effectiveness per different age groups (*P* values > 0.05) within a 95% confidence level.

Adverse events were reported in 4% (two of 46) patients in the pyridoxine group in the form of transient nausea that occurred at the beginning of treatment and later subsided spontaneously with no interventions. No other adverse events were reported, and no patients withdrew from the study.

Discussion

Levetiracetam is an efficacious antiseizure drug that has gained popularity over the past few years for the treatment of seizures in children due to its favorable side effect profile as well as its availability in both oral and intravenous formulations. Nevertheless, its neuropsychiatric side effects, seen in up to 13% of pediatric patients, can often lead to its discontinuation.[12-15] In this study, we demonstrate that the concomitant use of supplemental pyridoxine can mitigate some of these behavioral side effects. This is the first double-blind randomized placebo-controlled trial showing that supplementation of pyridoxine in children with levetiracetam-induced neuropsychiatric symptoms leads to up to a 12% reduction in behavioral symptoms. This beneficial effect was similar across the pediatric age groups.

Our results are in accordance with anecdotal evidence from case reports and retrospective chart reviews in both children and adults, suggesting a beneficial effect of pyridoxine in treating the neuropsychiatric side effects of levetiracetam.[16,18] Similar to these studies, the beneficial effect was noted as early as two weeks after initiation of treatment. In contrast to those studies, however, the extent of reduction of behavioral symptoms noted in our study was lower. Major et al. found that 41% (n = 22 patients) children who developed behavioral side effects after starting levetiracetam had a significant improvement in their symptoms,[16] whereas in adults, pyridoxine relieved symptoms of agitation and irritability in 66.6% (n = 34) of patients who developed these symptoms after taking levetiracetam.[18] A number of observations can explain this difference. For one, both studies were retrospective chart reviews and were not placebo controlled, and as such did not account for a placebo effect. As noted in this study, even patients in the placebo group had a marginal, yet statistically significant improvement in their behavioral symptoms, indicating the presence of a placebo effect. Second, the number of patients reviewed in both studies was smaller compared with our present study.

Pyridoxine is a water-soluble vitamin that acts as a cofactor in a multitude of enzymatic reactions including those involved in the biosynthesis and breakdown of neurotransmitter synthesis.[22] The beneficial effects of pyridoxine have not only been confirmed in the treatment of genetic causes of pyridoxine-dependent epilepsy[21] but also been suggested in some other medical conditions including in the treatment of emesis in hyperemesis gravidarum[22] and premenstrual syndrome.[24] Furthermore, in one study, pyridoxine was found to be better than placebo for treating hyperkinetic symptoms in a subgroup of patients with attention-deficit/hyperactive disorder,[25] and its potential role in the treatment of hyperactivity has also been proposed.[26] Nevertheless, the mechanism by which pyridoxine may mitigate the neuropsychiatric side effects of levetiracetam has not been established. There is no evidence from the literature that pyridoxine interacts, either directly or indirectly, with levetiracetam. Furthermore, although pyridoxine deficiency has been shown to occur in enzyme-inducing antiepileptic drugs, this is not the case for nonenzyme inducers such as levetiracetam.[27]

Although the dose of pyridoxine needed to treat pyridoxine-dependent seizures is well established at 30 mg/kg/day,[20] the optimal dose needed to reverse the neuropsychiatric side effects of levetiracetam is less clear. In the pediatric study by Major et al.,[16] the average daily dose of pyridoxine was 6 mg/kg/day (and up to 200 mg), whereas in the adult study by Taoufik et al.[18] the average dose of pyridoxine was 50 mg/day (range 50 to 100 mg/day). At these doses, pyridoxine is relatively safe because toxicity has only been established at doses exceeding 1000 mg/day, at which point pyridoxine is known to cause a painful sensory neuropathy.[22,23] In our present study, patients in the pyridoxine group received a starting dose of 10 mg/kg/day, which was increased to 15 mg/kg/day in the majority of patients, with the mean average dose reaching 197.2 mg/day in this group. Due to the unavailability of a true placebo, patients in the placebo group in our study received 0.5 mg/kg/day of pyridoxine (mean dose of 18.88 mg/day). Although this dose is considered low, it cannot be ruled out with

TABLE 3.
Comparison of Difference* in Effect Sizes Between the Placebo and the Pyridoxine Groups

	Mean	S.D.	Standard Error of Mean	95% Confidence Interval of the Difference		T	df	*P* Value
				Lower	Upper			
Effect size of pyridoxine-effect size of the placebo	0.178	0.0238	0.0119	0.140	0.216	14.9	3	0.001

* Despite the fact that the placebo had a significant effect in amelioration of the mentioned behavioral side effects, still the therapeutic dose was superior and had statistically significant superiority regarding this amelioration effect.

TABLE 4.
Comparison of Pyridoxine Effectiveness According to the Age Group

	N	Mean	SD	95% CI for Mean		F	df	*P* Value
				Lower Bound	Upper Bound			
Baseline								
2 years or less	3	40.00	2.65	33.427589	46.572411			
2 to 6 years	13	51.31	13.98	42.856990	59.758395			
>6 to 10 years	17	47.82	10.38	42.488855	53.158204	2.265	3	0.095
>10 to 17 years	13	41.00	9.87	35.038177	46.961823			
2 Weeks								
2 years or less	3	38.00	4.58	26.6163	49.3837			
2 to 6 years	13	48.54	14.27	39.9123	57.1646			
>6 to 10 years	17	41.12	9.01	36.4871	45.7482	2.073	3	0.118
>10 to 17 years	13	39.46	8.44	34.3600	44.5631			
4 Weeks								
2 years or less	3	37.00	6.25	21.4866	52.5134			
2 to 6 years	13	46.31	15.24	37.0955	55.5199	1.241	3	0.307
>6 to 10 years	17	40.47	9.15	35.7684	45.1728			
>10 to 17 years	13	39.08	8.82	33.7487	44.4051			
6 Weeks								
2 years or less	3	37.00	6.25	21.4866	52.5134			
2 to 6 years	13	44.38	13.90	35.9875	52.7817			
>6 to 10 years	17	41.29	11.90	35.1760	47.4122	0.631	3	0.599
>10 to 17 years	13	39.00	8.36	33.9441	44.0559			
6 Months								
2 years or less	3	37.00	6.25	21.4866	52.5134			
2 to 6 years	13	43.46	14.57	34.6573	52.2658	0.809	3	0.496
>6 to 10 years	17	42.24	12.01	36.0587	48.4119			
>10 to 17 years	13	37.39	7.29	32.9816	41.7877			

Abbreviation:
CI = Confidence interval
Values are reported as mean ± S.D. and analyzed by one way-ANOVA test. Statistically significant ($P < 0.05$).

certainty that pyridoxine at this dose did not exhibit a physiologic effect that may have explained the lower yet statistically significant reduction in behavioral symptoms noted in the placebo group.

One of the secondary objectives of this study was to determine whether use of pyridoxine to mitigate the side effects of levetiracetam had any significant adverse side effects. It is well established that at doses exceeding 1000 mg/day pyridoxine can cause a painful sensory neuropathy.[22,23] In the study by Major et al., in which pyridoxine was used at a dose of 6 mg/kg/day (and up to 200 mg), 18% of patients reported an increase in their seizure frequency, although the exact relation of this observation to pyridoxine supplementation was unclear.[16] In our study, no major adverse events were reported, and no patients reported an increase in their seizure frequency. Minor adverse events were reported in two patients (4%) in the pyridoxine group in the form of mild transient nausea that occurred at the initiation of the treatment and did not result in withdrawal of the patient from the study. Overall, this indicates that at the doses used in this study of up to 15 mg/kg/day (maximum 200 mg), pyridoxine is relatively safe.

One of the limitations of this study is the absence of a true placebo group. Although the dose of pyridoxine in the placebo group was considered low, as discussed above, the absence of a possible physiological effect that could possibly explain the beneficial reduction in behavioral symptoms noted even at this dose cannot be ruled out with certainty. Nevertheless, the findings of this study clearly demonstrate that at higher doses, the reduction in levetiracetam-induced behavioral symptoms were more prominent and almost double in the pyridoxine group. Another limitation is that the questionnaire used in the study was not fully validated. Further studies are needed to determine whether this beneficial mitigation of levetiracetam-induced neuropsychiatric side effects by pyridoxine is dose-dependent and more prominent at higher doses of pyridoxine (more than 200 mg) used within the safety margin.

Conclusions

This is the first double-blind placebo-controlled study showing a beneficial use of pyridoxine in epileptic children with levetiracetam-induced neuropsychiatric side effects. These results can guide physicians to attempt a trial of pyridoxine supplementation and avoid unnecessary discontinuation of levetiracetam especially in patients whose seizures are well controlled on this antiseizure drug but who have experienced behavioral side effects because of it.

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