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Original article

Efficacy and safety of pyridoxal in West syndrome: A retrospective study

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Abstract

Objective: To evaluate the efficacy and safety of pyridoxal for treating West syndrome.

Methods: We retrospectively investigated pyridoxal's efficacy and safety in 117 patients with West syndrome at Saitama Children's Medical Center from July 1993 to May 2016. Pyridoxal was administered at doses of 10–50 mg/kg/day. We evaluated seizure outcomes and electroencephalographic findings at 4 weeks after pyridoxal therapy. The responders were those with complete cessation of spasms for more than 4 weeks and those with resolution of hypsarrhythmia on EEG at 1–4 weeks after pyridoxal therapy.

Results: Five of the 117 patients (4.3%) were responders. The median duration between pyridoxal therapy to spasm cessation was 6 (5–13) days. Among the responders, four had hypsarrhythmia resolution, no spasm relapse, and no other seizure types more than 2 years after pyridoxal therapy. One responder had partial seizures and spasm relapse. No serious adverse effects occurred. There were no significant differences in sex, etiologies, complication, other seizure types preceding the spasms, onset age of spasms, age of pyridoxal therapy, treatment lag, initial and maintenance doses of pyridoxal, and adverse effects between pyridoxal responders and non-responders.

Conclusions: The efficacy rate of pyridoxal monotherapy as first-line treatment for West syndrome was low. However, pyridoxal therapy showed a rapid response within 1 week and was safe. We consider pyridoxal therapy as a kind of challenge therapy during the evaluation period concerning differential diagnosis and etiologies of West syndrome and immunological risks before adrenocorticotrophic hormone therapy or vigabatrin therapy.

Keywords: Adverse effects; Hypsarrhythmia; Spasms; Vitamin B6 therapy

1. Introduction

West syndrome is an age-related epilepsy during infancy; it is characterized by epileptic spasms in clusters and a peculiar interictal electroencephalographic pattern of hypsarrhythmia. Patients with West syndrome generally have severe developmental issues. The American Academy of Neurology and the Practice Committee of the Child Neurology Society recommends

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adrenocorticotropic hormone (ACTH) and vigabatrin (VGB), which has proven efficacy, as the first-line treatment of West syndrome [1]. ACTH is widely used to treat patients with West syndrome; however, sometimes, serious adverse effects occur, such as infection, subdural hematoma, hypertension, and electrolyte disturbances, resulting in extended hospital stays and considerable costs. VGB was reported to be as effective as ACTH and even better tolerated [2]. However, it increases the risk of irreversible visual field loss. Some reports have shown that oral vitamin B6 therapy (pyridoxal or pyridoxine) is effective in West syndrome without severe adverse effects [3–6]. Pyridoxine challenge was used for new-onset epileptic spasms in the United States: the spasms were treated with intravenous pyridoxine with electroencephalography (EEG) monitoring [7]. Pyridoxal was more effective than pyridoxine in patients with idiopathic intractable epilepsy including epileptic spasms [8]. Patients with West syndrome are commonly treated with pyridoxal therapy instead of intravenous vitamin B6 as the first-line treatment in Japan [9], probably to avoid serious irreversible effects such as severe infections, subdural hematoma, and visual field loss due to ACTH or VGB. Both the detailed mechanisms of action of pyridoxal and the characteristics of responders to vitamin B6 are unknown. The features that can predict the seizure outcomes may help pediatric neurologists to choose the appropriate treatment at an appropriate time. Therefore, we investigated the efficacy and safety of pyridoxal monotherapy in the treatment of West syndrome.

2. Methods

We retrospectively investigated the efficacy and safety of pyridoxal monotherapy in 117 patients with West syndrome at Saitama Children's Medical Center from July 1993 to May 2016. The diagnosis of West syndrome was confirmed by clusters of epileptic spasms with onset before the age of 2 years and hypsarrhythmia on EEG. We included patients who met the following criteria in this study: onset age of spasms was less than 2 years; age of start of pyridoxal therapy was less than 2 years; and no history of treatment with ACTH therapy, VGB, intravenous immunoglobulin therapy, and other anti-epileptic drugs before pyridoxal therapy. We excluded patients who were followed up for less than 2 years after pyridoxal therapy. The results of neurologic examinations were evaluated for all patients. Brain magnetic resonance imaging was performed in 116 patients, and computed tomography were performed in one patient. EEG findings of all patients were evaluated before pyridoxal therapy and at 1–4 weeks after pyridoxal therapy. EEG follow-ups were performed more than once in 6 months for 2 years after pyridoxal therapy. In all cases, EEG was recorded for more than 60 min, including both the states of wakefulness and sleep. Information regarding seizures including spasm relapse and occurrence of other types of seizures was obtained from parents or caregivers, every 1–3 months for the first-year follow-up and every 3–6 months after pyridoxal therapy.

All patients were treated with pyridoxal at a single center. Pyridoxal (10–50 mg/kg/day) was administered for 1 week. If pyridoxal therapy decreased the clusters of spasms within 1 week, pyridoxal was continued for another 1 week. If pyridoxal therapy failed to suppress spasms within 2 weeks of administration, ACTH, another anti-epileptic drug, or intravenous immunoglobulin was started.

2.1. Etiologies

Cryptogenic West syndrome was defined according to the following criteria: 1) normal pregnancy, normal development, and no eventful history, including no other types of seizures before the onset of the spasms, 2) no focal abnormalities on neurological examination, and 3) normal brain computed tomography images and/or magnetic resonance imaging. Symptomatic West syndrome was defined based on other factors.

2.2. Outcomes

We evaluated seizure outcomes at 4 weeks after pyridoxal therapy. Responders were defined as follows: 1) patients with complete cessation of spasms for more than 4 weeks after pyridoxal therapy and 2) patients with resolution of hypsarrhythmia on EEG at 1–4 weeks after pyridoxal therapy. We compared sex, etiologies, complications, other type of seizures preceding the spasms, onset age of spasms, age at which pyridoxal therapy was started, treatment lag, initial and maintenance doses of pyridoxal, and adverse effects between pyridoxal responders and non-responders.

Intelligence quotient (IQ) and developmental quotient (DQ) were evaluated using the Wechsler Intelligence Scale for Children Ⅳ or Enjoji Scale of Infant Analytical Development in Japanese at the age of 4 to 7 years in pyridoxal responders by using the following criteria: normal intelligence, IQ & DQ $\geq$ 75; mild intellectual disability, IQ & DQ $\geq$ 50 and IQ & DQ $<$ 75; moderate intellectual disability, IQ & DQ $\geq$ 25 and IQ & DQ $<$ 50; and severe intellectual disability, IQ & DQ $<$ 25.

This study was approved by the Saitama Children Medical Center Institutional Review Board (2014-04-010).

2.3. Statistical analyses

Mann-Whitney U and Fisher's exact tests were applied for statistical analysis using statistical software IBM SPSS Statistics 19. A p-value of 0.05 or less was considered to indicate a statistically significant difference.

3. Results

One hundred and seventeen patients (male, 62, cryptogenic, 28) were treated with pyridoxal therapy. Motor impairment and intellectual disability were noted in 84/117 (71.8%) and 84/117 (71.8%) patients, respectively. Other types of seizures preceded the spasms in seven patients, who were treated with the following antiepileptic drugs: phenobarbital (n = 2), valproate (n = 2), phenytoin (n = 1), combination therapy of valproate and levetiracetam (n = 1), and combination therapy of phenobarbital, valproate, and topiramate (n = 1). The median age at the onset of spasms was 5.0 months, for the range of 1–18 months. The median age at which pyridoxal therapy was started was 6.0 months, with a range of 2 to 23 months. The median treatment lag between the onset of spasms and pyridoxal therapy was 21 days, with a range of 2–345 days. The median initial dose of pyridoxal was 30 mg/kg/day, with a range of 10–50 mg/kg/day. The median maintenance dose of pyridoxal was 50 mg/kg/day, with a range of 10–50 mg/kg/day. All patients were followed up for more than 2 years except for four patients who died. The median duration of follow-up was 92 months, with a range of 2–232 months.

Five of the 117 patients were (4.3%) classified as responders to pyridoxal therapy. Table 1 shows the characteristics of the responders. The median duration between pyridoxal therapy and the cessation of spasms was 6 (range: 5–13) days. Among the five responders, four were administered maintenance treatment with pyridoxal for 3–33 months. Four patients had no relapse of spasms, no other types of seizures, and resolution of hypsarrhythmia more than 2 years after pyridoxal therapy. Patient 3 presented elevation in aspartate aminotransferase and alanine aminotransferase activities with pyridoxal 50 mg/kg/day; therefore, pyridoxal was discontinued on the 10th day of pyridoxal therapy. The aspartate aminotransferase and alanine aminotransferase activities decreased after discontinuation of pyridoxal therapy. The patient had focal motor seizures at the age of 8 months, which were treated with valproate. The frequency of focal motor seizures decreased thereafter. He also had relapse of spasms at the age of 1 year, and the spasms disappeared with levetiracetam treatment. One cryptogenic patient (Patient 1) showed normal intelligence. The other patients had moderate to severe intellectual disability. Among the 112 pyridoxal

Table 1
Clinical data of responder to pyridoxal therapy.

Patient	Etiology	Onset age of spasms (m)	Treatment lag (d)	Pyridoxal therapy				Outcomes		
				Duration between pyridoxal therapy and cessation of spasms (d)	Initial doses (mg/kg/d)	Maintenance doses (mg/kg/d)	Treatment duration	Relapse (cessation duration of spasms)	Other types of seizures (onset age)	Developmental outcomes
1	Cryptogenic	5	15	5	30	50	31 m	–	–	normal
2	PVL	10	16	6	30	50	33 m	–	–	moderate
3	Cerebral atrophy	4	76	6	30	50	10 d	+ (5 m)	+ (8 m)*	severe
4	Cryptogenic	6	23	12	20	30	55 m	–	–	severe
5	Down syndrome	7	15	13	20	50	3 m	–	–	severe

d, day; m, month; PVL, periventricular leukomalacia.
* Focal motor seizures.

non-responders, 71 (63.4%) patients were treated with ACTH therapy or intravenous immunoglobulin within 2 weeks after first pyridoxal administration. It took more than 2 weeks to start the next treatment from pyridoxal administration in 41 patients: these patients failed prompt induction of subsequent therapy due to infection, elevation in aspartate aminotransferase and alanine aminotransferase activities, delay of EEG evaluation, and coordination of re-admission schedule.

We compared sex, etiologies, complications, other types of seizures preceding the spasms, onset age of spasms, age of start of pyridoxal therapy, treatment lag, initial and maintenance doses of pyridoxal, and adverse effects between responders (n = 5) and non-responders (n = 112) (Table 2). There were no significant differences in sex, etiologies, complications, other types of seizures preceding the spasms, onset age of spasms, age of pyridoxal therapy, treatment lag, initial and maintenance doses of pyridoxal, and adverse effects between pyridoxal responders and non-responders.

The rate of adverse effects was 23.1% (27/117): poor sucking, elevation in aspartate aminotransferase and alanine aminotransferase activities, and vomiting were noted in one, five, and 21 patients, respectively. Nineteen patients could not reach the maximum dose of pyridoxal due to adverse effects. These adverse effects resolved after the discontinuation of pyridoxal. No serious adverse effects were noted.

4. Discussion

To our knowledge, this is the first study of pyridoxal monotherapy as the first-line treatment for West syndrome in many patients. Pyridoxal was effective in 4.3% of patients with West syndrome in our study. Table 3 shows the efficacy of vitamin B6 therapy for West syndrome in previous studies [3–6]. Ohtsuka et al. reported complete cessation of spasms due to pyridoxal therapy in 13.9% of patients [5]. The efficacy of pyridoxal therapy in our study was lower than that in the previous study. Pyridoxal was administered as a monotherapy for West syndrome in our study, while in the previous study, pyridoxal monotherapy and pyridoxal were administered as an add-on therapy to other agents. Furthermore, the authors did not describe the number of patients who were treated with pyridoxal as monotherapy or as an add-on therapy. Our study demonstrated that pyridoxal monotherapy is rarely effective as the first-line treatment in West syndrome. This is the most reliable information pertaining to the application of pyridoxal therapy for West syndrome.

The median duration between pyridoxal therapy and cessation of spasms was 6 (5–13) days in 5 out of the 117 patients of our study. Ohtsuka et al. showed that pyridoxal therapy suppressed spasms within 16 days [10]; their results are similar to those of our study. Among the five responders, three responders had cessation of spasms within 1 week of pyridoxal administration, and they continued to exhibit cessation of spasms for more than 4 weeks (Table 1). Pyridoxal therapy produced a more rapid response compared with those produced by benzodiazepines or valproate, which suppressed spasms after a few weeks [11,12]. We can evaluate the efficacy of pyridoxal therapy within 1 week. When newly suspected cases of with West syndrome are encountered, we should evaluate the findings of ictal and interictal EEG, brain magnetic resonance imaging, blood tests, immunological status, cerebrospinal fluid test, electroretinography, urine test, and screening of congenital infection including infection with cytomegalovirus during several days before ACTH therapy and VGB therapy. We recommend that the patients should be treated with pyridoxal therapy as the first-line treatment during this period before ACTH therapy and VGB therapy. ACTH therapy or VGB therapy should be started when pyridoxal therapy does not suppress the clusters of spasms within 1 week of pyridoxal administration.

Table 2
Comparison between responders and non-responders to pyridoxal therapy.

		Responders n = 5	Non-responders n = 112	*p*
Sex (Male, Female)		3:2	59:53	n.s.
Etiology	Cryptogenic	2	26	n.s.
	Symptomatic	3	86	
Complication	Motor impairment	3	81	n.s.
	Intellectual disability	3	81	n.s.
Other types of seizures preceding the spasms		0	15	n.s.
Onset age of spasms (m)	median (range)	6 (4–10)	5 (1–18)	n.s.
Age of pyridoxal therapy (m)	median (range)	6 (5–10)	6 (2–23)	n.s.
Treatment lag (d)	median (range)	16 (15–76)	21 (2–345)	n.s.
Initial doses of pyridoxal (mg/kg/d)	median (range)	30 (20–30)	30 (10–50)	n.s.
Maintenance doses of pyridoxal (mg/kg/d)	median (range)	50 (30–50)	50 (10–50)	n.s.
Adverse effects	n (%)	1 (20%)	26 (23.2%)	n.s.

d, day; m, month; n.s., not statistically significant.

Table 3
Previous studies of vitamin B6 therapy for West syndrome.

Author	Patients (n)	Onset age of spasms (m)	Age of vitamin B6 therapy (m, range)	Doses of vitamin B6 therapy (mg/kg/d)	Therapeutic method	Complete cessation of spasms	Duration between vitamin B6 therapy and cessation of spasms	Adverse effects
Pietz et al (1993)	17	7.2	NA	Pyridoxine	Monotherapy	5/17 (29.4%)	<4 w	Loss of appetite 12 (70.6%)
	Cryptogenic 4	(2.5–13.0)		Initial dose 100		Cryptogenic 0/4 (0%)		Restlessness 10 (58.8%)
	Symptomatic 13			Maintenance dose 300		Symptomatic 5/13 (38.5%)		Vomiting 8 (47.1%)
								Diarrhea 6 (35.3%)
								Constipation 5 (29.4%)
								Aphaty 5 (29.4%)
Ito et al (1991)	13	6.0	NA	Pyridoxine	Monotherapy	1/13 (7.7%)	NA	None
	Cryptogenic 1	(1.0–10.0)		Initial dose 10–20		Cryptogenic 0/1 (0%)		
	Symptomatic 10			Maintenance dose 20–50		Symptomatic 1/10 (10.0%)		
	unknown 2					Unknown 0/2 (0%)		
Ohtsuka et al (2000)	216	NA	2.0–12.0	Pyridoxal	Monotherapy, add-on therapy	30/216 (13.9%)	<20 d	NA
	Cryptogenic 25			30–400 mg/day		Cryptogenic 8/25 (32.0%)		
	Symptomatic 191					Symptomatic 22/191 (11.5%)		
Toribe et al (2001)	50	NA	NA	Pyridoxal	NA	6/50 (12.0%)	<2 w	42%
	Cryptogenic 5			Initial dose 20–30		Cryptogenic 0/5 (0%)		
	Symptomatic 45			Maintenance dose 40–50		Symptomatic 6/45 (13.3%)		
Present study	117	5.0	6.0	Pyridoxal	Monotherapy	5/117 (4.3%)	6 (5–13) d	Vomiting 21 (17.9%)
	Cryptogenic 28	(1.0–18.0)	(2.0–23.0)	10–50		Cryptogenic 2/28 (7.1%)		Elevation in AST and ALT 5 (4.3%)
	Symptomatic 89					Symptomatic 3/89 (3.4%)		Poor sucking 1 (1.0%)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; d, day; m, month; NA, not available from literature study.

One cryptogenic patient who responded to pyridoxal in the early phase showed normal intelligence in our study. Ohtsuka et al. reported that all eight of the cryptogenic patients who had complete cessation of spasms had normal to borderline intelligence [5]. Cryptogenic patients who showed complete cessation of spasms with effective therapy in early phases had favorable developmental outcomes [13,14]. Complete cessation in cryptogenic patients and in early phases may be related to favorable developmental outcomes after pyridoxal therapy.

Pyridoxal doses did not significantly differ between responders and non-responders. An appropriate dose of pyridoxal had not been determined. Ohtsuka et al. demonstrated that pyridoxal could be administered at 30–400 mg/day without serious adverse effects [5]. All responders in our study showed complete remission of spasms after the pyridoxal dose was increased to 30–50 mg/kg/day. Pyridoxal therapy may show dose-dependent responses. Further investigation is therefore required to determine the appropriate doses of pyridoxal.

The main adverse effects in our study were vomiting and elevation in aspartate aminotransferase and alanine aminotransferase activities, which resolved after the discontinuation of pyridoxal. No irreversible adverse effects occurred in our study. Previous studies also demonstrated no serious adverse effects (Table 3). ACTH therapy caused infection in 14% of the patients [15], and subdural hematoma occurred despite the use of a low dose [16]. Pyridoxal therapy is safe and we recommend it for patients with severe brain atrophy or an immunocompromised state.

The detailed action mechanisms of pyridoxal in West syndrome are still unknown. Pyridoxal 5′ phosphate is an active form of vitamin B6. This is a cofactor that converts glutamic acid to gamma aminobutyric acid in the central nervous system. Pyridoxal phosphate-dependent seizures are caused by deficiency in the enzyme pyridoxine 5′ phosphate oxidase (PNPO). The level of pyridoxal 5′ phosphate in patients with PNPO mutations was lower than that in the controls [17]. Some patients with PNPO mutations responded to pyridoxal therapy [18]. Pyridoxal might modify neuronal function of gamma aminobutyric acid in patients with West syndrome. Further investigation is required to elucidate the action mechanisms of pyridoxal.

A limitation of our study is that the EEG of all patients was not evaluated at 1 week after pyridoxal therapy. When pyridoxal was administered on admission, we evaluated the EEG every week. However, when pyridoxal was administered during outpatient visit, the EEG was not conducted promptly at our centre except for the first visit. It takes 2–4 weeks from booking to performing an EEG. Therefore, patients wait for approximately 1–4 weeks after pyridoxal therapy for EEG.

5. Conclusions

This study demonstrated pyridoxal monotherapy has a low efficacy rate when used for treating West syndrome. However, pyridoxal therapy showed a rapid response within 1 week of treatment, and it was safe. We consider pyridoxal therapy as a type of challenge therapy during evaluation period concerning the differential diagnosis for and etiologies of West syndrome and immunological risks before ACTH therapy or VGB therapy. Our study provides the most reliable information pertaining to pyridoxal therapy for West syndrome.

6. Declarations of interest

None.

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