ORIGINAL ARTICLE

# Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy

**H-S Wang, M-F Kuo, M-L Chou, P-C Hung, K-L Lin, M-Y Hsieh, M-Y Chang**

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See end of article for authors' affiliations

Correspondence to: Dr M-F Kuo, Division of (Pediatric) Neurosurgery, Department of Surgery, National Taiwan University Hospital, 7 Chung-Shan S. Road, Taipei 100, Taiwan; wanghs444@cgmh.org.tw

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**Aim:** To study the difference between pyridoxine (PN) and its active form, pyridoxal phosphate, (PLP) in control of idiopathic intractable epilepsy in children.

**Methods:** Among 574 children with active epilepsy, 94 (aged 8 months to 15 years) were diagnosed with idiopathic intractable epilepsy for more than six months. All received intravenous PLP 10 mg/kg, then 10 mg/kg/day in four divided doses. If seizures recurred within 24 hours, another dose of 40 mg/kg was given, followed by 50 mg/kg/day in four divided doses. For those patients whose seizures were totally controlled, PLP was replaced by the same dose of oral PN. If the seizure recurred, intravenous PLP was infused followed by oral PLP 50 mg/kg/day.

**Results:** Fifty seven patients had generalised seizures (of whom 13 had infantile spasms) and 37 had focal seizure. Eleven had dramatic and sustained responses to PLP; of these, five also responded to PN. Within six months of treatment with PLP or PN, five of the 11 patients were seizure free and had their previous antiepileptic medicine tapered off gradually. Two were controlled with pyridoxine and the other three needed PLP to maintain seizure freedom. The remaining six responders needed PLP exclusively for seizure control. Six of the 11 responders to PLP had infantile spasms (46%); four of them needed PLP exclusively. The other five responders were in the remaining 81 patients with other seizure type.

**Conclusions:** PLP could replace PN in the treatment of intractable childhood epilepsy, particularly in the treatment of infantile spasms.

The value of pyridoxine (PN) in the treatment of epilepsy cannot be overemphasised.[1–5] Since the report of Spies *et al* in 1940,[6] several studies regarding the use of PN in the treatment of epilepsy have been reported.[7–12] After the first attempt to treat West syndrome with high dose vitamin $B_6$ (that is, PN),[13] PN has been recognised as a treatment of choice in West syndrome.[14 15] Vitamin $B_6$ consists of three closely related pyrimidine derivatives: PN, pyridoxal, and pyridoxamine and their respective 5′-phosphorylated esters. The former three natural compounds are absorbed in the jejunum and enter the circulation in mainly the non-phosphorylated forms.[16] A proportion of the absorbed vitamin $B_6$ is transported to the liver; it enters the hepatocytes by diffusion followed by metabolic trapping. After phosphorylation by pyridoxal kinase, pyridoxine phosphate and pyridoxamine phosphate are oxidised to pyridoxal phosphate (PLP), which is then bound by apoenzymes or released into plasma. Because essentially all tissues have pyridoxal kinase, but few have significant amounts of the pyridoxine phosphate or pyridoxamine phosphate oxidase, it is thought that the liver is responsible for converting dietary PN and pyridoxamine to pyridoxal, and that other tissues take up pyridoxal from the circulation and convert it to PLP.[17] PLP, the most important member of the vitamin $B_6$ group, is the active coenzyme for more than 100 enzymes, including glutamic acid decarboxylase (GAD), an enzyme involved in gamma-amino butyric acid (GABA) synthesis.[18] It was once believed that the inability of GAD to synthesise adequate GABA in the brain contributes to pyridoxine dependent epilepsy (PDE).[16 19] However, some recent studies suggested that there might be other proteins involved in the metabolism of GABA that are responsible for PDE rather than mutation of GAD.[19 22 23]

The difference between PN and PLP in seizure control had not been noted until our previous report of a female infant whose seizures were controlled by PLP but not by PN.[20] It was speculated that the pathway from absorption, transportation, phosphorylation, and oxidation of PN to PLP in this case may be defective.[20] Clayton *et al* reported a case of neonatal epileptic encephalopathy, which responded dramatically to PLP.[21] Defective conversion of PN to PLP due to deficiency of pyridox(am)ine phosphate oxygenase was thought to be the cause.[21] This open prospective study was designed to evaluate the efficacy of PLP therapy in children with intractable epilepsy and to determine the differences in the antiepileptic effects of PN and PLP.

## METHODS

From April 1999 to March 2001, with permission from our Institute Review Board, children with intractable seizures who fulfilled the following criteria were enrolled in this study after the consent of their parents or caregivers: (1) the seizure frequency was more than once per day; and (2) the epilepsy had persisted for more than six months under regular administration of more than three kinds of antiepileptic drugs (AEDs) but without vitamin $B_6$. Those with underlying structural (congenital malformation, tumour, chromosomopathy, and dysmorphic syndromes), infectious (febrile seizure, gastroenteritis, meningitis, and encephalitis), or metabolic (inborn error of metabolism, electrolyte, and endocrine disorders) aetiologies were excluded. MRI (T1 and T2) of brain, serum electrolytes, lactate, pyruvate, urine organic acid (GC-MS), and serum amino acid (Tandem-MS) studies were all negative. Their age at onset, and seizure type, frequency, and duration were recorded in detail.

All patients enrolled in this study received the same protocol as illustrated in fig 1. After admission to the epilepsy ward, patients were infused intravenously with PLP (10 mg/kg) while being monitored by electroencephalography (EEG)

**Abbreviations:** AED, antiepileptic drug; EEG, electroencephalography; GABA, gamma-aminobutyric acid; PDE, pyridoxine dependent epilepsy; PLP, pyridoxal phosphate; PN, pyridoxine

for fear of electrocortical voltage suppression. Infusions of 10 mg/kg/day were then given in four divided doses over the following three days. If the seizure recurred within 24 hours, another 40 mg/kg of PLP was infused, giving a total dose of 50 mg/kg PLP. A dose of 50 mg/kg/day of PLP was then given in four divided doses for three days. If the seizures did not recur, the parenteral form of PLP was replaced with oral PN of the same dose. In cases of seizure recurrence, PLP was infused again to control the seizure; the oral form of PLP (50 mg/kg/day) was used instead of PN for further seizure control. For those patients free of seizures for one month, previous AEDs were gradually tapered one by one at our epilepsy clinics. EEG was performed when seizures improved or deteriorated. To determine the lowest dosage of PN or PLP for seizure control, a dose of less than 50 mg/day was reduced once a week. This kind of dosage reduction was not encouraged to be done by the caregivers, and they were informed of the possibility of seizure recurrence. Patients treated with high dose vitamin $B_6$ were carefully monitored for symptoms and signs of vitamin $B_6$ intoxication (such as skin rash and photosensitivity). Both sensory and motor nerve conduction velocities were measured at three month intervals in these patients.

Other treatment programmes for epilepsy, such as those involving new AEDs, ketogenic diet, and epilepsy surgery were available to those patients who did not respond or only partially respond to the present treatment protocol.

## RESULTS

During the period of this study, 574 children with active epilepsy were referred to our Paediatric Neurology Department. After appropriate management, 219 patients had medically intractable epilepsy. Excluding those with underlying structural, infectious, and metabolic disorders, 94 children (59 boys and 35 girls), aged between 8 months and 15 years, were defined as having idiopathic intractable epilepsy and were enrolled in this study. This group accounts for 16% of the children with epilepsy. The mean age at onset of seizure was 64 months. The major seizure types were focal type in 37 patients and generalised type in 57 patients. The latter group included 13 patients with infantile spasms.

Eleven of the 94 patients responded dramatically to intravenous infusion of PLP, achieving a seizure-free status (table 1). Three of the 11 patients responded to a dose of 10 mg/kg/day (cases 7, 8, 11). The other eight patients needed a dose of 50 mg/kg/day. When the oral form of PN was used to replace parenteral form of PLP, seizures recurred in 6 of the 11 patients (cases 1, 2, 5, 6, 10, 11). Intravenous infusion of PLP controlled the seizures again within one week. The oral form of PLP was then used for further seizure control in these cases who were categorised as the ''PLP maintenance group'' (four with infantile spasms, two with focal epilepsy; four older than 2 years). The seizures were controlled successfully with oral PN in the remaining five patients. They were categorised as the ''PN maintenance group''. Three of the six patients in the PLP maintenance group and two of the five patients in the PN maintenance group patients remained seizure-free after other AEDs were tapered off over an average of 11 months. The remaining six patients needed 1–3 kinds of AEDs to control their seizures in addition to PLP or PN.

According to seizure type, vitamin $B_6$ (including PLP and PN) was effective in five of the 81 seizures other than infantile spasms (6%). However, vitamin $B_6$ had a satisfactory effect in 46% (6/13) of the patients with infantile spasms. The infantile spasms in these patients began before the age of 15 months, and the age of receiving $B_6$ therapy was under 18 months. The mean age of seizure onset in vitamin $B_6$ responders and vitamin $B_6$ non-responders was 6.3 and 72 months respectively. The eldest responder to vitamin $B_6$ therapy was 15 years of age.

The mean age at onset of seizures in the PN maintenance group was 6.6 months. The dosage of PN for seizure control in this group ranged from 5 to 40 mg/kg/day (average, 18 mg/kg/day). The mean age at onset of seizure in the PLP maintenance group was 6.3 months. The final dosage of PLP was 41, 36, and 28 mg/kg/day, respectively, in three patients after the caregivers reduced the dosage from 50 mg/kg/day for economic reasons. The other three patients in the PLP maintenance group continued to take the initial dosage of 50 mg/kg/day calculated on the basis of their initial body weight, without increasing the dose for the increasing weight. At the latest follow up, their dosages of PLP were 38, 30, and 7 mg/kg/day, respectively, without seizure recurrence. The average of the final dosage of PLP in the PLP maintenance group was 30 mg/kg/day, which was significantly higher than the average dosage of PN (18 mg/kg/day) in the PN maintenance group.

No immediate EEG suppression occurred in our patients after intravenous infusion of PLP. Significant improvement in follow up EEG was noted for those free of seizures with vitamin $B_6$. There was no toxicity or other side effects of

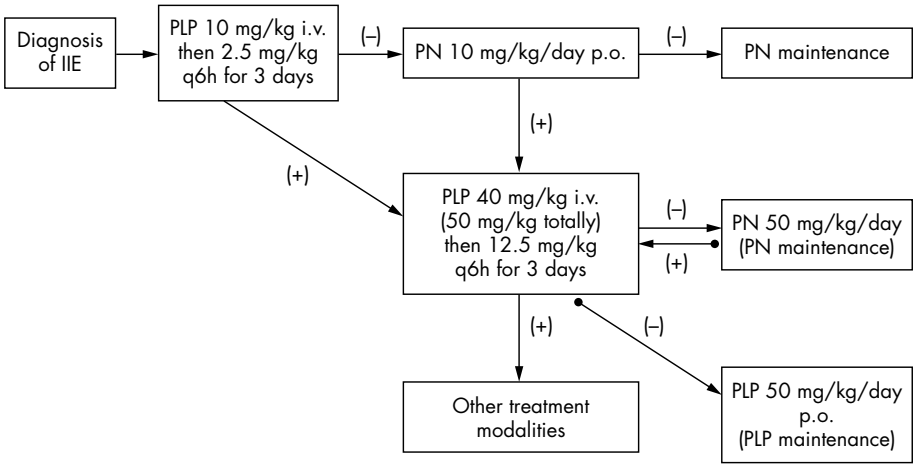


**Figure 1** Vitamin $B_6$ treatment protocol for children with idiopathic intractable epilepsy. IIE, idiopathic intractable epilepsy; PLP, pyridoxal phosphate; PN, pyridoxine. (+), seizure recurs; (–), seizure free.

**Table 1** The 11 children whose idiopathic intractable epilepsy was well controlled with PLP or PN

| Case no. | Seizure type | Gender | Age at treatment | Age at onset of seizure | EEG before vitamin $B_6$ | EEG after vitamin $B_6$ | PLP or PN maintenance | Final dosage of PN or PLP (mg/kg/day) | Other AED (kinds) | Duration of follow up |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | IS | f | 8 mth | 1 mth | Hypsarrhythmia | Focal | PLP | 41 | – | 12 mth |
| 2 | IS | f | 14 mth | 3 mth | Hypsarrhythmia | Focal | PLP | 36 | + (2) | 12 mth |
| 3 | IS | f | 15 mth | 9 mth | Hypsarrhythmia | Negative | PN | 20 | – | 6 mth |
| 4 | IS | m | 18 mth | 6 mth | Hypsarrhythmia | Focal | PN | 18 | + (1) | 24 mth |
| 5 | IS | f | 4 y | 15 mth | Multifocal | Negative | PLP | 38 | – | 12 mth |
| 6 | IS | m | 5 y | 3 mth | Generalised polyspike | G polyspike | PLP | 30 | + (3) | 30 mth |
| 7 | G | f | 2 y | 5 mth | Generalised polyspike | G spike | PN | 8 | + (1) | 28 mth |
| 8 | G | f | 6 y | 3 mth | Generalised polyspike | G polyspike | PN | 5 | + (1) | 18 mth |
| 9 | F | m | 13 mth | 8 mth | Multifocal | Focal | PN | 40 | – | 15 mth |
| 10 | F | m | 2 y | 7 mth | Multifocal | Multifocal | PLP | 28 | + (2) | 21 mth |
| 11 | F | m | 15 y | 9 mth | Generalised polyspike | Negative | PLP | 7 | – | 18 mth |

IS, infantile spasms; G, generalised other than IS; F, focal; f, female; m, male; PLP, pyridoxal phosphate; PN, pyridoxine; AED, antiepileptic drugs.

vitamin $B_6$ in our patients during the 6–30 months of therapy. Examination for sensory and motor nerve conduction velocity every three months also found no abnormalities.

The effect of PLP did not occur in an all-or-none fashion. Six patients had a 25–50% decrease in their seizure frequency, and a 15 year old boy had a paradoxical increase in seizure activity under PLP add-on therapy. These patients used other antiepileptic regimens, such as new AEDs, ketogenic diet, and epilepsy surgery for their seizure control.

## DISCUSSION

Baxter, in 1999, commented: ''Because of the rarity of pyridoxine dependency, trials of pyridoxine for seizures are frequently unrewarding''.[4] However, patients with PDE usually present with intractable seizures that prevent normal activity, and they finally suffer from developmental and mental retardation if their seizures are not well controlled.[24–26] In patients with PDE, a sufficient dosage of vitamin $B_6$ may cause improvement by normalising the glutamate level in the cerebrospinal fluid.[27] Vitamin $B_6$ is not only used in PDE, but is also widely used as an adjuvant therapy for seizure control. Based on the results of a randomised, controlled trial of intravenous PN (up to 50 mg/kg) infused within 2–4 hours of seizure in Chinese children, it was thought that PN is an effective, safe, well tolerated, and relatively inexpensive adjuvant to routine AEDs for the treatment of recurrent seizures.[28] To confirm the diagnosis of PDE, vitamin $B_6$ is stopped, and any subsequent seizure recurrence must respond to further doses of vitamin $B_6$ again. We did not perform this diagnostic procedure to achieve the diagnosis of ''PLP dependent epilepsy'' in the six cases of our PLP maintenance group (three were younger than 2 years old; three were older than 4 years old) because of humanitarian considerations. We believe that a placebo response was unlikely in the young children, but obviously it is necessary to control for a placebo response in older children. A double blind trial should be performed in the future.

PLP, in most studies, has been used to control infantile spasms.[29–34] It has also been used to treat an adult patient with intractable status epilepticus successfully.[35] Our present study showed that PLP was effective in controlling up to 46% of the patients with intractable infantile spasms. In this study the patients were highly selected according to the exclusion criteria, which included those already controlled with AEDs, steroids, or ketogenic diets. Patients with focal epilepsy and generalised epilepsy (excluding infantile spasms) had a PLP responsive rate of 8% and 5%, respectively. Until 2002, the difference between PLP and PN in the treatment of intractable epilepsy had not been reported. The authors reported a female infant with intractable seizures who was responsive to PLP therapy but resistant to PN therapy.[20] The biochemical finding did not mimic aromatic L-aminoacid decarboxylase deficiency, which was shown in a patient with neonatal epilepsy encephalopathy.[21] The patients responded to PLP instead of PN. The present study shows that PLP is effective in controlling the seizures of 11.7% of children with idiopathic intractable epilepsy. The oldest patient was 15 years old. In only five of them could PN replace PLP. Since PLP can readily be a substitute for PN, and perhaps not vice versa, any patient with different ages and seizure types might benefit from PLP treatment if their seizures are difficult to control.

The necessity for EEG monitoring to detect severe electroclinical suppression at the start of vitamin $B_6$ therapy cannot be overemphasised, though this tragic situation did not occur in our 94 patients.[36] The possible side effects of vitamin $B_6$ after long term, high dose therapy, including neuronopathy, peripheral neuropathy with paraesthesia, hyperaesthesia, bone pains, muscle weakness, numbness or

fasciculation on bilateral extremities, contact dermatitis, and photosensitivity, should be closely monitored.[35 37–41] Our patients have received vitamin $B_6$ therapy for a period of 6–30 months only and require regular monitoring for the presentation of vitamin $B_6$ intoxication.

The presence of six patients with partial response to PLP in this study raises the question of the optimal dose of PLP for the treatment of intractable epilepsy. Some studies suggested a megadosage of 300–1000 mg/kg/day of PN for the treatment of infantile spasms.[4 30 35] PLP at a higher dosage might achieve better efficacy; however, the cost and safety need to be weighed up carefully. Additionally, the single case of a paradoxical increase of seizure activity after PLP treatment denotes that the antiepileptic mechanism of vitamin $B_6$ activity may not be simply GABA related.[42]

In conclusion, our data suggest that PLP is more effective than PN in some children with idiopathic intractable epilepsy, particularly children with infantile spasms. A double blind controlled trial should be conducted to confirm the efficacy of PLP in the future. The optimal dosage of PLP and the mechanism by which PLP works need to be studied further.


## Authors' affiliations

**H-S Wang, M-L Chou, P-C Hung, K-L Lin, M-Y Hsieh, M-Y Chang,** Division of Pediatric Neurology, Chang Gung Children's Hospital, and Medical College of Chang Gung University, Taoyuan, Taiwan
**M-F Kuo,** Division of Neurosurgery, Department of Surgery, National Taiwan University Hospital, and National Taiwan University College of Medicine, Taipei, Taiwan


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