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

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 seizures. 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.
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 B6 were carefully monitored for symptoms and signs of vitamin B6 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 in the PLP 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. 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 B6. There was no toxicity or other side effects of

![Figure 1](http://adc.bmj.com/)  
**Figure 1** Vitamin B6 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

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Seizure type</th>
<th>Gender</th>
<th>Age at onset of seizures</th>
<th>Duration of follow up</th>
<th>Other AEDs (kind)</th>
<th>Final dosage of PLP or PN (mg/kg/day)</th>
<th>Electroencephalography before vitamin B6</th>
<th>EEG after vitamin B6</th>
<th>Electroencephalography after vitamin B6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IS f</td>
<td>8 mth</td>
<td>12 mth</td>
<td>1 mth</td>
<td>Hypsarrhythmia</td>
<td>Focal PLP 41</td>
<td>Negative PLP 12 mth</td>
<td>Positive</td>
<td>Focal 12 mth</td>
</tr>
<tr>
<td>2</td>
<td>IS f</td>
<td>14 mth</td>
<td>3 mth</td>
<td>3 mth</td>
<td>Hypsarrhythmia</td>
<td>Focal PLP 36</td>
<td>Positive PN 12 mth</td>
<td>Positive</td>
<td>Focal 3 mth</td>
</tr>
<tr>
<td>3</td>
<td>IS f</td>
<td>15 mth</td>
<td>9 mth</td>
<td>9 mth</td>
<td>Hypsarrhythmia</td>
<td>Negative PN 20</td>
<td>Positive PN 6 mth</td>
<td>Positive</td>
<td>Negative 9 mth</td>
</tr>
<tr>
<td>4</td>
<td>IS m</td>
<td>18 mth</td>
<td>6 mth</td>
<td>6 mth</td>
<td>Hypsarrhythmia</td>
<td>Focal PN 18+</td>
<td>Positive PN 24 mth</td>
<td>Positive</td>
<td>Focal 6 mth</td>
</tr>
<tr>
<td>5</td>
<td>IS f</td>
<td>4 yr</td>
<td>15 mth</td>
<td>15 mth</td>
<td>Hypsarrhythmia</td>
<td>Multifocal PLP 38</td>
<td>Positive PN 12 mth</td>
<td>Positive</td>
<td>Multifocal 15 mth</td>
</tr>
<tr>
<td>6</td>
<td>IS m</td>
<td>5 yr</td>
<td>3 mth</td>
<td>3 mth</td>
<td>Hypsarrhythmia</td>
<td>Generalised polyspike PLP 30</td>
<td>Negative PN 30 mth</td>
<td>Positive</td>
<td>Generalised polyspike 30 mth</td>
</tr>
<tr>
<td>7</td>
<td>G f</td>
<td>2 yr</td>
<td>5 mth</td>
<td>5 mth</td>
<td>Hypsarrhythmia</td>
<td>Generalised spile PN 8</td>
<td>Negative PN 28 mth</td>
<td>Positive</td>
<td>Generalised spile 28 mth</td>
</tr>
<tr>
<td>8</td>
<td>G f</td>
<td>6 yr</td>
<td>3 mth</td>
<td>3 mth</td>
<td>Hypsarrhythmia</td>
<td>Generalised spile PN 5</td>
<td>Negative PN 18 mth</td>
<td>Positive</td>
<td>Generalised spile 18 mth</td>
</tr>
<tr>
<td>9</td>
<td>F m</td>
<td>13 mth</td>
<td>8 mth</td>
<td>8 mth</td>
<td>Hypsarrhythmia</td>
<td>Multifocal PN 40</td>
<td>Positive PN 15 mth</td>
<td>Positive</td>
<td>Multifocal 15 mth</td>
</tr>
<tr>
<td>10</td>
<td>F m</td>
<td>2 yr</td>
<td>7 mth</td>
<td>7 mth</td>
<td>Hypsarrhythmia</td>
<td>Multifocal PLP 28</td>
<td>Negative PN 21 mth</td>
<td>Positive</td>
<td>Multifocal 21 mth</td>
</tr>
<tr>
<td>11</td>
<td>F m</td>
<td>15 yr</td>
<td>9 mth</td>
<td>9 mth</td>
<td>Hypsarrhythmia</td>
<td>Generalised polyspike PN 7</td>
<td>Negative PN 18 mth</td>
<td>Positive</td>
<td>Generalised polyspike 18 mth</td>
</tr>
</tbody>
</table>

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

DISCUSSION

Baxter, in 1999, commented: "Because of the rarity of pyridoxine dependency, trials of pyridoxine for seizures are frequently unrewarding". 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. In patients with PDE, a sufficient dosage of vitamin B6 may cause improvement by normalising the glutamate level in the cerebrospinal fluid. Vitamin B6 is not only 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. To confirm the diagnosis of PDE, vitamin B6 is stopped, and any subsequent seizure recurrence must respond to further doses of vitamin B6 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 is 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. It has also been used to treat an adult patient with intractable status epilepticus successfully. 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. The biochemical finding did not mimic aromatic L-aminoacid decarboxylase deficiency, which was shown in a patient with neonatal epilepsy encephalopathy. 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 B6 therapy cannot be overemphasised, though this tragic situation did not occur in our 94 patients. The possible side effects of vitamin B6 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.43 45–47 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.48

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.

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