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HIGH-DOSE ORAL PYRIDOXINE FOR TREATMENT OF PEDIATRIC RECURRENT INTRACTABLE SEIZURES

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ABSTRACT

Intractable epilepsy is a common clinical problem in pediatrics and approximately 13% of children with epilepsy experience intractable seizures. To determine the efficacy of pyridoxine in treating seizures, 30 infants and children with recurrent seizures were enrolled in the present study. All of them were treated with high-dose oral pyridoxine (40 mg/kg/day), as an adjunct to antiepileptic drugs.

Clinical efficacy criteria were based on the daily frequency of seizures after therapy was initiated during the following three weeks.

The results indicated that the mean frequency of seizures decreased significantly from the first (16.2±11) to the fourth visit (7±6.2) ($p<0.001$, t=4). Three patients became completely seizure free. No adverse effects of pyridoxine were apparent during the observation period.

We conclude that pyridoxine is a safe, effective, and well-tolerated adjunct to routine antiepileptic drugs for the treatment of recurrent intractable seizures in children.

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INTRODUCTION

Recurrent seizures and intractable epilepsies are common clinical problems of hospitalized pediatric patients.[1] They also constitute a considerable number of outpatient visits of any pediatric neurologist. In spite of advances in the treatment of epilepsy, a significant number of children with epilepsy do not respond appropriately to antiepileptic drugs (AEDs). There is no precise definition of intractable epilepsy. Seizure frequency, seizure type, severity of attacks, and impact on quality of life are considered as factors for this definition. Before seizures are deemed intractable it is necessary to be certain that the correct drugs with correct dosage and duration have been administered. Complex partial seizures are more likely to be intractable than tonic-clonic or other common forms of epilepsy.[3]

Several AEDs are used for urgent treatment of recurrent or prolonged seizures. In certain clinical circumstances, pyridoxine (vitamin B_6) has been used to minimize side effects and to enhance the therapeutic efficacy of AEDs.[4-7]

In this study we assessed high-dose oral pyridoxine as an adjunct to AEDs in the treatment of recurrent intractable seizures in children.

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PATIENTS AND METHODS

The study was performed between April 1998 and

April 2000, on 30 children (11 months to 10 years of age, 17 boys and 13 girls) with recurrent intractable seizures that were referred to the pediatric neurology clinic of Imam-Reza hospital, Mashhad, Iran.

The inclusion criteria for pyridoxine administration were:

1) No response to at least 2 major AEDs with appropriate dosages and time.

2) Rule-out of pseudo-seizure and probability of inappropriate drug usage.

3) Cooperative parents in follow up visits and drug usage.

Each of these children had received different combinations of several AEDs, (such as phenobarbital, primidone, clonazepam, phenytoin, sodium valproate, carbamazepine, ethosuximide, nitrazepam and vigabatrin). All had been under treatment for at least six months and had a fixed drug regimen for at least one month before the study.

After counseling parents about drug benefits and adverse effects and obtaining parental consent, pyridoxine 40 mg/kg/day as tablets was given orally, in three divided doses as an adjunct to other AEDs. Then the frequency of seizures and adverse effects of this new treatment were evaluated before and for 3 weeks after starting treatment. We used the general condition and frequency of seizures in each child in the first visit as the basis of our comparison after administering the drug.

RESULTS

In this study the mean age of children was 4.8±3.5 years of age and the mean age of disease onset was 13.5±2.9 months of age.

Fifty percent of children had seizures at sleep-time, 35% during the day and 15% at both wake and sleep times. Seizure type in 30% of patients was generalized tonic clonic, 26.7% infantile spasms, 6.7% myoclonic, 23.3% Lennox-Gastaut and 13.3% had complex partial seizures. In 50% the underlying etiology was neonatal asphyxia, and other etiologies such as trauma, hypoxia secondary to foreign bodies, and febrile infectious disorders had lower prevalence, about 3.3% each. In 40% of children there was no known predisposing factor. Sixty-six percent were mentally retarded and in 33%, the neurological examination was abnormal. Electroencephalograms (EEGs) and CT-scans were abnormal in 87% and 60% respectively.

Finally, the frequency of seizures which was measured in the first visit decreased significantly after three weeks in the fourth visit (Table I). The mean frequency of seizures decreased from 16.2±11 seizures/day to 7±6.2 seizures/day (Table II). Fifty percent of parents were completely satisfied with the result and 60% of patients were more alert and responsive. In this study patients with infantile spasms and Lennox-Gastaut syndrome had the best response.

DISCUSSION

According to a multi-institutional study on intractable childhood epilepsy in Japan, approximately 13% of children with epilepsy experienced intractable seizures.[8] Several therapeutic regimens have been proposed by different authors in the past decades for these types of seizures. In the recent four decades the administration of pyridoxine has been introduced in the literature.[9]

Numerous essential metabolic reactions within the nervous system are dependent upon pyridoxine (vitamin B_6) in the form of its aldehyde derivative, pyridoxal-5-phosphate, as a coenzyme. In animals receiving a pyridoxine-deficient diet, both decarboxylation of glutamic acid to GABA, and transamination of glutamic acid to α-ketoglutaric acid are impaired.[2] Therefore, it is not surprising that some metabolic/epileptic disorders known as 'pyridoxine-dependent' or 'pyridoxine-responsive' seizures respond appropriately to pyridoxine treatment.[1] It is proposed that CNS irritability and seizures are due to alteration in the pyridoxine-dependent synthesis of GABA in each of these clinical conditions, whereas resolution of clinical seizures and improvement in the EEG occur with large doses of pyridoxine.[1] These observations indicate that in humans, clinical derangements of neurophysiologic function can be the result of both pyridoxine deficiency and pyridoxine dependency. The recognition of this relationship stimulated interest in the role pyridoxine plays in disorders of the CNS. For example more recently, prolonged seizures were seen in an infant fed powdered goats milk, a preparation devoid of pyridoxine and folic acid, which was unresponsive to treatment with the usual anticonvulsant medications, but responded to pyridoxine (100 mg).[2]

Although it is known that pyridoxine is effective in treating seizures due to pyridoxine deficiency, pyridoxine dependency, and isoniazid intoxication, use of vitamin B_6 to control seizures due to other etiologies has also been proposed.[1] For example high-dose vitamin B_6 (pyridoxine-HCl, 300 mg/kg/day orally) was introduced as the initial treatment of recently manifested infantile spasms and was effective in some patients.[5] A new combination therapy, high-dose pyridoxal phosphate (40 to 50 mg/kg daily) and low-dose corticotropin (0.01 mg [0.4 IU]/kg daily), is a promising new therapy in patients with infantile spasms.[4] In another report, twenty patients with infantile spasms were treated with high doses of vitamin B_6, valproic acid, or both. The investigators suggested that the combination of vitamin B_6 and valproic acid is effective and safe in the treatment of infantile spasms.[6]

Table I: The effect of pyridoxine on seizure frequency (number of seizures per day) in four visits.

Seizure frequency	Visit			
	First	Second	Third	Fourth
0	0%	3.3%	6.7%	10%
<10	50%	50%	83.3%	80%
10-20	6.7%	40%	6.7%	10%
>20	43.3%	6.7%	3.3%	0%
Sum	100%	100%	100%	100%

Table II: The comparison of mean and standard deviation of seizure frequency (number of seizures per day), before and after pyridoxine therapy in every visit.

Seizure frequency	Visit			
	First	Second	Third	Fourth
Mean + SD	16.2+11	13+8.5	8+7.4	7+6.2
T	_	1.28	3.4	6
Df	_	29	29	29
P	_	0.2	0.01	0.001

Oral pyridoxine has also been shown to improve the outcome of infants treated for neonatal tetanus.[7]

Pyridoxine dependent seizures (PDS) occur mostly as refractory seizures in the early infantile period that respond dramatically to intravenous administration of pyridoxine.[10] However, it is recognized that pyridoxine-dependent seizures may present beyond infancy and that this cause of seizures needs to be considered in all children who present with intractable epilepsy, at least up to 3 years of age.[14-17] Since Hunt et al. reported in 1954,[18] nearly 100 patients have been described.[15] In status seizures in children less than 3 years of age whose seizures do not respond to major AEDs, intravenous administration of pyridoxine has been recommended.[19-20]

In a study by Jiao et al, forty children with recurrent convulsions were treated with high-dose pyridoxine (30 or 50 mg/kg/day) by intravenous infusion, and 50 subjects served as controls. The results indicated that total response rates in the pyridoxine group and control group were 92.5% and 64%, respectively. Pyridoxine demonstrated no adverse effects during the observation period.[1] The literature contains a single report of a patient with idiopathic neonatal seizures who developed a temporary exacerbation of clinical and electrographic seizures after a single 100 mg dose of pyridoxine.[21]

In our study, after three weeks follow-up we observed that the seizure frequency decreased significantly (Tables I and II). Seizures resolved completely in three patients (one case with tonic-clonic seizures and two cases with infantile spasms). The last patient discontinued therapy shortly after our study, which resulted in seizures, controlled again after oral pyridoxine administration was resumed. It's now two years that this patient has been seizure-free.[22]

In a study by Pietz et al. on 17 patients with infantile spasms by administration of 300mg/kg/day pyridoxine, seizures stopped in 5 patients after 2 weeks. The most commonly encountered complications in his patients were gastrointestinal symptoms that resolved after decreasing the drug dosage. Because of its fewer adverse effects and its higher efficacy they preferred pyridoxine to sodium valproate.[5] In our study 87% of patients with infantile spasm recovered completely (26.7% of our patients had infantile spasms). No adverse effects of pyridoxine were apparent during the observation period in our patients.

It is significant that pyridoxine treatment did reduce the daily frequency of seizures. Therefore, administration of pyridoxine is recommended for all children with intractable recurrent seizures.

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