

The Use of Vigabatrin in Infantile Spasms in Asian Children

S K H Tay,*^{MBBS, M Med (Paed), MRCP (UK)}, H T Ong,**^{MBBS, M Med (Paed)}, P S Low,***^{M Med (Paed), MD, FRCP (Edin)}

Abstract

Background: The use of adrenocorticotrophic hormone (ACTH) and prednisolone in the management of infantile spasms has been well established, but is associated with significant morbidity and cannot be used as long-term medication. Since the introduction of vigabatrin, results have been promising with suggestions currently that it should be used as first-line management of infantile spasms. **Aim:** The aim of this study was to establish the efficacy, tolerability and problems associated with the use of vigabatrin in Asian children with infantile spasms. **Materials and Methods:** Eighteen local Asian patients with infantile spasms were given vigabatrin, in 8 as first-line monotherapy and in 10 patients as add-on therapy to pre-existing anti-convulsants. **Results:** Thirty-nine per cent (7/18) showed 100% suppression of seizures at 2 weeks and 50% (9/18) showing complete suppression of seizures at 4 weeks after starting therapy. There was however, a high relapse rate (56%) in complete responders within the first 6 months of therapy. This was probably due to a lower maintenance dose in the patients, as those who relapsed were on an average dose of 59 mg/kg/day at the time of relapse and responded to a stepped up dose of 83 mg/kg/day. Vigabatrin was well tolerated and only 2 patients developed somnolence and irritability. **Conclusion:** A dose of at least 70 mg/kg/day may be necessary to achieve adequate control and yet avoid the common adverse affects of vigabatrin.

Ann Acad Med Singapore 2001; 30:26-31

Key words: Add-on therapy, Infantile spasms, Monotherapy, Retrospective study, Vigabatrin

Introduction

Infantile spasms are a form of age-dependent myoclonic epilepsy that is difficult to control.¹ Agents such as adrenocorticotrophic hormone (ACTH) and prednisolone have been used as first-line therapy,^{2,3} but are associated with major side effects. Furthermore, neither of these has been shown to conclusively improve the long-term outcome of infantile spasms. Other antiepileptic drugs such as sodium valproate and the benzodiazepines often do not offer satisfactory control or reduction of seizure frequency. Since the introduction of vigabatrin, a new generation antiepileptic drug that is an irreversible gamma-aminotransferase inhibitor, greater promise of better control of seizures has been seen.^{4,5} It has been recommended that vigabatrin be used as a first-line therapy for infantile spasms.⁶ In this study, we reviewed the response of infantile spasms to vigabatrin both as first-line monotherapy and as add-on therapy, and also assessed the tolerability of the drug in local patients.

Materials and Methods

Eighteen patients with infantile spasms who presented to the National University Hospital from August 1995 to August 1999 were reviewed retrospectively. The diagnosis

of infantile spasms was made clinically based on the typical clinical features, as well as based on classical hypsarrhythmia on electroencephalography.

These patients were classified into the symptomatic and cryptogenic types.⁷ The underlying aetiology was assessed in the patients with history, clinical examination and investigations such as neuroimaging (magnetic resonance imaging or computed tomography) of the brain, as well as with metabolic screens where necessary. The cryptogenic group was characterised by a history of normal development prior to the onset of seizures and the absence of any definable aetiological factors in the history, clinical examination and investigations. The symptomatic group was defined as cases with pre-existing encephalopathy, abnormal developmental milestones, abnormal neurological signs and abnormal neuroimaging.

Vigabatrin was started for all patients regardless of pre-existing antiepileptic therapy. Starting doses of 20 to 40 mg/kg/day were used, with increase to a therapeutic dose of 50 to 150 mg/kg/day over 1 week. Pre-treatment seizure frequency was recorded from parents and caregivers. Parents were also given seizure diaries to record the frequency, duration and severity of seizures daily. The patients were

* Registrar

** Consultant

*** Senior Consultant

Department of Paediatrics

National University Hospital

Address for Reprints: Dr Stacey Tay, Department of Paediatrics, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

reassessed by one of the authors at 2 and 4 weeks after starting vigabatrin. Evaluation of response and reporting of adverse effects were recorded at these visits. The patients were subsequently followed up at 1 to 3 monthly intervals after stabilisation of the medication dose and seizures.

Results

Patient Profile (Table I)

There was a total of 18 patients (11 males and 7 females)

with a mean age of presentation of 8.1 months (range 4 to 21 months; SD 4.9 months). Fourteen patients (77.7%) were Chinese and 4 patients (22.2%) were Malay. There were no Indians or other minority races in the study population. Seven patients were classified as having cryptogenic infantile spasms, and 11 patients had symptomatic spasms (Fig. 1). Of the symptomatic group, 2 patients had tuberous sclerosis, 2 had evidence of perinatal asphyxia, 1 had postnatal hypotension from surgery, 1 had

TABLE I: PATIENT PROFILE

Patients	Age (mo)	Sex	Race	Age of presentation (mo)	Aetiology	Neuro-imaging	Type of therapy	Seizure reduction at 2 weeks	Seizure reduction at 4 weeks	Dose at 2 weeks (mg/kg)	Dose at 4 weeks (mg/kg)	Maximum dose (mg/kg)
1	24	F	Mal	6	Cryptogenic	Normal	First line	100%	100%	36	40	40
2	29	F	Chi	4	Cryptogenic	Normal	First line	50-75%	100%	64	93	75
3	42	F	Chi	21	Cryptogenic	Normal	First line	100%	100%	45	50	50
4	13	F	Chi	4	Cryptogenic	Normal	Add on	50-75%	50-75%	85	108	108
5	43	M	Chi	16	Cryptogenic	Normal	Add on	100%	100%	55	75	75
6	44	M	Chi	5	Cryptogenic	Normal	Add on	100%	100%	55	55	55
7	71	M	Chi	5	Cryptogenic	Normal	Add on	50-75%	50-75%	40	60	60
8	50	F	Mal	8	Tuberous sclerosis	Cortical and periventricular tubers	First line	100%	100%	62	62	80
9	50	M	Chi	15	Tuberous sclerosis	Cortical and periventricular tubers	Add on	50-75%	100%	100	136	136
10	24	M	Chi	9	Vascular insult	Haemorrhagic infarcts	First line	<50%	<50%	66	94	94
11	36	M	Chi	9	Cerebral malformation	Cerebral atrophy	First line	100%	100%	56	80	80
12	38	M	Mal	4	Cerebral malformation	Microcephaly Cerebral atrophy	First line	50-75%	50-75%	45	77	77
13	36	F	Chi	5	Cerebral malformation	Microcephaly	Add on	50-75%	50-75%	57	57	57
14	23	M	Chi	4	Cerebral malformation	Porencephalic cyst and encephalomalacia	Add on	<50%	50-75%	85	108	108
15	9	M	Mal	4	Cerebral malformation	Cortical dysplasia	Add on	50-75%	50-75%	52	104	104
16	19	M	Chi	9	Neonatal hypoglycaemia	Cerebral atrophy	First line	50-75%	50-75%	40	77	77
17	28	M	Chi	7	Perinatal hypoxia	Delayed gray-white differentiation	Add on	50-75%	50-75%	71	102	102
18	34	F	Chi	11	Hypoxia from neonatal tetanus	No neuro-imaging done	Add on	100%	100%	42	72	72

Chi: Chinese; F: female; M: male; Mal: Malay

neonatal hypoglycaemia and 5 patients had cerebral abnormalities like cortical dysplasia, encephalomalacia with porencephalic cyst or microcephaly. Nine patients with symptomatic infantile spasms were found to have abnormalities on computed tomography and magnetic resonance imaging. None of the patients had any family history of seizures. 61.1% (11/18) of the patients had evidence of developmental regression with the onset of infantile spasms. Ten patients had already been on pre-existing antiepileptic drugs, such as sodium valproate, clonazepam, nitrazepam and phenobarbitone. Eight patients had not been on any previous antiepileptic drugs and were thus started on vigabatrin as a first-line drug.

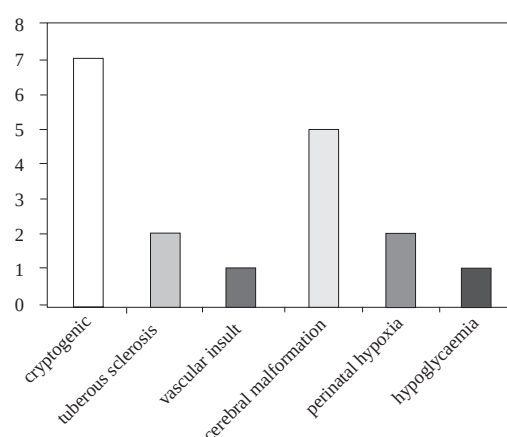


Fig. 1. Aetiology of infantile spasms.

At the end of 2 weeks after the onset of vigabatrin therapy (Fig. 2), it was found that there was significant improvement with 39% (7/18) patients showing 100% reduction in seizure frequency. Fifty per cent to 75% reduction of seizure frequency was seen in 50% (9/18) and 2 patients (11%) remained resistant to vigabatrin with reduction of seizure frequency being less than 50%. At the end of 4 weeks of therapy (Fig. 3), it was found that 50% (9/18) patients had 100% reduction in seizure frequency, 44% (8/18) had 50% to 75% reduction in seizure frequency and 1 patient remained with <50% reduction in seizure frequency. Subsequently, 6 of 10 (60%) patients on vigabatrin as add-on therapy were able to have the other antiepileptic drugs weaned off so that they were on vigabatrin monotherapy.

Response to Vigabatrin (Table I)

Several predictors of response were found. There was complete response for the 2 patients with tuberous sclerosis, both having 100% reduction of seizures. The response to vigabatrin was better for the cryptogenic group than the symptomatic group (excluding tuberous sclerosis). There was complete suppression of seizures in 71.4% (5/7) of

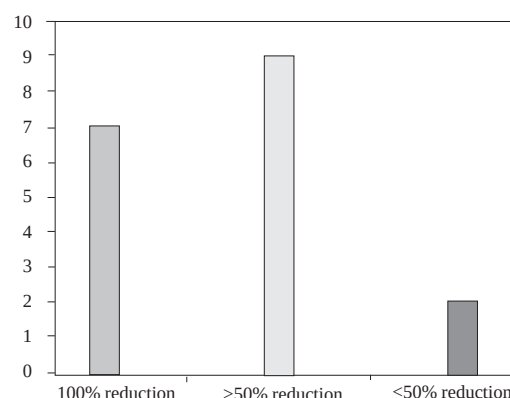


Fig. 2. Response to vigabatrin at 2 weeks of therapy.

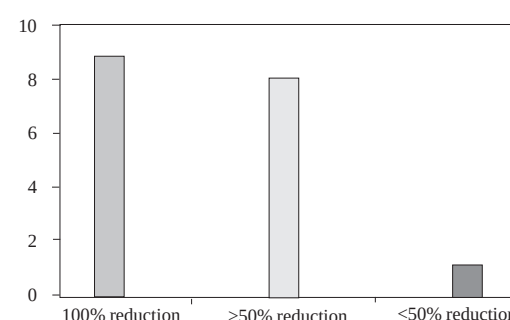


Fig. 3. Response to vigabatrin at 4 weeks of therapy.

patients with cryptogenic infantile spasms. For the symptomatic group, there was a poorer response with only 4 of 11 patients (36.3%) with 100% response and 1 patient remaining unresponsive to vigabatrin. The response would have been poorer still (22.2% were complete responders) if patients with tuberous sclerosis had been excluded.

For the 8 patients in whom vigabatrin was used as first-line monotherapy, 62.5% (5/8) showed 100% response, 25% (2/8) showed 50% to 75% response and 12.5% (1/8) showed <50% response. In comparison, for patients who were on vigabatrin as add-on therapy, 40% (4/10) became seizure free after the drug was started, and 60% (6/10) patients had reduction of seizures by 50% to 75%. Looking at the patient background in both the first-line and add-on groups, patients with complete response showed a similar age of onset of infantile spasms (8.4 months for first-line group and 7.6 months for add-on group). However, there appeared to be a higher dose used for the add-on group, with a mean dose of 85.8 mg/kg/day being used compared with a mean of 71.6 mg/kg/day being used for the first-line group. The difference in the mean doses between the 2 groups did not reach statistical significance according to the Mann-Whitney U test.

Loss of Efficacy

Relapse of seizures was seen in 55.6% (5/9) of those who

had complete response to vigabatrin. The recurrence of seizures occurred within 6 months of starting therapy. In 4 of the 5 patients, there was good response to stepping up the doses of vigabatrin. The recurrence of seizures occurred between 4 and 6 months after starting medication. These children had a dosage of 68 mg/kg/day when initial control was achieved and the dosages were not increased in the subsequent months. Because of progressive weight gain, there was an average dose of 52 mg/kg/day at the time of relapse, responding to an increase of dosage to 72 mg/kg/day on average. For 1 patient, there was no attempt to increase the dose as the seizures did not recur subsequently.

16.7% (3/18) of the patients had appearance of new types of seizures on follow up, such as complex partial seizures and atypical absence seizures.

Tolerability of Vigabatrin

Two patients reported irritability and somnolence, but no other adverse side effects were reported such as insomnia, weight gain, hyperkinesia, behavioural problems, facial oedema or exacerbation of seizures. None of the patients needed withdrawal of vigabatrin due to side effects. Because the study population belonged to a younger age group and a good number were cognitively poor, formal visual field testing with Goldmann perimetry could not be carried out routinely for the patients.

The patients were followed up from 8 to 43 months, with a mean duration of 24.8 months and a standard deviation of 8.7 months.

Discussion

The management of infantile spasms has always been a difficult issue. This form of epilepsy carries a poor prognosis in terms of mental development as well as control of seizures. Adrenocorticotrophic hormone and prednisolone were previously used as first-line agents, but although they have been found to be efficacious, the effects are often transient, and side effects are common with reported mortality as high as 5% from steroid treatment.⁸ These drugs are also not recommended for long-term use because of the known side effects. Other antiepileptic drugs have been found to have variable efficacy and are not without their own side effects.

Vigabatrin has been shown to be particularly efficacious in infantile spasms, and also in other refractory partial epilepsies.⁹ It may actually worsen the course of progressive myoclonic epilepsy. Since its introduction, vigabatrin has been used in various centres around the world. There have been reports of its efficacy and tolerability amongst European children.⁶ As the drug is relatively new, there have not been many reports of experience with this drug

among Asian children.

Although the study population was small in this case, the information collected is useful in assessing the effects of vigabatrin on local Asian patients. The demographic characteristics of our patient population are comparable to published epidemiological studies of infantile spasms.¹⁰ There were some significant differences in the average doses achieved in the patient group, being about 81 mg/kg/day as compared to 99 mg/kg/day in other studies such as that performed by Aicardi et al in the Sabril Investigator Group.⁶ Our patient population did show less efficacy but better tolerability of the drug, and higher relapse rates compared with the Sabril Investigator Group, as will be illustrated further.

The efficacy of vigabatrin as monotherapy and add-on therapy appears to be less than that reported in other open studies.¹¹⁻¹⁵ Nabbout et al¹⁶ reported a reduction in seizure frequency of 70% in 178 patients, with complete response in 30% (54/178). Better results were obtained by the Sabril Investigator Group⁶ with reduction of seizures in 87.5% (168/192) and complete response in 68.2% (131/192). Similar results were reported by Kwong (1997)¹⁵ and Koo (1999)¹⁷ with complete response in 57% (4/7) and 64% (16/25), respectively. Our patient population appeared to have a poorer response overall with seizure reduction of 88.9% (16/18) but complete response only in 50% (9/18). The degree of response appears to be related to the underlying aetiology. In tuberous sclerosis, the efficacy was extremely encouraging in our patients, with complete cessation of seizures with the use of vigabatrin. The response of patients with cryptogenic infantile spasms was also impressive, with 71.4% patients having complete response, demonstrating that similar to other studies, vigabatrin has better effect on cryptogenic than symptomatic infantile spasms. Response of symptomatic infantile spasms was poorer as expected.

There appeared to be a difference in efficacy when vigabatrin was used as a first-line drug compared to an add-on therapy. The degree of response was worse in the add-on group, and this group similarly required a higher maintenance dose too. The demographics of both groups were not quite identical as there were more patients with symptomatic infantile spasms in the add-on group. Nonetheless, it is encouraging that 6 of the 10 patients on add-on therapy were able to switch completely to vigabatrin monotherapy.

Our experience indicates that the efficacy of the drug can be assessed within the first 2 weeks of therapy. Increasing the duration of assessment does not significantly increase the information acquired about the efficacy of vigabatrin, provided an adequate dose of at least 70 mg/kg/day has been attained.

One of the concerns about vigabatrin therapy is that of the recurrence of seizures. Loss of efficacy has been said to range between 12% and 21%.^{6,9} In this population however, it was found that the rate of relapse was as high as 55.6%. The marked difference in the rate of relapse could be explained in part by the dosages being used. In fact, for the patients who relapsed, they were on lower average doses of 52 mg/kg/day that responded to increase to 72 mg/kg/day. There was good response to the step-up of the dose of vigabatrin. When the patients who responded to the step-up dose of vigabatrin were excluded, the relapse rate was actually 11.1%, in keeping with published figures. As such, it is likely that these patients needed more than the minimum recommended dosage for their weight. Nonetheless, dosing in our patients had been kept as low as possible to achieve control because of the higher cost of vigabatrin compared with other older antiepileptic drugs, the fact that it was a new antiepileptic drug with a wide range of recommended dosage and there was no means of measuring drug levels in the blood. Noteworthy too is the fact that there may be an optimum dose of vigabatrin in each patient and exceeding that dose may result in deterioration of the spasms instead of further improvement.¹⁷

Perhaps it should be considered that although the recommended dosage of vigabatrin is 50 to 150 mg/kg/day, a minimum dosage of 70 mg/kg/day may be necessary to decrease the chances of relapse. At this point in time, as there are no facilities available for monitoring of vigabatrin levels in the blood, using a higher dosage for maintenance may be necessary.

Only 2 of the patients reported adverse effects, and none required withdrawal of medication due to side effects, which again may be due to the lower doses administered. Long-term control may be dependent on the escalation of the dose appropriately. It remains to be seen what is the optimal. By the end of the study, 6 of the 10 patients on add-on therapy had their initial medication withdrawn successfully, and as a result, 77.7% (14/18) of the patients were on vigabatrin monotherapy, of whom 57.1% (8/14) have since remained completely seizure-free. Further follow-up is required for this group of patients as it is well known that reduction of co-medication has a risk of relapse and of further intractability.¹⁶

Recently, one of the serious side effects of vigabatrin is that of concentric visual field defects, which have been clearly reported in adult patients with Goldmann perimetry.¹⁸ Unfortunately, the age group of our study population precluded the use of Goldmann perimetry for the assessment of visual field defects. At present, it is not within our ability to search for visual field defects for the patients with special visual evoked responses, but this particular complication remains an important consideration in the use

of vigabatrin in our population. A risk-benefit assessment is thus necessary when considering the use of vigabatrin. In our study population where vigabatrin was extremely efficacious in children with tuberous sclerosis and infantile spasms, and also showed good results in the group with cryptogenic infantile spasms, the benefit of the choice of vigabatrin may outweigh the risk of retinal toxicity. For patients with cryptogenic infantile spasms, the use of vigabatrin is likely to be short term and thus is unlikely to incur any long-term side effects. Adequate monitoring needs to be instituted however, which requires a special method based on visual evoked potentials, but more studies need to be done to validate this method as well.

21.4% of patients developed new seizures, which is comparable to other studies that cited rates of 11% to 23%. These partial seizures had little impact on the patients' global function and overall improvement.

Although our study group was small, the study of Asian children has confirmed the earlier findings in Caucasian children of the excellent tolerability of vigabatrin. Although serious concern remains about the effects of vigabatrin on visual fields, we suggest that because of the efficacy of vigabatrin in comparison with other antiepileptic agents, vigabatrin should be considered as the drug of choice in infantile spasms, whether as first-line therapy or as add-on therapy. At present, the other established drugs for infantile spasms such as ACTH and prednisolone, although much cheaper, are associated with significant morbidity and occasionally mortality, and cannot be used as long-term therapy. New anticonvulsants such as topiramate have also not been studied adequately as yet, although there is some evidence for its efficacy and tolerability in refractory infantile spasms in a small cohort of 11 patients.^{19,20} Further studies are needed to compare the efficacy, tolerability and cost effectiveness of the new antiepileptic agents such as vigabatrin and topiramate.

We also propose that should vigabatrin be used for infantile spasms, a minimum dose of 70 mg/kg/day should be used even if control is achieved on lower doses, so as to decrease the incidence of early relapse within the first 6 months after treatment.

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