Vigabatrin in Infantile Spasms: Preliminary Result

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Abstract

Purpose: To evaluate the efficacy of vigabatrin in the treatment of infantile spasms in Thai children.

Patients & Method: From March 1996 to May 1998, patients aged under 2 years presenting with infantile spasms at Ramathibodi Hospital were initiated with vigabatrin 35-50 mg/kg/day in two-divided doses. The dosage was escalated by 25 mg/kg weekly until spasms ceased or the maximum dose of 130 mg/kg was reached.

Result: There were 20 patients enrolled. The ages ranged from 3 to 23 months (mean 7.6 months). They were categorized as 4 cryptogenic and 16 symptomatic. Infantile spasms were completely controlled in 12 patients (60%). Six patients (30%) had at least 50 per cent reduction of seizure frequency. There were 2 patients whose seizure frequencies and severity were not altered. Only one patient whose infantile spasms partially responded to vigabatrin developed orofacial dyskinesis which disappeared after discontinuation of vigabatrin. Five patients had their vision evaluated which was unremarkable. Based on parental global evaluation, there was an increase in alertness, cheerfulness and interaction to the environment and stimulation in 8 out of 15 patients who were still taking vigabatrin and responded to treatment.

Conclusion: Vigabatrin is effective for infantile spasms. A long-term follow-up of these patients is necessary to evaluate its efficacy and side-effects.

Key Word : Infantile Spasms, Children, Vigabatrin, Efficacy, Side-effects

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Infantile spasms are a unique epileptic syndrome occurring restrictively in children almost entirely in the first year of life[1-5]. They are resistant to most conventional antiepileptic drugs such as phenobarbital, sodium valproate or benzodiazepines[1-3,5]. The results in seizure-control vary from one drug to the other. ACTH which is one of the recommended drugs was able to control infantile spasms in around 50 per cent of the cases with a high rate of seizure recurrence[1,3,6]. Prednisolone is another alternative drug[6-8]. However, the long term outcome of these drugs has not been conclusively improved and recurrent seizure is also high (6,9,10). Both of them may cause side-effects such as hyperglycemia, hypertension and disturbance of electrolytes. Suppression of the immune response is the major side effect which increases the risk of serious infection[8,11]. Favorable seizure control may be obtained from a high dose of sodium valproate but it might cause liver failure and thrombocytopenia in infants[12,13]. Vigabatrin (γ-vinyl γ-aminobutyric acid) is one of the new antiepileptic drugs which has been used on multiple trials in infantile spasms with satisfactory results. Equal or better results in comparison to other drugs have been demonstrated in many reports especially from European countries[10,14-22]. This drug is now proposed as the drug of first choice in the treatment of infantile spasms[10,21-25].

In Thailand, there is no reported incidence or prevalence of this devastating epileptic disorder. The available antiepileptic drugs such as phenobarbital, prednisolone, sodium valproate, benzodiazepines and ACTH have been used without any report of efficacy and outcome. ACTH has to be given by intramuscular injection once or twice daily and usually the patient needs to be hospitalized for the treatment. It is not available in the country at present. A newly available, orally-administered antiepileptic drug such as vigabatrin might be more practical in the treatment of infantile spasms. We, therefore, evaluated the efficacy and the practicability in administration of vigabatrin in Thai children with infantile spasms.

PATIENTS AND METHOD

From March 1996 to May 1998, all patients who presented to the Department of Pediatrics, Ramathibodi Hospital with infantile spasms were included in this study. Fundamental data including pre, peri and post natal periods, family histories, developmental milestones, previous medical treatment, the age at onset of infantile spasms, physical and neurological findings were collected. Frequency of infantile spasms and other types of seizure, if relevant, were recorded. All children had routine blood tests which included complete blood count, electrolytes, glucose, calcium and magnesium levels. Urine ferric chloride test was performed to exclude Phenylketonuria (PKU) and Maple Syrup Urine disease (MSUD). Routine or video-monitored EEG recording was performed in each patient upon first evaluation. The patients were categorized into two groups, cryptogenic and symptomatic, according to documented findings such as past medical history and the brain imaging studies.

After obtaining either verbal or written consent from the legal guardians, Vigabatrin (Sabril® 500 mg / tablet) was prescribed to each patient with the initial dose of 30-50 mg/kg/day given in two-divided doses. Escalation of the dosage approximately 25 mg/kg/day was done every 1-2 weeks initially until cessation of seizures or the maximum dose of 130 mg/kg/day was reached. Then each patient would be followed every one to two months. Seizure frequency and severity, change in behaviour, developmental milestones and complete neurological examination as well as suspicious side-effects were evaluated and recorded upon follow-up evaluation.

The patients were categorized into 3 groups according to responsiveness to the treatment as follows :-

1. complete control: no infantile spasms observed by the parent or caregiver.

2. partial control: 50 per cent or more than 50 per cent reduction of seizure frequency

3. unresponsive: less than 25 per cent seizure reduction

The dose of vigabatrin which was either able to reduce the seizure frequency to 50 per cent or to control seizures was recorded and analysed. The duration from the onset of the seizure to the initiation of treatment and from the initiation of the treatment to reduction of seizures was recorded.

Follow-up EEG recordings were performed on each patient according to the change of the seizure frequency and at one year after the seizures had been controlled. Any emerging different type of seizure was recorded and an additional antiepileptic drug was administered only when 130 mg/kg/day of vigabatrin was reached. Pre-

viously taken antiepileptic drugs were maintained without alteration of the dosage.

RESULTS

Eleven boys and 9 girls were included in this study. The ages ranged from 3 to 23 months (mean 7.6 months) upon initiation of vigabatrin. The period from the onset of infantile spasms to the initiation of vigabatrin ranged from 1 week to 21 months (mean 2.73 months). There were 4 and 16 patients in the cryptogenic and the symptomatic groups respectively. Table 1 demonstrates pre-treatment information.

There were 8 patients who had not received any treatment prior to the initiation of vigabatrin. Twelve patients were placed on combinations of multiple antiepileptic drugs including phenobarbital (11 patients), nitrazepam (7 patients), sodium valproate (3 patients), phenytoin (2 patients) and ACTH (1 patient). The result of vigabatrin treatment is shown in Table 2. There were 12 patients whose infantile spasms were complelely controlled ranging from 3 weeks to 8 months (mean 2.29 months). Partially control was obtained in 18 patients within 9 months (mean 2.08 months). The mean dosage of vigabatrin taken by the patients whose infantile spasms were completely controlled was 86 mg/kg/day (range 35-130).

There were 15 patients who responded to vigabatrin treatment and were followed at least 6 months (range 6 to 28 months). Table 3 shows duration from initiation of treatment to 50 per cent reduction and complete control of infantile spasms. The two patients who did not respond to vigabatrin had been taking combinations of sodium valproate, phenobarbital and nitrazepam without significant reduction of their seizure frequencies since discontinuation of vigabatrin. All except two patients were followed at least 6 months (range 6-28 months, mean 16.6 months). Physical and neurological signs did not significantly change. Based on parental global evaluation, there were increases in alertness, cheerfulness and interaction to the environment and stimulation in 8 of 15 patients. Four patients who initially had normal developmental milestones continued to do so. Repeated EEG recording was performed in 7 patients out of 15 who were followed. Five of these seven patients had a normal EEG recording. Among these five, there are two patients who have remained seizure-free until the date of this report.

Only one patient, who initially had partial response to vigabatrin, developed orofacial dyskinesia 5 months after the initiation of vigabatrin. This abnormal movement ceased after discontinuation of the drug but the infantile spasms became worse. A

Table 1. Patients' information.

	mean (months)	Range (months)	No of patients
Sex :			
Male			11
Female			9
Age:			
at onset	4.8	1-9	
at initiation of Rx.	7.6	3-23	
Pretreatment AED			
Phenobarbital			11
Nitrazepam			7
Sodium valproate			3
Phenytoin			2
ACTH			1

Table 2. Responsiveness of treatment according to causes of infantile spasms.

Causes	Complete	Partial	No response
Cryptogenic	4	0	0
Symptomatic			
Tuberous sclerosis	2	0	0
Post vaccination	1	0	0
Perinatal asphyxia	2	3	2
Perinatal meningitis	2	1	0
Stroke	0	1	0
Cortical dysplasia	1	1	0
Total	12	6	2

Table 3. Dosage & duration to the onset of responsiveness.

	Complete (n = 12)	Partial (n = 6)	Total (n = 18)
Mean dosage (mg/kg/day)	86	110	100
Duration to 50% reduction			
mean (months)	1.04	4.16	2.08
range (months)	0.25-5	1-9	0.25-9
Duration to complete control			
mean (months)	2.29		
range (months)	0.75-8		

course of synthetic ACTH was started which was able to temporarily reduce her seizure frequency. She is still under follow-up evaluation and taking the combination of phenobarbital, sodium valproate and nitrazepam without complete control of the seizures.

DISCUSSION

For infantile spasms, there is no promising antiepileptic drug which has been proved to be very effective. ACTH and corticosteroids have been used in controlling seizures with a success rate of 40-50 per cent[1,26]. ACTH which was proved to be superior to prednisolone is frequently not available when it is needed[6]. Administration of ACTH usually needs hospitalization of the child to monitor the effects and the side-effects which in some occasions is not practical. Other antiepileptic drugs such as sodium valproate must be given with high dose which might cause some serious side-effects such as thrombocytopenia and liver failure especially in infants[12,13]. Benzodiazepines including nitrazepam and clonazepam are not as potent and are easily tolerated by the patients. Frequently they cause marked hypotonia and drooling in infants which might create respiratory problems[26-29]. Vigabatrin which has been used in Western countries has been on trial in the treatment of infantile spasms for years with satisfactory efficacy and may replace ACTH as the drug of first choice[10,14, 16-19,21,25,30].

This study which is the first study in Thai children demonstrated a satisfactory efficacy in controlling infantile spasms. Complete control of infantile spasms was observed in 60 per cent of the patients and significant reduction of seizure frequency in 30 per cent. There were only 2 patients (10 per cent) who did not show acceptable response. This efficacy obtained in our study is similar to or even better than previously reported in Western countries[16,17,21,23,26,30]. In addition, we observed that the parents were more comfortable in stepping-up the dose of vigabatrin in the fashion that we did which was every week initially, biweekly and monthly with close follow-up both in person and by telephone. The patients who had complete response to vigabatrin treatment demonstrated 50 per cent reduction of the seizure frequency sooner than in the partial response group (mean 1.04 and 4.16 months respectively). This observation implies that complete control of infantile spasms might be expected in any child whose seizure frequency is reduced in the early stage of treatment.

In this study, four patients who were classified to the cryptogenic group and ultimately had complete control of seizures took a longer period for the seizures to be controlled when compared to the symptomatic group (mean 3.06 months *vs* 1.9 months). The number of patients was too small for statistical calculation. There was no difference in the dose of vigabatrin used between the two groups of infantile spasms with complete response to vigabatrin (mean 86.25 *vs* 85.87 mg/kg/day).

There was no serious side-effect observed in our study except the one who had orofacial dyskinesia. There was no other side-effect reported in other studies[17,21,26,31]. On the other hand, among 15 patients, who continued to take vigabatrin and are being followed, there were 8 patients whose parents reported improvement of developmental milestones especially social aspect. There was no disturbance of mood or behaviour observed in any of our patients as has been observed in adults taking vigabatrin[32-34]. There were some different opinions in the cognitive effects of vigabatrin[32, 35-37]. Clarification of this issue is yet to be established.

Optic neuropathy and peripheral visual field contraction which might be dose-related has been demonstrated with high concern in many recent reports[38-44]. It is not practical and possible to evaluate vision and visual fields in young children especially in infants. In our study, there were five patients who had routine check-up of vision by an ophthalmologist which did not elicit any abnormality. The awareness of this serious adverse effect, close evaluation of infant vision upon follow-up visits and complete evaluation of vision with reliable test should be done whenever it is possible in any patient receiving vigabatrin.

Because this report is the preliminary result of short-term follow-up, definite conclusion especially the recurrence of infantile spasms after discontinuation or tapering-off vigabatrin, the evolution of other types of seizure and the long term side-effects of vigabatrin has to be evaluated. However, upon follow-up evaluation and interviewing the parents, satisfaction in reduction of seizures by this drug was clearly demonstrated. At present, we have started to taper off vigabatrin in the child who has been free from seizures for 2 years with normalized EEG recording. Completion of this study may need

at least one to two years more. Nevertheless, we feel more comfortable using this antiepileptic drug with three more new patients, gaining more experience with this drug in the treatment of children and infants who have infantile spasms and are looking forward to completing our study in the near future.

(Received for publication on February 12, 1999)

REFERENCES

1. Jeavons PM, Bower BD, Dimitrakoudi M. Long term prognosis of 150 cases of "West syndrome". Epilepsia 1973; 14: 153-64.
2. Lacy JR, Penry PK. Infantile spasms. New York: Raven Press, 1976.
3. Hrachovy RA, Frost JD Jr. Infantile spasms. Pediatr Clin North Am 1989; 36: 311-29.
4. Didenvall R. Eeg-Olofsson O. Epidemiology of infantile spasms in Sweden. Epilepsia 1995; 36: 572-4.
5. Duchowny M, Harvey AS. Pediatric epilepsy syndromes: an update and critical review. Epilepsia 1996; 37(suppl1): S26-S40.
6. Glaze DJ, Hrachowy RA, Frost JD, et al. Prospective study of outcome of infants with infantile spasms treated during controlled studies of ACTH and prednisolone. J Pediatr 1988; 112: 389-96.
7. Hellstrom B, Oberger E. ACTH and corticosteroid treatment of infantile spasms with hyperrhythmia. Acta Pediatr Scand 1965; 54: 180-7.
8. Riikonen R, Donner M. ACTH therapy in infantile spasms: Side effects. Arch Dis Child 1980; 55: 664-72.
9. Appleton RE. Vigabatrin in the management of generalized seizures in children. Seizure 1995; 4: 45-8.
10. Chiron C, Dumas C, Dulac O, et al. Vigabatrin versus hydrocortisone as first line monotherapy in infantile spasms. Epilepsia 1995; 36 (suppl 3): S265.
11. Kellaway P, Frost JD, Hrachovy RA. Infantile spasms. In: Antiepileptic Drug Therapy. Morselli PL, Pippenger CE, Pencry JK eds. New York: Raven Press, 1983: 115-36.
12. Siemes H, Spohr HL, Michael TH. Therapy of infantile spasms with valproate: results of a prospective study. Epilepsia 1988; 29: 553-60.
13. Prats JM, Garaizar C, Rua MJ, et al. Infantile spasms treated with high doses of sodium valproate: Initial response and follow-up. Dev Med Child Neurol 1991; 33: 617-5.
14. Livingston JH, Beaumont D, Arzimanogi A, Aicardi J. Vigabatrin in the treatment of epilepsy in children. Br J Clin Pharmac 1989; 27: 109S-112S.
15. Luna D, Dulac O, Pajot N, Beaumont D. Vigabatrin in the treatment of childhood epilepsy, a single placebo-controlled study. Epilepsia 1989; 30: 430-7.
16. Dulac O, Chiron C, Luna D, et al. Vigabatrin in childhood epilepsy. J Child Neurol 1991; 6(suppl 2): S30-S37.
17. Vles JSH, van der Heyden AMHG, Ghiji A, Troost J. Vigabatrin in the treatment of infantile spasms. Neuropediatrics 1993; 24: 230-1.
18. Fois A, Buoni S, Di Bartolo RM, Di Marco V, Mostardini R. Vigabatrin treatment in children. Child's Nerv Syst 1994; 10: 244-8.
19. Urdrall P, Alving J, Gram L, Hogenhaven H. Vigabatrin in childhood epilepsy: A 5-year follow-up study. Neuropediatrics 1995; 26: 253-6.
20. Vigevano F. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia 1997; 38: 1270-4.
21. Aicardi J, Sabril IS. Investigator and Peer Review Groups, Mumford JP, Dumas C and Wood S. Vigabatrin as Initial Therapy for Infantile Spasms : A European Retrospective Survey. Epilepsia 1996; 37: 638-42.
22. Fisher RS. Emerging antiepileptic drugs. Neurol 1993; 43(suppl 5): S12-S20.
23. Schmitt B, Wohlrab G, Boltshauser E. Vigabatrin in newly diagnosed infantile spasms. Neuropediatrics 1994; 25:54.
24. Buti D, Rota M, Lini M, Bardini MR, Guarnieri M, Marvulli I. First line monotherapy with vigabatrin in infantile spasms: long term clinical and EEG evolution in 12 patients. Epilepsia 1995; 36 (suppl 3): S102.
25. Fisher RS, Kalviainen R, Tanganelli P, Regesta G. Newer antiepileptic drugs as monotherapy: Data on vigabatrin. Neurology 1996; 47 (suppl 1): S2-S5.
26. Chiron C, Dulac O, Luna D, et al. Vigabatrin in infantile spasms. Lancet 1990; 335: 363-4.
27. Driefuss F, Farwell J, Holmes G, et al. Infantile spasms. Comparative trial of nitrazepam and corticotropin. Arch Neurol 1986; 43: 1107-10.
28. Farrel K. Benzodiazepines in the treatment of children with epilepsy. Epilepsia 1986; 27 (suppl 1): S45-S52.
29. Chamberlain MC. Nitrazepam for refractory infantile spasms and the Lennox-Gastaut syndrome. J Child Neurol 1996; 11: 31-4.
30. Appleton RE. The role of vigabatrin in the management of infantile epileptic syndrome.

Neurology 1993; 43(suppl 5): S21-S23.
31. Mumford JP, Cannon DJ. Vigabatrin. Epilepsia 1994; 35 (suppl 5): S25-28.
32. Sander JWAS, Hart YM, Trimble MR, Shorvon SD. Vigabatrin and behavioural disturbance. Lancet 1990; 335:57.
33. Naumann M, Supprian T, Kornhuber J, Lange KW, Reiners K. Bipolar affective psychosis after vigabatrin. Lancet 1994; 343: 606-7.
34. Aldenkamp AP, Vermeulen J, Mulder OG, et al. Gamma-vinyl GABA (vigabatrin) and mood disturbances. Epilepsia 1994; 35: 999-1004.
35. Dodrill CB, Arnett JL, Sommerville KW, et al. Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy. Neurology 1993; 43: 2501-7.
36. Monaco F. Cognitive effects of vigabatrin; a review. Neurol 1996; 47 (suppl 1): S6-S11.
37. Monaco F, Torta R, Cicolin A, et al. Lack of association between vigabatrin and impaired cognition. J Inter Med Res 1997; 25: 296-301.
38. Crofts K, Brennan R, Kearney P, O'Connor G. Vigabatrin-induced optic neuropathy. J Neurol 1997; 244: 666-7.
39. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 1997; 314: 180-1.
40. Wong IC, Mawer GE, Sander JWAS. Severe persistent visual field constriction associated with vigabatrin. Reaction might be dose dependent. BMJ 1997; 314(7095): 1693-4.
41. Krauss GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology 1998; 50: 614-8.
42. Mackenzie R, Klistorner A. Severe persistent visual field constriction associated with vigabatrin. Asymptomatic as well as symptomatic defects occur with vigabatrin. BMJ 1998; 316: 233.
43. Rao GP, Ah Fat F, Kyle G, Leach JP, Chadwick DW, Batterbury M. Study is needed of visual field defects associated with any long term antiepileptic drug. BMJ 1998; 317: 206.
44. Ruether K, Pung T, Kellner U, Schmitz B, Hartmann C. Electrophysiologic evaluation of a patient with peripheral visual field contraction associated with vigabatrin. Arch Ophthalmol 1998; 116: 817- 9.

ผลการรักษาอาการชักชนิดอินแฟนไทล์ สปาสมด้วยวิกาบาทริน : รายงานเบื้องต้น

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ผู้รายงานได้ศึกษาผลของยา vigabatrin ในรักษาอาการชักชนิด infantile spasms ในผู้ป่วยเด็กจำนวน 20 คน ซึ่งมีอายุระหว่าง 3 เดือน ถึง 23 เดือน และได้รับการรักษาที่โรงพยาบาลรามาธิบดี ในระหว่างเดือนมีนาคม พ.ศ.2539 ถึงเดือนพฤษภาคม พ.ศ.2541 ด้วยขนาดยาเริ่มต้น 35–50 มก./กก./วัน แบ่งให้วันละ 2 ครั้ง และเพิ่มขนาดของยา 25 มก./กก./วัน ทุก 1–2 สัปดาห์ จนควบคุมอาการชักชนิดนี้ได้หรือจนถึงขนาดยาสูงสุด 130 มก./กก./วัน ผู้ป่วยทุกคนจะต้องได้รับยานี้เป็นเวลาอย่างน้อย 6 เดือนและจะได้รับการประเมินผลการรักษาตามความถี่ของอาการชักที่ลดลง มีผู้ป่วย 4 และ 16 คน จัดอยู่ในกลุ่ม cryptogenic และ symptomatic ตามลำดับ พบว่า vigabatrin สามารถควบคุมอาการชักชนิดนี้ในผู้ป่วยจำนวน 12 คน (ร้อยละ 60) และสามารถลดความถี่ของการชักลงได้มากกว่าร้อยละ 50 เป็นจำนวน 6 คน (ร้อยละ 30) มีผู้ป่วย 2 คนซึ่งไม่ตอบสนองต่อการรักษาด้วยยานี้เมื่อให้ขนาดสูงสุด 130 มก./กก./วัน ผู้ป่วย 1 คน ที่มีการเคลื่อนไหวผิดปกติของกล้ามเนื้อใบหน้า (orofacial dyskinesia) ภายหลังได้รับยาเป็นเวลา 5 เดือน และอาการหายไปเมื่อหยุดยา จากผลของการศึกษาเบื้องต้นนี้ คณะผู้รายงานมีความเห็นว่า vigabatrin ได้ผลดีในการรักษาอาการชักชนิด infantile spasms แต่จะต้องมีการติดตามการรักษาต่อเนื่องในระยะยาว เพื่อประเมินผลการรักษาและผลข้างเคียงที่อาจจะเกิดขึ้น

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