Vigabatrin Therapy in Infantile Spasms

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Abstract

Rationale : To determine the clinical outcome and side effects of vigabatrin (VGB) in the treatment of infantile spasms (IS) and its long-term outcome.

Method : All children with IS treated with vigabatrin were studied. Clinical data regarding age of onset, duration of IS before therapy started, recurrence of IS, types of seizures that relapse, clinical outcome and side effects were monitored.

Results : 36 children (17 girls, 19 boys) with IS participated in the study. The mean age of onset of IS was 115.55 ± 67.3 days old (range, 15 to 300 days). Six were cryptogenic IS and 30 were symptomatic IS. The etiologies of symptomatic IS in this study were tuberous sclerosis[6], hypoxic ischemic encephalopathy (HIE) / periventricular leukomalacia[11], porencephaly[1], partial agenesis of corpus callosum[1], hemimegalencephaly[1], cortical dysplasia[7], and microcephaly[3]. 66.67 per cent (24 of 36) of patients responded to VGB within a mean 2.95 ± 2.25 days (range, 1 to 7 days). In those who responded to VGB, 3 patients developed recurrent IS within 69.3 ± 46.7 days (range, 30 to 121 days). Five patients developed epilepsy with different types of seizure during long-term follow-up. The mean duration of subsequent epilepsy after cessation of IS was 16.4 months (range, 5 months to 3 years 10 months). The mean duration of follow-up was 2.74 years (range, 1.09 years to 5.76 years). 10 patients were successfully weaned off VGB after a mean IS free period of 22.5 ± 5.5 months (range, 12 to 27 months). Transient drowsiness was seen in 4 patients. Three patients had transient abnormal sleep patterns and irritability. Visual field abnormalities were not found but difficult to assess fully in this study.

Conclusion : VGB therapy has a high response rate for the control of IS and is well tolerated in most children. All patients who responded to VGB and were spasm free for more than one year were successfully weaned off VGB therapy. Because serious side effects such as visual field abnormalities are difficult to monitor, the authors propose that VGB could be withdrawn or switched to another AED after a spasm-free period of more than one year.

Key word : Vigabatrin, Infantile Spasm, Outcome

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Infantile spasms (IS) are one of the most refractory epileptic syndromes of childhood. Failure of treatment usually leads to developmental regression and refractory epilepsy. In the past, only adrenocorticotropic hormone (ACTH) has been recommended as the treatment of choice for this particular syndrome[1,2]. However, ACTH has many side effects relating to these of steroids[3]. The supply and availability of ACTH in Thailand also poses a major problem. The supply of ACTH has been uncertain and unreliable for many years. Currently, ACTH is not available in Thailand. This causes a major obstacle in managing children with infantile spasms. In the past, the authors used other alternative anticonvulsant therapy such as valproic acid, benzodiazepines, and prednisolone. However, most alternative drugs are either ineffective or not tolerated due to side effects.

Vigabatrin (VGB) was first introduced as add-on therapy in refractory IS in 1991[4]. Later studies have reported the effectiveness of VGB as monotherapy in the treament of IS[5-8]. VGB was first available in Thailand in 1995. Since then all the IS children in our institution have been treated with VGB as initial therapy.

The purpose of this study was to present the authors' experience with VGB regarding its efficacy, side effects, and long term outcome in the treatment of IS.

PATIENTS AND METHOD

All patients with IS who were treated with VGB between 1995 and 1999 were studied retrospectively. Pertinent clinical data including age of onset of IS, the etiology of IS, EEG, CT/MRI, seizure frequency, clinical outcome, and side effects were collected. IS patients were classified into 1) symptomatic (underlying cause identified); 2) cryptogenic (developmental delay without definable etiology; 3) idiopathic (normal development throughout the evolution). All patients had either 1 hour 32 channel digital EEG or prolonged video EEG recordings to ascertain the diagnosis of IS. EEG findings were classified as typical hypsarrhythmia or hypsarrhythmia variants according to Hrachovy et al[9]. Patients were started with an initial dose of VGB of 50 mg/kg per day as a once daily dose. The daily VGB dosage was titrated up to a maximum of 150 mg/kg/day depending on the patient's clinical responses. The clinical outcome was classified as a responder if total disappearance of clinical spasms was observed by parents or physicians for a period of more than 2 weeks. Developmental assessment by a physician with parental global assessment at the latest follow-up visit was used as the developmental assessment measurement.

RESULTS

Between 1995 and 1999, there were 45 children with IS treated with VGB in our hospital. Nine were excluded from the study due to incomplete data. A total of 36 patients with IS treated with VGB were analyzed in this study. Six patients had cryptogenic IS, 30 patients had symptomatic IS. The etiologies of IS in the symptomatic IS patients were tuberous sclerosis[6], hypoxic ischemic encephalopathy (HIE) / periventricular leukomalacia[11], porencephaly[1], partial agenesis of corpus callosum [1], hemimegalencephaly[1], cortical dysplasia[7], and microcephaly[3]. The mean age of onset of IS was 115.55 ± 67.3 days old (range, 15 to 300 days). Clinical data are summarized in Table 1.

Of the 36 patients with IS treated initially with VGB, there were 24 responders. This gave a response rate of IS to VGB of 66.67 per cent (24 of 36). The mean duration until a response was observed was 2.95 ± 2.25 days (range 1 to 7 days). However, there were 4 patients who had recurrent

Table 1. Patients characteristics.

Sex	
Males	19
Females	17
Age of onset of IS	115.55 ± 67.3 days (15 to 300 days)
Etiology of IS	
Cryptogenic IS	6
Symptomatic IS	30
Tuberous sclerosis	6
HIE* / periventricular leukomalacia	11
Porencephaly	1
Partial agenesis of corpus callosum	1
Hemimegalencephaly	1
Cortical dysplasia	7
Microcephaly	3
EEG	
Hypsarrhythmia	10
Hypsarrhythmia variants	26

* HIE = Hypoxic ischemic encephalopath

Table 2. Clinical outcome of IS treated with VGB (n = 36).

Infantile Spasms response	
Complete cessation of IS for more than 2 weeks	24 (24/36), (66.67%)
Mean duration of treatment before response seen	2.95 ± 2.25 days (1 to 7 days)
Relapsing of IS	4 (4/24, 16.67%)
Mean duration before relapse seen	69.3 ± 46.7 days (30 to 121 days)
Late epilepsy (excluding IS)	5 (5/24, 20.83%)
Mean duration of other seizures relapsing	16.4 months (5 months to 3 years 10 months)
Non-responder	12 (12/36, 33.3%)

Table 3. Type of seizures and onset of seizures in a patient who subsequently developed epilepsy.

Case No	Onset of other seizure type that relapsed after VGB treatment (months)	Types of seizure seen following relapse
2	5	Partial seizures
3	12	Partial seizures
7	46	Partial seizures
11	10	Myoclonic seizures, Partial seizures
14	8	Generalized tonic-clonic, Myoclonic seizures, Partial seizures

IS with new and different types of seizures within a mean of 69.3 ± 46.7 days (range from 30 to 121 days). Another 5 patients subsequently developed epilepsy during long-term follow-up. All developed different kinds of seizures without recurrence of IS within a mean of 16.4 months (range, 5 months to 3 years 10 months). The total recurrence rate was 37.5 per cent (9 of 24 patients). The type of seizures that relapsed and the onset of relapse after VGB treatment are summarized in Table 3.

VGB was well tolerated in all patients in this study. Four patients developed transient drowsiness and three patients developed transient abnormal sleep patterns and irritability, which subsided after decreasing the total dosage of VGB. 10 patients were successfully weaned off VGB after a mean IS free period of 22.5 ± 5.5 months (range, 12 to 27 months). None of the patients reported any problem with their visual fields. However, visual field testing could not be fully assessed due to their young age.

Of the 24 patients who initially responded to VGB, 6 patients had a normal developmental outcome at the latest follow-up visit. Four of these 6 patients have tuberous sclerosis and belonged to a group that has a very good response to VGB without relapsing IS. Nine of 24 patients who initially responded to VGB had an improved developmental outcome at the latest visit. The remaining 9 patients who initially responded to VGB had no change in their developmental outcome.

DISCUSSION

The authors present their clinical experience of IS treated with VGB. All cases of clinical IS were validated by either routine 1 hour recording EEG or video EEG. Overall, the response rate of IS to VGB in our study was 66.67 per cent (24/36). Our results suggest that VGB is a very effective drug in the treatment of IS. Its onset of response was immediate and a dramatic response occurred in most cases. A clinical response of IS to VGB usually occurred within a week (mean, 2.95 ± 2.25 days). In all cases that responded, the response occurred within the first week of VGB administration. Those symptomatic IS patients with tuberous sclerosis showed a dramatic response to VGB in our study. All six symptomatic IS patients with tuberous sclerosis responded to UGB. Furthermore, four of these 6 with tuberous sclerosis had a normal deve-

Table 4. Long term outcome of patients with IS - VGB responder (n = 24).

Normal Development	6
Delayed Development - some improvement	9
Delayed Development - no improvement	9

lopmental outcome at long-term follow-up. Four were successfully weaned from VGB. Our findings support many previous studies that have shown a dramatic response of IS to VGB therapy[10-12]. However, in order to obtain the best outcome, VGB therapy should be initiated as soon as possible. One patient with symptomatic IS caused by tuberous sclerosis showed some improvement in the long-term neurological outcome. This patient had IS for a period of 6 months before being referred. After starting VGB and the cessation of IS, his motor development gradually improved to almost normal for his actual age at the latest clinic visit but his speech and language development remained delayed. This probably occurred because of the delay in treating and controlling the IS. The neurological outcome of this patient might have been different if he had been on VGB since IS first manifested.

However, the response may not last long in some cases. 9 out of 24 cases that initially responded to VGB (37.5%) developed recurrent seizures. Four of these developed recurrent IS (16.67%). The mean duration of relapsing IS in these 4 patients was 69.3 ± 46.7 days (30 to 121 days). Five developed subsequent epilepsy (other than IS) during long-term follow-up (Table 3). Most of the subsequent epilepsy (other than IS) occurred later in the course of treatment.

Regarding duration of VGB therapy after cessation of IS, the authors propose that VGB should be continued for at least 1 spasm-free year before weaning off the medication. From our data, 10 patients were successfully weaned off VGB after 22.5 ± 5.5 months of treatment (range, 12 to 27 months). In the cases that showed a complete response with no relapsing of IS, the developmental outcomes were good but the chances of developing epilepsy in the long term remained dictated by the underlying etiology of IS[13]. Side effects seen in our patients were transient drowsiness and irritability, which were found in 7 of 36 cases treated with VGB (19.9%). However, serious long-term side effects such as visual field abnormalities could not be thoroughly evaluated in these patients[14]. This should be followed-up in the long-term.

In summary the authors think VGB should be tried as an initial therapy for IS, especially for those with symptomatic IS caused by tuberous sclerosis. The immediate or short-term side effects of VGB are mild and usually well tolerated. However, the long-term side effects remain to be evaluated further.

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การใช้ยาไวกาบาทรินในผู้ป่วย Infantile Spasms

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หลักการและเหตุผล : เพื่อศึกษาถึงประสิทธิภาพและผลข้างเคียงของยา Vigabatrin (VGB) ในการรักษาภาวะ Infantile spasms และการติดตามผลการักษาในระยะยาว

วิธีการ : ผู้ป่วยเด็กที่มีอาการชักแบบ Infantile spasms จะเข้าร่วมในการศึกษา ข้อมูลทางคลินิกของผู้ป่วยเกี่ยวกับอายุที่เริ่มแรกมีอาการ ระยะเวลาที่มีอาการชักก่อนเริ่มรักษา การเกิดซ้ำหลังการรักษา และชนิดของอาการชักซ้ำหลังการรักษา ผลการรักษาและผลข้างเคียงจะถูกบันทึก

ผลการศึกษา : ผู้ป่วยเด็ก 36 คน แบ่งเป็นเด็กชาย 19 คน เด็กหญิง 17 คน ที่มีภาวะ Infantile spasms ได้เข้าร่วมการศึกษาอายุโดยเฉลี่ยเมื่อผู้ป่วยเริ่มแรกมีอาการคือ 115.55 $\pm$ 67.3 วัน (15–300 วัน) ผู้ป่วย 6 คน เป็น Infanfile spasms แบบ cryptogenic และ 30 คน เป็นแบบ symptomatic โดยสาเหตุย่อยในกลุ่ม symptomatic ได้แก่ tuberous sclerosis 6 ราย, hypoxic ischemic encephalopathy (HIE), periventricular leukomalacia 11 ราย, porencephaly 1 ราย, partial agenesis corpus callosum 1 ราย, hemimegalencephaly 1 ราย, cortical dysplasia 7 ราย และ microcephaly 3 ราย 66.67% (24 ใน 36) ของผู้ป่วยตอบสนองมีต่อ VGB ภายใน 2.59 $\pm$ 2.25 วัน (1–7วัน) ผู้ป่วยที่ตอบสนองต่อ VGB 3 คน จะมีการการเกิดซ้ำ ของ infantile spasms ภายใน 69.3 $\pm$ 46.7 วัน (30–121 วัน) ผู้ป่วย 5 คน มีอาการชักในหลายแบบจากการติดตามในระยะยาว โดยจะมีอาการโดยเฉลี่ยใน 16.4 เดือน (5 เดือน–3 ปี 10 เดือน) ผู้ป่วยจะได้รับการติดตามโดยเฉลี่ย 2.74 ปี (1.09–5.76 ปี) ผู้ป่วย 10 รายสามารถหยุดยา VGB ได้ โดยมีระยะเวลาที่ผู้ป่วยหายปลอดจาก infantile spasms โดยเฉลี่ย 22.5 $\pm$ 5.5 เดือน (12–27 เดือน) อาการง่วงซึมเกิดขึ้นชั่วคราวพบในผู้ป่วย 4 ราย ผู้ป่วย 3 รายมีพฤติกรรมการนอนหลับผิดปกติและงอแง ไม่พบภาวะลาดสายตาผิดปกติ ในกลุ่มผู้ป่วยที่ทำการศึกษา

สรุป : การรักษาภาวะ infantile spasms โดยใช้ VGB ได้ผลดีมาก ผู้ป่วยทนต่อยาได้ดีผู้ป่วยทุกรายตอบสนองต่อ VGB ได้ดี และไม่มีอาการชักแบบ infantile spasms มากกว่า 1 ปี และสามารถหยุดยาได้ในที่สุด เนื่องจากผลข้างเคียงที่สำคัญของการใช้ยา VGB คือ ปัญหาเรื่องลาดสายตาผิดปกติ และการทำการตรวจวัดในผู้ป่วยเด็ก ทำได้ค่อนข้างยาก ผู้ศึกษาจึงเสนอให้หยุดการใช้ยา VGB เป็นยาอื่น เมื่อผู้ป่วยไม่มีอาการชักแบบ infantile spasms นานมากกว่า 1 ปี

คำสำคัญ : ไวกาบาทริน, Infantile Spasms, โรคลมชัก

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