Vigabatrin in Infantile Spasms

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Abstract

Vigabatrin (VGB) is an effective treatment of infantile spasms (IS) that controls spasms of all etiologies in about 50% of patients when used as monotherapy. In tuberous sclerosis complex, VGB controls spasms in up to 95% of patients and should be used as the drug of choice. Higher VGB doses correlate with shorter times to response and higher response rates. Its most serious side effect is retinal toxicity characterized by irreversible bilateral concentric constriction of the visual fields (BCCVF). Maximum VGB dose, total VGB dose, and duration of VGB treatment constitute risk factors for BCCVF. In each particular patient, dose and duration of treatment should be kept at a minimum, while ensuring effectiveness and preventing relapse. Every effort should be made to evaluate retinal function, even though it may require specialized ophthalmological services. The addition of this new US Food and Drug Administration (FDA)-approved drug as an alternative in the treatment of IS represents a major contribution to an armamentarium that contains only one other treatment.

Keywords

Vigabatrin, tuberous sclerosis complex, infantile spasms, visual field constriction, children, side effect

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Vigabatrin (VGB) was only recently approved by the US Food and Drug Administration (FDA) as monotherapy for infantile spasms (IS). Nonetheless, considerable experience is available, since VGB has been used for more than 10 years in other countries. The delay in approval in the US relates in part to its safety profile, since it can cause irreversible retinal toxicity.

VGB is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), which has a favorable pharmacokinetic profile since it is not metabolized by the liver, is excreted by the kidney, has low protein binding, and has a long effective half-life, allowing once- or twice-daily dosing. Interaction with other antiepileptic drugs is minimal.

Ample evidence has been provided to support the use of VGB in the treatment of IS, and for many years European neurologists have considered VGB to be the drug of choice for the symptomatic treatment of IS.¹⁴ Used as a first line of treatment in monotherapy, the percentage of children who are rendered seizure-free averages around 50%.¹⁵ Efficacy is lower in refractory cases, but still approaches total control in 30% of children.¹⁵ Tuberous sclerosis complex (TSC) represents a particularly successful story for the use of VGB, since the drug controls spasms in up to 95% of patients.¹⁵,¹⁷,¹⁸

When VGB is compared with hormonal (corticosteroid) treatment for IS, the response to hormonal treatment is faster and initially benefits a higher percentage of patients. However, assessed again at 14 months of age, patients exhibit comparable response rates as a result of fewer subsequent relapses following VGB use.¹⁹ Early studies had suggested that symptomatic IS respond better to VGB than idiopathic IS,¹⁹ particularly IS resulting from cerebral malformations.¹⁹ These results have not been replicated in the more recent studies.

Cognitive outcomes overall seem to be similar with VGB or hormonal treatment, but infants with no known underlying cause have better cognitive outcomes following hormonal treatment.²⁰ On the other hand, superior cognitive outcome has been reported with VGB in TSC²¹ and with other etiologies.²²

The exact dosing of VGB treatment is still being debated. Elterman¹⁰ established that in children receiving higher doses (100–148mg/day versus 18–36mg/day), times to response were shorter and response rates significantly higher. An earlier review of 20 patients found that some individuals responded to doses as low as 25mg/kg and suggested starting at a low dose and gradually increasing until IS control was achieved.¹⁰ Since in some studies retinal toxicity correlates with the highest VGB level, this risk has to be weighed against the potential benefits of faster control of IS...
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and better cognitive outcome. Most studies have used doses of 100-200mg/kg.

Regarding the duration of treatment, here, too, there is no clear consensus. This issue is of particular importance, since recurrent spasms can be extremely resistant and the duration of VGB treatment, as well as the highest level, is also a potential risk factor for retinal toxicity. Relapse of IS after complete control following suspension of VGB after one to five years of treatment has been reported in cases of focal cortical dysplasia, with IS being refractory to restarting treatment with VGB. Short-term treatment (six months) seems to be safe regarding the risk for relapse in patients with Down syndrome and for cryptogenic and post anoxic IS.

VGB is generally well tolerated and has few cognitive side effects, but may cause irritability, agitation, depression, or psychosis. These side effects are reversible upon dose reduction or discontinuation and rarely represent a major problem.

Retinal toxicity, characterized by bilateral concentric constriction of the visual fields (BCCVF), is a significant and irreversible side effect that occurs in around 30% of adults, although numbers ranging from 20 to 70% have been reported. The typical defect is often more pronounced in the nasal field and can range from mild to severe, but is usually asymptomatic and can only be detected by visual field testing. Most cases of BCCVF have no accompanying retinal changes on fundoscopy, and there is no evidence for central visual acuity changes in relation to VGB.

The risk factors that have been reported for BCCVF in adults include maximum VGB dose, total VGB dose, male gender, and duration of VGB treatment. The overall impression is that most BCCVF occurs over the first two years of VGB treatment. In children the abnormalities occur between six months and one year of starting VGB treatment.

The prevalence of retinal toxicity in children who were treated with VGB at two years and older is around 20-30%. The prevalence in children treated at younger ages for IS is unknown. The most recent studies with VGB for infantile spasm did not report visual field testing or other indirect measures.

In young or mentally handicapped children, who cannot co-operate with traditional visual field testing, behavioral visual field testing has detected BCCVF at similar rates to those seen in adults. Other indirect measures that correlate with visual field defects and have been used in these populations include the electroretinogram (ERG), ocular coherence tomography, and scanning laser polarimetry. The ERG is a sensitive tool that can be carried out under anesthesia in children who are unable to co-operate with conventional visual field testing. Abnormal 30Hz flicker cone b-waves are associated with visual field reduction, and a relationship between visual field defects and abnormal photopic latencies has been described.

Field-specific visual evoked potentials have also been shown to be sensitive to BCCVF. Since retinal nerve fiber layer thickness is reduced in these patients, methods such as ocular coherence tomography and scanning laser polarimetry can aid in the diagnosis. One study suggested that VGB-related visual field constrictions can be reversible in children, but this finding has not been replicated.

Twenty-two to 32% of children treated with VGB for IS also showed transient magnetic resonance imaging (MRI) abnormalities in the basal ganglia, thalami, anterior commissure, or midbrain with hyper-intense T2 weighting, and restricted diffusion on diffusion-weighted images. Desguerre reported similar abnormalities in six children with IS and interpreted them as expression of non-convulsive status epilepticus. These abnormalities were transient and resolved completely, even during ongoing VGB treatment, and did not appear to be associated with any clinical sequelae. They were less prevalent in pediatric and adult patients receiving VGB for complex partial seizures, and did not differ significantly from their incidence in epileptic patients who did not get VGB. Such abnormalities might be related to histopathological changes characterized by microvacuolization within myelin laminae observed in rodents and dogs receiving the drug and were completely reversible upon discontinuation of VGB.

Summary

In summary, VGB is an effective treatment of IS. Its most serious side effect is retinal toxicity. In each particular patient, dose and duration of treatment should be kept at a minimum, while ensuring effectiveness and preventing relapse. Every effort should be made to evaluate retinal function, even though it may require specialized ophthalmological services. In tuberous sclerosis patients VGB should be used as the first drug of choice. Catastrophic childhood epilepsies are a major challenge for every pediatric neurologist, and IS represent a particularly urgent and difficult-to-treat syndrome. The addition of this new FDA-approved drug as an alternative in the treatment of IS represents a major contribution to an armamentarium that contains only one other treatment.

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